UNIVERSITAT DE BARCELONA

Inflammation, Autoimmunity, and Psychopathology: A Study in Children and Adolescents with Acute Psychiatric Conditions and in Children of Women with Systemic Lupus Erythematosus

Maria Gariup

Doctoral dissertation

Inflammation, autoimmunity and psychopathology: a study in children and adolescents with acute psychiatric disease and in offspring of women with Systemic Lupus Erythematosus

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Doctoral dissertation

Inflammation, autoimmunity and psychopathology: a study in children and adolescents with acute psychiatric disease and in offspring of women with Systemic Lupus Erythematosus.

Doctoral dissertation report submitted by Maria Gariup to obtain a doctoral degree by the University of Barcelona

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Informe director/s /tutor sobre l'autorització del dipòsit de la tesi

Dr./a.s Astrid Morer y Luisa Lázaro, com a director/tutor de la tesi doctoral titulada "Inflammation, autoimmunity and psychopathology: a study in children and adolescents with acute psychiatric disease and in offspring of women with Systemic Lupus Erythematosus " i, d'acord amb el que s'estableix a l'article 35 Normativa reguladora del Doctorat a la Universitat de Barcelona, emeto el següent:

INFORME

(Informe detallat i motivat sobre el contingut de la tesi i sobre l'autorització de dipòsit de la tesi que s'ha demanat)

Es nuestra opinión, esta tesis contribuye de manera significativa a ampliar los conocimientos tanto sobre el papel de la inflamación y del estrés en psicopatología de la infancia y la adolescencia, como sobre la comorbilidad entre trastornos psiquiátricos y somáticos, en particular los trastornos autoinmunes.

La amplia revisión de la literatura acerca de mecanismos y sistemas fisiológicos implicados permite entender el desarrollo de los procesos clínicos. Destaca la sólida evidencia recogida sobre la comorbilidad somática y psiquiátrica y sobre el papel del estrés y las infecciones, así como la evidencia que apoya un abordaje transdiagnóstico en psiquiatría, permitiendo todo ello una visión global y muy actual de salud y enfermedad.

Los resultados de los trabajos originales son interesantes, mostrando alteraciones inflamatorias difusas en pacientes psiquiátricos menores de edad, y también en hijos de madres con Lupus Eritematoso Sistémico no descritas anteriorment e, y ligadas a medidas que evalúan est rés.

La discusión, además de incidir sobre el marco teórico de los estudios originales , profundiza en el posible impacto de otros estresores , similares a los que se encuentran en una mayoría pacientes a lo largo de su enfermedad, lo que enlaza con teorías de la psicología social y del desarrollo y el concepto del apego.

Finalmente, destacar que las propuestas de medidas de intervención e investigación, de fácil aplicabilidad y sostenibilidad, proporcionan sugerencias útiles para trabajos futuros.

Por todo lo mencionado, autorizamos a la doctoranda al deposito de la presente tesis

Barcelona, 10 d'/de Octubre de 2021 .

(signat)

Dr./a **Astrid Morer y Luisa Lázaro**

Un cop s'hagi emplenat l'informe, s'ha d'adjuntar i s'ha de fer arribar al doctorand o al president de la Comissió Acadèmica del programa de doctorat responsable de la tesi.

Acknowledgments

A warm thank to my directors Astrid and Luisa, who have encouraged and accompanied me in this journey. To Astrid, for raising my interest in the immunological hypotheses in psychiatry, for designing and finding the foundings for the original studies, and for giving me the opportunity to contribute to this investigation. For her high spirits and flexibility. To Luisa for the ongoing support, guidance and advice. To both, for the cheerful moments shared in these years, and for making me realize the importance of getting help in challenging circumstances.

Thanks to the patients and the families I have met in Spain and in Denmark, working with them has enriched my research, and provided inspiration for this work.

To the colleagues and teachers, I have met along this experience, at work, conferences, courses, and who have transmitted me the interest in combining biological research with study of life circumstances.

To my friends, for having been there. And to my family, who have always supported me, even when they did not agree. To them I dedicate this work.

“Reasonable hopes are always shared hopes”

Giuseppe Tibaldi

Table of contents

Acknowledgments 5

Table of contents 7

Thesis format: Thesis in the form of a collection of published articles 12

SUMMARY OF THE THESIS IN SPANISH - RESUMEN DE LA TESIS EN CASTELLANO 13

FRAMEWORK 23

INTRODUCTION: *A panoramic review of inflammation, neurodevelopment, stress and a transdiagnostic approach in psychopathology* 24

1.1 Inflammation and immune alterations in psychopathology: current evidence 25

1.1.1 Adult studies 25

1.1.2 Children and Adolescent studies 29

1.2 Evidence for inflammation being able to cause psychiatric symptoms 30

1.2.1 Evidence from longitudinal studies 30

1.2.2 Effects of exogenous inflammation 31

1.2.3 Endogenous inflammation: correlates with brain function. Data on functional connectivity 34

1.2.4 How peripheral inflammation can access the brain 37

1.3 Mechanism for inflammation to affect the brain 38

1.3.1 Cytokines 38

1.3.2 Microglia: roles and effects of peripheral inflammation 38

1.3.3 Monoamines and glutamate: roles and effects of peripheral inflammation 41

1.3.4 HPA axis: effects of inflammation 42

1.3.5 Conclusions about effects of peripheral inflammation on the brain 44

1.4 Maternal Immune Activation and Lupus pregnancies: effects on neurodevelopment 44

1.4.1 Effects of MIA on neurodevelopment 46

1.4.2 Effects of MIA on Physical health 55
1.4.3 Conclusions - effects of MIA on offspring psychophysical health 57
1.4.4 Lupus pregnancies and offspring: a model of MIA 58
1.5 Comorbidity and interplay between somatic and psychiatric conditions 64
1.5.1 Adult studies: 64
1.5.2 Children studies: 65
1.5.3 Family studies: 66
1.6 The role of Infections 68
1.7 Inflammation as the common soil for the chronic diseases 70
1.8 The role of stress on health and inflammation 71
1.8.1 Prenatal maternal stress: a MIA model 71
1.8.2 Psychosocial stress in early life 72
1.8.3 Stress in adolescence and adulthood 76
1.8.4 Stress: conclusions from epidemiological evidence 77
1.9 Mechanisms for stress to affect health 78
1.9.1 Stress and the HPA axis 78
1.9.2 Stress and the Autonomous Nervous System 82
1.9.3 Stress and the Immune System – the role of Monocytes 83
1.9.4 Effects of stress on brain cells and network development 84
1.9.5 Stress and telomere length 88
1.9.6 Stress and microbiome 88
1.9.7 Stress and timing. The three main hypotheses: stress generation, stress sensitization, and stress accumulation 89
1.10 The theoretical models, from the DOHaD and beyond. 91
1.10.1 The Developmental Origins of Health and Disease hypothesis (DOHaD) 91

1.10.2 Integrative models within neurosciences 92
1.11 A transdiagnostic approach in psychopathology 98
1.11.1 Support for a transdiagnostic approach in psychopathology 98
1.11.2 The Research Domain Criteria 99
1.11.3 The Hierarchical Taxonomy of Psychopathology 101
1.11.4 Symptom-focused models: the Symptom Network Modelling and the Cambridge Model 103
1.11.5 Connectomics: the Human Connectome Programs and Neural Circuit Taxonomies 105
1.11.6 Conclusions about the transdiagnostic approach 109
1.12 Conclusions from the introduction 110
2 HYPOTHESES 111
3 AIMS 112
3.1 Global aim 112
3.2 Specific aims 113
4 MATERIALS AND METHODS - SCIENTIFIC PUBLICATIONS 114
4.1 STUDY 1 115
Title: 115
AIM: 115
RESÚMEN EN CASTELLANO: 116
Paper 1 117
4.2 STUDY 2 134
Title 134
AIM 134
RESÚMEN EN CASTELLANO: 135
Paper 2 136

4.3 UNPUBLISHED RESULTS 148
Title 1: 148
Title 2: 148
Work 1 149
Work 2 162
5 DISCUSSION 166
5.1 Main findings 166
5.2 Interpretation of the findings in the frame of the theoretical models 168
5.3 The role of parental and social bonds on health: the buffering function 177
5.3.1 Family strain and parent-child conflict: impacts on health 177
5.3.2 Parental sensitivity and support: impacts on health 178
5.3.3 Results and efficacy of preventive interventions 180
5.3.4 The role of social connections versus loneliness on mental and physical health 182
5.3.5 Conclusions about the concept of stress 184
5.4 The parallels between Early Stress Embedding and Attachment Theory and Research 186
5.4.1 Attachment and inflammation and health 188
5.4.2 Attachment and stress systems 189
5.4.3 Attachment and mental health 189
5.4.4 Mechanisms implied 190
5.4.5 Attachment as a measure of perceived stress: conclusions 192
5.5 Implications and future directions 193
5.5.1 Research to characterize inflammation in mental conditions 194
5.5.2 Further analyses of our samples 195
5.5.3 Research aiming to reduce inflammation and enhanced stress reactivity 196
5.5.4 Research on assessment of psychosocial stress 199

5.5.5 Research on psychosocial interventions 200
5.6 Limitations 205
6 CONCLUSIONS 206
References 207

Thesis format: Thesis in the form of a collection of published articles

This thesis consists of one General Aim, two Specific Aims, and two published papers:

Paper 1:

Maria Gariup, Azucena Gonzalez, Luisa Lázaro, Ferran Torres, Carles Serra-Pagès, Astrid Morer

IL-8 and the innate immunity as biomarkers in acute child and adolescent psychopathology, Psychoneuroendocrinology, Volume 62, 2015, Pages 233-242, ISSN 0306-4530, https://doi.org/10.1016/j.psyneuen.2015.08.017

IF 4.732; Q1 Scimago Journal Rank - Psychiatry

Paper 2:

Gariup M, Lera-Miguel S, Torres F, Varela E, Serra-Pagès C, González-Navarro A, Espinosa G, Lázaro L, Cervera R, Morer A.

Autoantibodies, elevated cytokines, and neurocognitive abnormalities in offspring of women with systemic lupus erythematosus: comparison with healthy controls.

Clin Rheumatol. 2019 Sep;38(9):2529-2539. doi: 10.1007/s10067-019-04495-4. Epub 2019 Apr 24. PMID: 31020474.

IF 2.980, Q2 Scimago Journal Rank – Rheumatology

SUMMARY OF THE THESIS IN SPANISH - RESUMEN DE LA TESIS EN CASTELLANO

RESUMEN DE LA TESIS

TÍTULO TRADUCIDO:

Inflamación, autoinmunidad y psicopatología: estudio en niños y adolescentes con patología psiquiátrica aguda y en hijos de mujeres con Lupus Eritematoso Sistémico (LES)

INTRODUCCIÓN:

En las últimas tres décadas numerosas investigaciones se han ocupado del papel de la inflamación y del estrés en la salud y la patología física y mental. Diferentes alteraciones inflamatorias se han detectado en todos los trastornos psiquiátricos en población adulta, con evidencia emergente también en la población infantil y adolescente. Estudios longitudinales sugieren un posible papel causal de la inflamación en la sintomatología. De forma paralela, las fronteras entre patología somática y psiquiátrica se han ido desdibujando y los conceptos de salud física y mental acercando. El estudio de las interrelaciones entre funciones cerebral y sistémicas ha revelado redes complejas, como las que unen el sistema nervioso con el sistema inmune y endocrino, o la red intestino-cerebro , asi como el papel del microbiota.

En psiquiatría, la clasificación categorial propuesta por el ICD-10 y el DSM-IV y 5 está siendo cuestionada tanto por la realidad de la práctica clínica, donde la comorbilidad es la norma más que la excepción, y por investigaciones que describen un riesgo familiar compartido entre los trastornos, respuesta a los mismos tratamientos farmacológicos, y alteraciones comunes tanto a nivel de marcadores, de neuroimagen y de genética.

Asimismo, trabajos recientes han revelado elevada comorbilidad entre enfermedades de base inflamatoria, como las alérgicas, autoinmunes y cardiovasculares, y la patología psiquiátrica. Diferentes factores causales comunes, como los genéticos, las infecciones, el estrés psicosocial ya desde fases tempranas de la vida se han implicado, y varios autores sugieren que muchos trastornos crónicos de la población adulta podrían entenderse como trastornos del desarrollo que comienzan de forma temprana (Shonkoff et al., 2011). Por otra parte, se ha implicado a la inflamación como posible mecanismo mediador común de las enfermedades crónicas, y al estrés psicosocial como uno de los posibles agentes causales.

Este estudio propone ampliar conocimientos acerca del papel de la inflamación y del estrés en la psicopatología, y de la comorbilidad entre patología psiquiátrica e inmune. En los trabajos originales, se estudian estas relaciones en un grupo poblacional, niños y adolescentes, donde las

enfermedades crónicas aún no suelen haber debutado; específicamente, en dos subgrupos de particular interés: pacientes con patología psiquiátrica aguda e hijos de mujeres con Lupus Eritematoso Sistémico.

La evidencia proveniente principalmente de estudios en adultos encuentra alteraciones inflamatorias comunes en todo el espectro de diagnóstico psiquiátrico. Este hallazgo común favorecería un enfoque transdiagnóstico en psiquiatría, que en la actualidad manejan varios autores. Partiendo de estas premisas, hemos optado por estudiar a pacientes jóvenes con todos los diagnósticos psiquiátricos, con la idea de que pudieran encontrarse alteraciones comunes.
Al mismo tiempo, los hijos de mujeres con LES emergen como una categoría emblemática, al estudiar la interacción entre el sistema inmunológico, el cerebro y el estrés. Estos niños han estado expuestos a la autoinmunidad materna (MIA) durante su desarrollo fetal, pueden tener un alto riesgo genético de desregulaciones autoinmunes y han estado conviviendo desde el nacimiento al estresor psicosocial de tener una madre con una enfermedad crónica. Además, un anticuerpo aislado de mujeres con LES, el anti-GluN2 o anti-DWEYS, puede tener efectos neurotóxicos al llegar al cerebro, y se ha implicado en modelos preclínicos de MIA. Se han descrito previamente problemas de aprendizaje y trastornos del desarrollo neurológico en esta población, pero no se había realizado una evaluación inmunitaria completa en estos niños, ni una descripción de la presencia de este anticuerpo

HIPÓTESIS

La principal hipótesis que subyace a este trabajo es que la psicopatología y los cambios inmunitarios están interrelacionados, que la inflamación es un potencial mediador común y que el estrés psicosocial y otras agresiones a lo largo del desarrollo son potenciales factores causales.
Estudiamos dos grupos de sujetos: niños y adolescentes hospitalizados por patología psiquiátrica aguda, e hijos de mujeres con lupus eritematoso sistémico, sujetos que han estado potencialmente expuestas a agresiones inmunitarias desde su vida fetal.
En cada grupo planteamos una hipótesis:

Hipótesis 1: Inflamación, inmunidad, estrés y psicopatología:

Se encontrarán cambios inflamatorios e inmunes en niños y adolescentes hospitalizados por patología psiquiátrica, a lo largo de todo el espectro diagnóstico. Estos cambios estarán relacionados con medidas de estrés psicosocial.

Hipótesis 2: Estado inmunológico, neurocognición y psicopatología en los hijos de mujeres con Lupus Eritematoso Sistémico.

Los hijos de mujeres con Lupus Eritematoso Sistémico mostrarán cambios en neurocognición, psicopatología y perfiles inmunes. Neurocognición, psicopatología y / o perfil inmunológico podrían estar relacionados con medidas de estrés psicosocial.

OBJETIVOS

Objetivo global

Aumentar el conocimiento sobre la relación entre la inflamación, la autoinmunidad, el estrés psicosocial y las condiciones psiquiátricas, en población infantil y adolescente.

Objetivos específicos

1. Explorar el perfil inflamatorio e inmunológico, y la relación de estos con medidas de estrés psicosocial, en una muestra de niños y adolescentes hospitalizados por patología psiquiátrica aguda, en comparación con una población de controles sanos.

2. Explorar perfiles inmunológicos, psicopatológicos y neurocognitivos y medidas de estrés psicosocial en un grupo de hijos de mujeres con LES en comparación con controles sanos. Buscar asociaciones de estas medidas entre ellas, y en relación con el estado materno.

INVESTIGATION-GAP:

1. Atendiendo a nuestro conocimiento, este es el primer estudio que evalúa un panel de marcadores tan amplio, y que considera tantos diagnósticos psiquiátricos a la vez en este grupo de pacientes.

2. Aunque los cambios en la neurocognición de hijos de mujeres con LES ya están descritos, este es el primer trabajo que analiza estos datos inmunológicos en este grupo de sujetos, y los correlaciona con determinadas variables maternas como condición física y síntomas afectivos.

MÉTODOS

En una muestra de 77 pacientes y 34 controles entre 8 y 17 años, se analizaron:

- un amplio panel de citocinas (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL_10, factor estimulante de colonias de granulocitos-macrófagos (GM-CSF), interferón (IFN) - γ, factor de necrosis tumoral (TNF) -α, proteína-10 inducida por IFN-γ (IP-10), proteína quimiotáctica de monocitos (MCP-1.), Glóbulos blancos, CRP;
- medidas de estrés representadas por escalas autoadministradas en hijos y padres (acerca de sus hijos), y por datos acerca de la formación familiar;
- diversos anticuerpos asociados a manifestaciones neuropsiquiátricas en la literatura, entre los que se encuentran los anti-DWEYS descritos neurotóxicos en pacientes con LES (resultados expuestos entre datos no publicados)

En una muestra de 21 hijos de 17 mujeres con LES, y 34 controles sanos, se analizaron:

a. los mismos datos inmunológicos y de estrés que en el punto 1 (excl. MCP-1 y IP-10)
b. perfiles neurocognitivos
c. Condición psicofísica y perfil inmunológico en las mujeres con LES.

PRINCIPALES RESULTADOS

En el primer estudio, los niños y adolescentes hospitalizados por trastorno psiquiátrico agudo, tenían un mayor recuento de monocitos y niveles más altos de cinco citocinas proinflamatorias (IL-1β, IL-6, IL-8, IP-10 y MCP-1) incluso después de ajustar (excepto en el caso de MCP-1) por otras posibles causas de inflamación como Indice de Masa Corporal (IMC), edad, sexo e fármacos prescritos al ingreso. Los pacientes provenían con mayor frecuencia de familias en las que no se conservaba la estructura biológica original (separación de los padres, divorcio, adopciones, custodia en instituciones públicas) y habían experimentado niveles más altos de estresores recientes. Los monocitos y varias citocinas se correlacionaban con medidas de estresores recientes, que resultaron más elevados en pacientes provenientes de familias que habían perdido su estructura original. La disrupción de la estructura familiar ha resultado ser un predictor independiente de la condición de ser paciente, junto con el recuento de monocitos, IL-8 e IP-10. La disrupción familiar ha mostrado también una tendencia a asociarse con niveles mayores de IL-1β e IL-6.

En el segundo estudio, hemos encontrado que los hijos de mujeres con LES tenían un perfil inmunológico diferente al de los controles, con niveles más altos de 8 citocinas (IL-1β, IL-2, IL-4, IL-5, IL-6, IL -10, IFN-γ y TNF-α), menor recuento de glóbulos blancos, mayores niveles de anti-DNAds y de anticuerpos anti-DWEYS. Este último es un anticuerpo descrito en mujeres con LES, con efectos neurotóxicos en estudios con animales, y un candidato plausible para daño neuronal y síntomas de neurolupus cuando está presente en el liquido cefaloraquideo (LCR) (Diamond et al., 2009; Faust et al., 2010). Los hijos también tenían una mayor tasa de autoinmunidad y asma que los controles. Además, presentaban más dificultades en la producción escrita y mayor lentitud en las habilidades visomotoras, y mejor control de la impulsividad en comparación con los sujetos sanos.

La PCR mostraba un incremento, y el recuento de leucocitos un decremento con la edad de los sujetos en el grupo de los hijos, y no en el grupo de controles. Asimismo, puntuaciones en atención y en memoria inmediata resultaban más altas en sujetos más jóvenes en los hijos, y no en los controles.

Aproximadamente una cuarta parte (23,9%) de los hijos cumplía los criterios para un diagnóstico psiquiátrico y la mitad de ellos presentaba síntomas subclínicos. Los diagnósticos encontrados han sido ansiedad, trastorno por déficit de atención con hiperactividad (TDAH), trastorno obsesivo-compulsivo (TOC) y síndrome de Tourette, con una prevalencia que ha sido significativamente superior a la estimada en la población general. Las puntuaciones de los hijos en las escalas de estrés y de depresión han mostrado correlación positiva. Varios índices de rendimiento neuropsicológico han mostrado una correlación negativa con las escalas maternas de depresión y de actividad de su enfermedad autoinmune.

Además, se han descrito algunos resultados no publicados, que muestran que los pacientes hospitalizados con patología psiquiátrica tenían mayor proporción de monocitos a linfocitos (MLR) que los controles. Los valores de anticuerpos anti-DWEYS aumentan progresivamente entre los grupos de controles, pacientes e hijos de mujeres con LES.

DISCUSIÓN

Los resultados del estudio 1 apoyan la presencia de un exceso de inflamación periférica y de activación de monocitos en pacientes psiquiátricos niños y adolescentes: el panel de citocinas que se encuentran elevadas (IL-1β, IL-6, IL-8, IP-10 y MCP-1) son todas producidas por monocitos

activados, y los recuentos de monocitos también han resultado más altos en el grupo de pacientes.

Es interesante que el estudio haya encontrado elevación en un amplio número de citocinas y en diferentes diagnósticos: en particular, IL-1β e IL-8 resultaron más altas que en los controles en todos los subgrupos diagnósticos, a pesar de la reducción en el tamaño de los grupos. La literatura anterior a menudo se centra en marcadores específicos (por ejemplo, IL-6 o PCR) en diagnósticos específicos, y nuestros hallazgos sugieren que se pueden alcanzar resultados más generales si se adopta un panel de amplio espectro y un enfoque transdiagnóstico.

Varios trabajos sugieren un papel potencial de estos marcadores en el desarrollo de psicopatología. Más allá del papel de los marcadores individuales, resulta relevante encontrar signos de inflamación sistémica elevada y cambios en el sistema inmunológico ya en pacientes psiquiátricos muy jóvenes, que además muestran un aumento en la fracción monocitos/ linfocitos (propuesto marcador de inflamación sistémica en trastornos psiquiátricos (Neutrophil-to-Lymphocyte, Platelet-to-Lymphocyte and Monocyte-to-Lymphocyte Ratio in Bipolar Disorder, 2021)), así como una tendencia a tasas más altas de enfermedades alérgicas (ambos resultados aún no publicados).

Estos resultados encajan con los del estudio 2, donde los hijos de mujeres con LES también muestran cambios inmunes como marcadores inflamatorios más altos, tasas más altas de asma y afecciones autoinmunes y algunos cambios en el perfil neurocognitivo, con respecto a los controles sanos, asi como tasas más altas que las esperadas de diagnóstico psiquiátrico.

Además, en ambos estudios, los marcadores inmunes resultaron predictivos de la condición del estudio: en el Estudio 1, IL8, IP10 y el recuento absoluto de monocitos predecían la condición de paciente, y en el Estudio 2, los anti-DWEYS y el recuento de leucocitos predecían la condición de hijos de madres con LES.

Esta coexistencia de cambios neuropsiquiátricos e inmunológicos en ambos grupos apoya la hipótesis de la elevada comorbilidad entre los trastornos psiquiátricos y enfermedades somáticas, y avala la hipótesis de que la inflamación podría ser un sustrato común de las enfermedades crónicas. En cuanto al hallazgo sobre los anticuerpos anti-DWEYS, más altos que en los controles tanto en los hijos de madres con LES que en los pacientes, su eventual papel patogénico versus epifenoménico queda por explorar.

Una pregunta que se cuestiona con la investigación es que papel específico juega la inflamación , si afecta a todos los pacientes o sólo a un subgrupo de ellos (Mondelli et al., 2017; Osimo et al., 2020). El hecho de que en el estudio 1 los marcadores de inflamación estuvieran claramente elevados en la mayoría de los subgrupos de pacientes, incluso al reducirse el tamaño de los subgrupos, parece respaldar las conclusiones de Osimo, e implica que la inflamación es una característica frecuente de todas las afecciones psiquiátricas.

Estos resultados permiten considerar también un posible papel causal del estrés psicosocial en inflamación y psicopatología. En el estudio 1 las medidas de estrés se correlacionaban con varias medidas inflamatorias, y la ruptura en la estructura familiar, variable utilizada como aproximación de los factores estresantes familiares acumulados a lo largo de la vida (Miller & Cole, 2012), resultó ser un predictor de la condición de paciente, y mostró una tendencia a asociarse con niveles más altos de dos citocinas. En el Estudio 2, la ansiedad física y mental materna, también las variables de estrés familiar, correlacionaban con puntuaciones más altas de depresión y menor rendimiento neuropsicológico en los hijos. Además, algunos parámetros inflamatorios y neurocognitivos en los hijos de mujeres con LES mostraron una correlación con la edad compatible con una tendencia inflamatoria progresiva. Estos resultados, aunque solo demuestran correlaciones, apoyan posibles interrelaciones entre estrés, inflamación, psicopatología y neurocognición, y permiten hacer hincapié en el posible efecto de estresores “comunes” como separación parental y síntomas depresivos maternos, sobre la salud psicofísica filial.

A partir de estos resultados, en la última parte de la discusión se ha revisado la evidencia que relaciona el vínculo parento-filial y el clima familiar con la salud de los niños, y se ha encontrado una evidencia robusta de que un sólido vinculo parental, caracterizado por sensibilidad, apoyo y afecto, no sólo es positivo, sino es capaz de neutralizar los efectos tóxicos de experiencias adversas sobre la salud psicofísica de los niños y adolescentes. A esta función se le denomina “*buffering function*”, *“efecto amortiguador”,* y a partir de la adolescencia se integraría con efectos parecidos proporcionados por otros vínculos sociales, como las amistades. El estrés tóxico en población infanto-juvenil se configura como "la activación fuerte, frecuente y / o prolongada de los sistemas de respuesta al estrés del cuerpo en ausencia de la protección amortiguadora del apoyo de los adultos”. Se ha discutido el concepto de apego, como constructo que representa las consecuencias de las experiencias vividas por un niño con sus cuidadores, y la evidencia que

conecta apego con salud psicofísica e inflamación. Se ha revisado evidencia reciente, acerca del impacto a largo plazo de intervenciones dirigidas a potenciar el vínculo parento-filial durante el desarrollo, sobre la salud de los hijos. Asimismo, evidencia reciente acerca de las consecuencias para la salud de la falta de soporte social.

Se completa la discusión con propuestas para aclarar la relación entre psicopatología y alteraciones inmunes, y descripción de intervenciones farmacológicas y psicosociales actuales o futuras para reducir inflamación y estrés.

CONCLUSIONES:

Las conclusiones que emergen de este trabajo son

- La psicopatología aparece asociada a la inflamación ya desde edades tempranas, con un patrón sugestivo de una activación de la inmunidad innata, especialmente de los monocitos y sus citocinas. La activación de los monocitos como sistema parcialmente precursor y relacionado con la microglia permite establecer cierta relación.
- Los hijos de mujeres con LES presentan cambios inflamatorios, alteraciones en su sistema inmune y en pruebas neuropsicológicas, y mayor tasa de psicopatología de lo esperado. No se puede concluir si estos cambios han sido provocados por una exposición temprana en el útero a la inmunidad materna, si reflejan una tendencia familiar o si son el resultado de la exposición a estrés psicosocial.
- El estrés psicosocial se relaciona con marcadores inflamatorios y psicopatología en pacientes psiquiátricos, y con alteraciones neurocognitivas en los hijos de madres con LES. Algunas de las medidas utilizadas para estimar el estrés, como la ruptura de la estructura familiar y la depresión materna, evidencian la importancia del impacto de la situación familiar y del vínculo parento-filial, en el estrés percibido por pacientes jóvenes.
- Los datos apoyan una evaluación más extensa de inflamación, función inmunitaria y estrés percibido, en pacientes psiquiátricos y poblaciones de riesgo, para aclarar relaciones y justificar intervenciones terapéuticas. Algunas de las medidas propuestas tienen un perfil eficiente.

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FRAMEWORK

This work aims at contributing to a vast body of research analysing how psychiatric and somatic conditions can in some cases co-occur and be interrelated, how inflammation and autoimmunity may be a common soil, and how stress and insults of diverse natures may be a common causal factor, especially when occurring in prenatal and early life.

The research will review the current evidence for these assumptions, the mechanisms implied, and the theoretical models proposed, among which the Developmental Origin of Health and Disease Hypothesis (DoHaD) (P. D. Gluckman et al., 2008; Heim et al., 2019; Wadhwa et al., 2009).

It will then present the results of an original research, analysing immune/inflammatory profiles and psychosocial stress levels in two group of adolescents, that according to the models would be at theoretical higher risk for immune alterations: psychiatric acute in-patients and offspring of women with Systemic Erythematosus Lupus (SLE). Both groups are compared with healthy controls. In theoretical models, adolescence is a time window considered crucial for later mental and physical health (Allen et al., 2004; Fraley et al., 2013; J. D. Jones et al., 2016a; Steinberg, 2005; Van Ryzin et al., 2011)

In the discussion, results will be read within the theoretical frame, and integrated with recent findings from the protective effects of parental and social support, and the links between attachment theory and health.

Future directions for investigation in these study samples, and general implications for research and treatment will close the discussion.

INTRODUCTION: *A panoramic review of inflammation, neurodevelopment, stress and a transdiagnostic approach in psychopathology*

This introduction will give an overview of the current evidence about:

- Presence of inflammation and immune alterations in psychopathology (§1.1)
- Evidence for a causal role of peripheral inflammation on psychopathology (§1.2), and mechanisms implied (§1.3)
- Role of prenatal maternal immune activation on offspring health. The case of Lupus pregnancies (§1.4)
- Evidence for comorbidity between psychiatric and somatic conditions (1.5), the special role of infections (§1.6) and the putative role of inflammation as the common soil for chronic disease (§1.7)
- Evidence for a causal role of prenatal, early life and adult stress on inflammation and health in later life (§1.8), and mechanisms implied (§1.9)
- Theoretical models for stress embedding, starting from the Developmental origins of Health and Disease (DoHaD) (§1.10)
- Rationale for a transdiagnostic approach: the existing transdiagnostic taxonomies and evidence supporting them (§1.11)

1.1 Inflammation and immune alterations in psychopathology: current evidence

This paragraph reviews evidence about the presence of inflammation across psychopathology and describes the markers that have been mostly involved. Evidence in Adults is reviewed in §1.1.1, and in Children and Adolescents in § 1.1.2.

1.1.1 Adult studies

Mounting data show several immune and inflammatory alterations across psychiatric conditions: higher levels of pro-inflammatory cytokines (CK), acute phase proteins as C-reactive protein (CRP), autoantibodies (auto-Ab) and abnormal counts and activity of lymphocyte subpopulations.

Serum cytokines and CRP: Meta-analytic and systematic reviews of cross-sectional studies in adults confirm alterations in serum cytokines, chemokines and CRP throughout the psychopathological spectrum: in major depression (Dowlati et al., 2010; C. A. Köhler et al., 2017; Valkanova et al., 2013), bipolar disorder (Modabbernia et al., 2013), schizophrenia (Frydecka et al., 2018; B. J. Miller et al., 2011; Zhou et al., 2021), first episode psychosis (Fraguas et al., 2019; Frydecka et al., 2018; Rodrigues-Amorim et al., 2018; Trovão et al., 2019), autism spectrum disorder (ASD) (Masi et al., 2014; Saghazadeh et al., 2019a, 2019b), post-traumatic stress disorder (PTSD) (Passos et al., 2015) and anorexia nervosa (AN) (Solmi et al., 2015). There is preliminary evidence for an inflammatory response in generalized anxiety disorder (GAD) (Costello et al., 2019) and attention deficit and hyperactivity disorder (ADHD) (Anand et al., 2017), while results for obsessive-compulsive disorder (OCD) (Cosco et al., 2018; Gray & Bloch, 2012) are still inconclusive. A recent cross-disorder review of 43 meta-analysis (Yuan et al., 2019) has given an overview summarizing the results of eight major psychiatric disorders (SCZ, BD, ASD, MDD, PTSD, sleeping disorder (SD), OCD and suicide). IL-6 and CRP were the two markers most often increased, changed in four disorders (see figure 1 below). The authors advocate for longitudinal studies to reveal acute and chronic changes, and trait and state biomarkers, analysis of shared set of cytokines, as well as studies on markers within the centrospinal fluid (CSF).

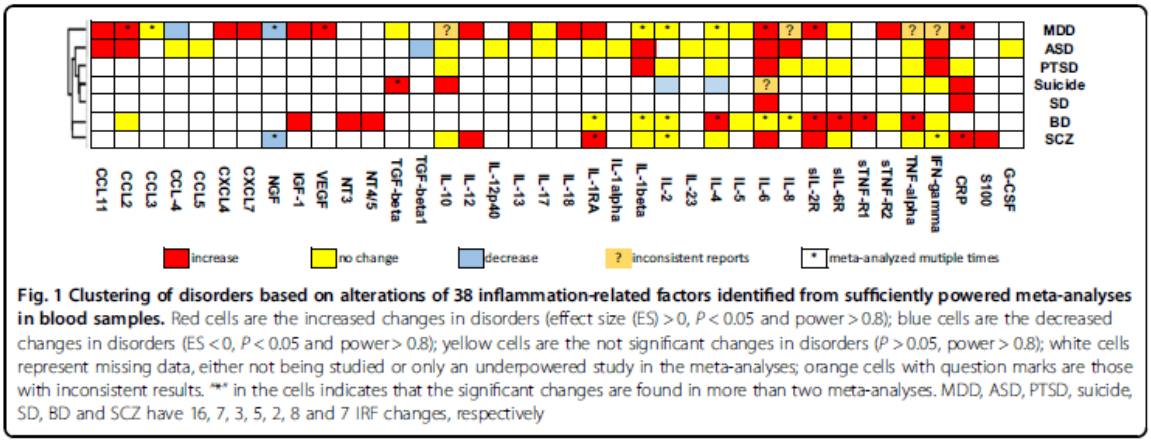

Fig. 1 Clustering of disorders based on alterations of 38 inflammation-related factors identified from sufficiently powered meta-analyses in blood samples. Red cells are the increased changes in disorders (effect size (ES) > 0, $P < 0.05$ and power > 0.8); blue cells are the decreased changes in disorders (ES < 0, $P < 0.05$ and power > 0.8); yellow cells are the not significant changes in disorders ($P > 0.05$, power > 0.8); white cells represent missing data, either not being studied or only an underpowered study in the meta-analyses; orange cells with question marks are those with inconsistent results. "*" in the cells indicates that the significant changes are found in more than two meta-analyses. MDD, ASD, PTSD, suicide, SD, BD and SCZ have 16, 7, 3, 5, 2, 8 and 7 IRF changes, respectively

Figure 1 from (Yuan et al., 2019)

Even though several authors speculate about the possibility of differentiating psychiatric disorders by using inflammatory biomarkers (Yuan et al., 2019), research is detecting similar conditions across the diagnostic categories. An interesting meta-analysis has compared cytokines between schizophrenia, bipolar disorder and depression during different phases. The authors found transdiagnostic similarities in the pattern of activated cytokine during both acute and chronic phases, suggesting common pathways for immune dysfunction across the disorders. (Goldsmith et al., 2016)

Cytokines in CSF : The brain is the ultimate affected tissue in psychiatric disorders, so it is relevant to study inflammation within it. Three recent meta-analysis (Enache et al., 2019; Orlovska-Waast et al., 2019; A. K. Wang & Miller, 2018) have reviewed levels of inflammation markers in CSF for major psychiatric disorder. The first work found higher CSF levels of IL-6 and TNF-α in MDD patients, and the second one found higher IL-6 and IL-8 levels in schizophrenia but not in affective disorders. The third study, from Miller's group (A. K. Wang & Miller, 2018), compared cytokine levels between SCZ, MDD, BD, and found similarities across disorders: both patients with SCZ and BD had higher levels of IL-1β compared to healthy controls (HC), and both patients with SCZ and MDD had higher IL-6 and IL- compared to HC , with many CSF alterations concordant with those in the peripheral blood. The authors point out the possibility of common underlying pathways of immune dysfunction across these disorders.

White Blood Cells and Lymphocyte subpopulations: The cytokines described above as elevated suggest activation of the innate immunity, mainly represented by monocytes and neutrophils. In line with these findings, circulating monocytes with a high inflammatory gene expression are described in both SCZ and BD (reviewed e.g. in (Bergink et al., 2014)), and also in adolescents with depression (Chiang et al., 2019).

Antibodies: several autoantibodies have been described in psychiatric patients, and their pathogenic role is investigated.

The first antibodies discovered to have a clear pathogenic role are those against the N-methyl-D-aspartate receptor (NMDAR), found in patients with autoimmune encephalitis. (Josep Dalmau et al., 2008) This disease affects mostly young subjects, often women with an ovarian teratoma, even though in 55-60% of the patients no trigger is identified. (J Dalmau et al., 2017). Psychiatric symptoms as psychosis or mania often precede the full neurological syndrome, that includes seizures, reduced verbal output, decreased level of consciousness, highly characteristic orofacial and limb dyskinesias, choreoathetosis, dystonic postures, rigidity, autonomic dysfunction and eventually coma. (Dube et al., 2003) About 80% of the patients have full or substantial recovery after immunotherapy directed to remove the antibodies and antibody-producing plasma cell and removal of the tumor if present (Titulaer et al., 2013). Experimental studies have shown that the antibodies cause internalization of NMDA receptors both at the postsynaptic level of the glutamatergic synapse and at inhibitory interneurons, leading to reduced NMDA receptor-mediated synaptic currents, impaired long-term potentiation, hyperglutamatergic state, and the syndrome characterized by encephalopathy, memory deficits, and other neuropsychiatric manifestations (reviewed in (J Dalmau et al., 2017)).

Those findings boosted the search for CSF autoantibodies in other encephalitis and neurological syndromes, and several other antibodies against neuronal antigens have been described, that show intense reactivity with brain tissue and the neuronal cell surface: e.g. antibodies against AMPA (alfa-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and GABAb receptor (gamma-aminobutyric acid type B) in limbic encephalitis, against amphiphysin in Stiff-person syndrome and various others (reviewed in (J Dalmau et al., 2017)). Even though the pathogenic effects of most

these antibodies have been demonstrated in cultured neurons, for only few of them pathogenicity has been confirmed in animal models. (J Dalmau et al., 2017)

Results from NMDAR encephalitis have opened a new investigation field also within psychiatry: some works suggests that about 4% of patients with NMDAR encephalitis would present with only psychotic symptoms, without developing the full syndrome or abnormalities in MRI or EEG, and were thus not distinguishable from a psychotic episode (Kayser et al., 2013; Lancaster et al., 2011; Lennox et al., 2017; Pathmanandavel et al., 2015). The possibility that a first psychotic episode is an incomplete form of autoimmune encephalitis has led some authors suggest that all patients with first-episode psychosis should be screened for anti-NMDAR antibodies at first presentation (Lennox et al., 2017; Zandi et al., 2010).

These results have stimulated the search for antibodies with a pathogenic role in psychosis and other psychiatric disorders. Various works have found higher titers of antibodies against neuronal and other antigens across the psychiatric spectrum (Hoffmann et al., 2016; Lennox et al., 2017; Pathmanandavel et al., 2015; T. A. Pollak et al., 2019; Xu et al., 2021; Zandi et al., 2010; S Zong, 2017; Shenghua Zong et al., 2020), though a clear causative role is mostly not proven yet (J Dalmau et al., 2017; Hoffmann et al., 2016; D. Martino et al., 2020).

Of all, two categories of antibodies have received particular attention, and are especially relevant to this research*: a) antibodies described in women with Systemic Lupus Eritematosus* as potentially causal of some of the neuropsychiatric manifestations seen in Neurolupus, and within them, a subclass of the anti-DNA antibodies, with reactivity against the GluN2 subunit of NMDAR with described neurotoxicity in animals and potentially in humans (B. Diamond et al., 2009; Faust et al., 2010; Huerta et al., 2006; Kowal et al., 2004; J. Y. Lee et al., 2009), and *b) maternal antibodies against fetal brain antigens*, that potentially during pregnancy could access the fetal brain through an immature blood–brain barrier (BBB) and alter fetal brain development. Maternal antibodies that recognize proteins in the developing fetal brain are e.g. thought to lead to a subphenotype of ASD that has been termed maternal autoantibody related (MAR) ASD (reviewed in (Karen L. Jones & Van de Water, 2019)).

The two categories are not disjointed, as the antibodies found in women with SLE, might also access the developing brain of their offspring during gestation, and contribute to some of the

neuropsychiatric alterations described in SLE-offspring (reviewed in (É Vinet et al., 2014; Yousef Yengej et al., 2017)).

1.1.2 Children and Adolescent studies

Data on inflammation in children and adolescent psychopathology are more limited, though emerging. A systematic review from 2014 indicates strongest evidence for elevated inflammation in ASD, and preliminary findings for elevated inflammatory markers across the other diagnoses as major depressive disorder, bipolar disorder, post-traumatic stress disorder, obsessive-compulsive disorder, Tourette's disorder, attention-deficit/hyperactivity disorder, and schizophrenia (Mitchell & Goldstein, 2014).

A new meta-analysis on 21 studies on depression in children and adolescents has found positive associations between depressive symptoms and concurrent and future inflammatory measures: depression was a significant predictor of IL-6 and conversely, inflammation measured by CRP or IL-6 predicted future depression, suggestive of bidirectional associations (Colasanto et al., 2020).

A recent work studied for the first time the transcriptional profiles in depressed adolescents: adolescents with clinically significant levels of depressive symptoms exhibited upregulated expression of inflammation-related genes and downregulated expression of antiviral-related genes compared to their peers with lower levels of depressive symptoms. This differential expression was mediated by greater activity of the pro-inflammatory transcription factor, nuclear factor-kappa B (NF-κB), and reduced activity of glucocorticoid receptors (GRs). Sources for gene expression were mainly monocytes, B cells, and dendritic cells: such signature confirms a link between depression and altered immunity already from adolescence. (Chiang et al., 2019)

1.2 Evidence for inflammation being able to cause psychiatric symptoms

Paragraph 1.1 has reported on a cross-sectional association between inflammation and psychiatric symptoms, without informing about causality.

Support for a causal role of inflammation in determining psychiatric symptoms comes from various fields: from longitudinal studies, that show how markers of inflammation predict increases in psychiatric symptoms over time; from experimental studies that analyze the effects of exogenously induced inflammation on psychiatric symptoms; from work studying associations between peripheral inflammation and changes in brain function; and from research investigating how peripheral inflammation can access the brain. This paragraph reviews such evidence.

1.2.1 Evidence from longitudinal studies

Longitudinal evidence suggests that peripheral inflammation predicts increased risk for subsequent depressive and psychotic disorders.

Within children and adolescents, a series of studies from the Avon Longitudinal Study of Parents and Children (ALSPAC) report association between higher levels of IL-6 and/or CRP in childhood, and subsequent development and persistence of depressive (G. M. Khandaker et al., 2018; Golam M. Khandaker, Pearson, et al., 2014) and psychotic (Golam M. Khandaker, Pearson, et al., 2014) symptoms in adolescence and young adult age. In particular, IL-6 at age 9 years was associated with diurnal mood variation, concentration difficulties, fatigue and sleep disturbances at 19 years (Chu et al., 2019). Another work reported that within-person increases in TNF-α predicted increases in depressive symptoms, specifically dysphoria, in adolescents (Moriarity et al., 2020). In a cohort of young patients with a first episode psychosis, an inflammatory-metabolic factor accounting for high-sensitivity CRP (hsCRP), triglycerides and BMI, predicted positive and overall symptoms severity, general psychopathology and treatment response at 1-year follow-up (Maria Antonietta Nettis et al., 2019).

Adult studies find similar results, of inflammatory markers predicting debut and more severe course of psychiatric symptoms.

A meta-analysis from 2013 on 9 longitudinal studies found small but significant associations between increased baseline IL-6 and CRP, and the subsequent development of depressive symptoms (Valkanova et al., 2013). Increased CRP levels were also associated with increased risk for hospitalization for depression in a large Danish population study (Wium-Andersen et al., 2013). Recent data from a study of twin pairs—which holds constant shared genetic and early environmental factors—showed that higher baseline IL-6 predicted depressive symptoms 7 years later (Huang et al., 2019).
In the adult NESDA (Netherlands Study of Depression and Anxiety) population-based longitudinal cohort, higher baseline IL-6 in depressed women predicted subsequent chronic course of depression at 2- and 6-years follow-up (Lamers et al., 2019). In the veteran longitudinal cohort of the Mind Your Heart Study, several markers related to inflammation at baseline predicted a poorer course of PTSD, with WBC count and platelets count remaining significant after all adjustments (Eswarappa et al., 2019).

Evidence supports also the opposite association, that psychiatric symptoms can predict later inflammation (Matthews et al., 2010; J. C. Stewart et al., 2009). In the prospective population-based Great Smoky Mountains Study assessing young people at different time-points between ages 9 and 21, cumulative depressive episodes predicted later CRP levels (Copeland et al., 2012). The same findings are reported in adults studies: the NESDA study finds also that depressive diagnosis and symptom severity predicted later IL-6 (Lamers et al., 2019), and depression scale predicted later CRP in the twin study (Huang et al., 2019).

Current longitudinal evidence supports therefore bidirectional causal associations between inflammation and psychiatric symptoms both in young and adult population.

1.2.2 Effects of exogenous inflammation

Paradigms inducing inflammation and analyzing subsequent psychiatric symptoms have also shade light about how inflammation can induce psychopathology.

Some of the earliest evidence of a link between inflammation and depression came from clinical observations of patients treated with IFN-α for Hepatitis C or cancer, who commonly develop clinically significant depressive symptoms after the initiation of IFN-α therapy (Raison et al., 2005). Since then, evidence has gathered. Data come from experimental studies in animal and healthy humans where inflammation is exogenously induced.

1.2.2.1 Animal studies on exogenous inflammation

In animal models, peripheral inflammation is usually induced by challenges with LPS or live bacteria. Such triggers have shown to induce depressive-like behaviors, as anhedonia (e.g., reduced sucrose consumption), decrease in exploratory, novelty-seeking and social behaviors, reduced food intake, and sleep disturbances. Block of inflammatory cytokines or their signaling pathways exclusively in the periphery or exclusively in the brain prevents these alterations, which suggests that peripheral immune responses are an essential element of the inflammation-induced depressive-like behavior in laboratory animals. (reviewed in (Dooley et al., 2018)).
At the same time, LPS stimuli have shown to increase passive affiliative behavior in both Rhesus monkeys and rats, who spent more time (vs saline) affiliating with their cage-mates, including being in close proximity to and huddling with them (Willette et al., 2007; Yee & Prendergast, 2010). This suggest that inflammation may also increase some kinds of social behaviors and the search for social support (Moieni & Eisenberger, 2018).

1.2.2.2 Human studies on exogenous inflammation

In human studies, an inflammatory state is mainly induced by one of three models: treatment protocols with interferon-α (IFN-α) in chronic patients, and injection of bacterial endotoxin or typhoid vaccination in healthy controls. The effects have been measured with subjective measures, psychological tests, and functional neuroimaging techniques assessing brain activity and connectivity, as PET (positron emission tomography) and fMRI (functional magnetic resonance imaging).
IFN-α is used within treatment frames of duration of months, stimulates the release of other proinflammatory cytokines such as IL-6, and models the effects of exposure to chronic inflammation at mild or moderate levels. Endotoxin induces a robust but short-term inflammatory

response, resolving within 6-hours from administration, and thus modeling the acute effects of exposure to high levels of inflammation. Typhoid vaccine models the effects of mild, acute increases in inflammation, comparable to the elevations in inflammation seen in some individuals with psychiatric diagnoses (Dowlati et al., 2010; Raison & Miller, 2011), and typically not associated with fever, nausea, or other physical illness symptoms. Its possible psychopathological effects are thus not simply attributable to illness symptoms, but rather to more direct effects of cytokines on the brain. (all reviewed in (Dooley et al., 2018)).

A recent review (Dooley et al., 2018) has summarized the effects of exogenous inflammation on four endophenotypes that, though validated for depression, are in fact transdiagnostic: *somatic syndrome, exaggerated reactivity to negative information, altered process of reward,* and *cognitive function*. Researchers found evidence for associations with at least the first three. Across studies, exogenous inflammation would consistently induce fatigue, psychomotor slowing, and sleep disruptions, i.e. “sickness behaviour” (Dantzer et al., 2007), and would induce exaggerated reactivity to negative information: e.g. more negative mood after stress tasks (N. A. Harrison et al., 2009), and higher feelings of social disconnection after socially threatening images (Inagaki et al., 2012).

Exogenous inflammation reduces also responsivity to anticipation (Eisenberger et al., 2010) or receipt (Capuron et al., 2012) of monetary rewards, and to novel stimuli (N. A. Harrison et al., 2016). This dampening in motivational and approach behavior clinically corresponds to anhedonia. These effects appear mediated by attenuated activity in and within the basal ganglia, especially ventral striatum (VS) and substantia nigra. Effects seem mediated by cytokine-induced alterations in dopaminergic function, similar to those seen in Parkinson's disease (Capuron et al., 2012). Some authors posit that the reduction in striatal dopamine would reduce willingness to expend effort for monetary rewards, by increasing the perceived cost of effort, rather than by reducing the value of the reward itself. (A. H. Miller et al., 2013; Treadway et al., 2019)

At the same time, studies report also higher sensitivity to positive social stimuli and experiences: e.g. greater desire to be around support figures after seeing their images (Inagaki et al., 2015), and increased neural activity in the ventral striatum (VS) and ventromedial PFC (vmPFC) after seeing such images (Inagaki et al., 2015) or receiving positive feedback ((Muscatell et al., 2016), all

reviewed in (Eisenberger et al., 2017; Eisenberger & Moieni, 2020)). VS ad vmPFC are regions often implicated in processing reward.
Various authors argue that these adaptations altogether would favor increased vigilance and withdrawal in aversive environments (Dooley et al., 2018; A. H. Miller et al., 2013; Slavich & Irwin, 2014; Treadway et al., 2019), as well as increased approach-related responding to close ones or to friendly others who could provide help and support. (Eisenberger & Moieni, 2020).

Some changes would be mediated by hyperactivation of amygdala and anterior cingulate cortex (ACC) (N. A. Harrison et al., 2009; Muscatell et al., 2016).: these are threat-related neural circuits that may increase physiological arousal, e.g. by downstream modulating sympathetic nervous system and hypothalamic-pituitary axis (HPA) activity (Muscatell & Eisenberger, 2012). Recent meta-analytic evidence on neuroimage studies confirms that exogenous inflammation affect activity in limbic, basal ganglia, brainstem and cortical regions: amygdala, hippocampus, hypothalamus, striatum, insula, midbrain, brainstem, and cortical regions involving medial prefrontal and temporal cortices (Kraynak et al., 2018). Authors review how these are regions that support sickness behavior (limbic regions), regulate autonomic and neuroendocrine outflow (dorsal anterior cingulate cortex/dACC-dmPFC, and amygdala and hippocampus), hypervigilance towards environmental external threats (dACC-dmPFC) and mood and reward processes (corticostrial network including ventral striatum, subgenual ACC, and medial orbital FC).

These results altogether support that exogenous inflammation consistently associates with changes in feelings and behaviour, and with changes in the activity of a reliably detected group of brain regions.

1.2.3 Endogenous inflammation: correlates with brain function. Data on functional connectivity

Just like exogenous inflammation, also endogenous, spontaneous inflammation correlates with changes in brain function. Interesting data come from studies on resting state functional connectivity (rsFC).

Within the studies of functional connectivity, there are the studies of task-related, and those of resting state functional connectivity (rsFC). rsFC is the intrinsic activity of the brain when a person is not engaged in a task. It is coordinated by a set of large functional networks, anchored to anatomically distributed nodes, and stable within the individual since late childhood (Grayson & Fair, 2017). rsFC can thus measure stable traits within the individuals (Gratton et al., 2018), by examining large-scale brain networks that are not constrained by the parameters of a task (Bressler & Menon, 2010). Mounting evidence has described dysfunction across various functional networks in both task-based and rsFC, in adults and in young psychiatric patients across the diagnostic spectrum (Consortium et al., 2013; Kaiser et al., 2015; Kolesar et al., 2019; Kunimatsu et al., 2020; Lichenstein et al., 2016; C. H. Miller et al., 2015; O'Neill et al., 2019; Sundermann et al., 2014; S. Tang et al., 2018; B. Zhang et al., 2016).

Following these findings, recent works have analyzed relations between endogenous inflammation and brain function as measured by rsFC in psychiatric patients and other groups. Studies in unmedicated stable patients with depression found that increased CRP predicted decreased functional connectivity between networks involving amygdala, striatum and PFC (J. C. Felger et al., 2016; Mehta et al., 2018; Yin et al., 2019), and that reduced connectivity correlated with symptoms of higher anxiety (Mehta et al., 2018), anhedonia and motor slowing (J. C. Felger et al., 2016), and mediated association between CRP and symptoms.

Similar results have been found in two samples of youth and young adults African Americans, where monocytes and a composite inflammatory index associated with reduced rsFC in two brain networks implied in emotion regulation and executive functions (Nusslock et al., 2019).

A study on task-related connectivity in youth with diverse psychiatric symptoms, found also association of peripheral cytokines with activation of networks during reward processing, confirming a link between inflammatory processes and neural reward dysfunction (Bradley et al., 2019). Another recent study in a community sample of adolescents (N=70) found that TNF-α associated with higher rsFC between subcortical regions - right amygdala and left striatum – whose connections are still developing during adolescence (Swartz et al., 2021). Authors hypothesize that such hyperactivation in regions working together to process information about reward and punishment, may shift the individual's focus in reward learning towards more aversive or punishing stimuli, as observed in depressed individuals.

Cross-sectional works do not allow to infer on causality, and it is also possible and likely, that altered patterns of rsFC and of brain activation could influence levels of peripheral inflammation via efferent pathways, e.g. by leading to heightened stress sensitivity and higher peripheral inflammation in response to stress. (Kraynak et al., 2018)

At the same time, longitudinal studies and experimental paradigms do support that peripheral inflammation can induce psychiatric symptoms, and determine a more severe course in psychiatric disorders. (G. E. Miller & Cole, 2012; Valeria Mondelli et al., 2017)

1.2.4 How peripheral inflammation can access the brain

Peripheral immune responses appear to drive central reactions and changes in behavior, but how can peripheral inflammatory signals reach the brain? The blood-brain barrier (BBB) primarily consists of endothelial tight junctions, and provides a selective filter for the CNS, allowing only certain components to enter and generally preventing access of inflammatory agents (Liebner et al., 2011). Cytokines are too large to freely pass through it, yet their signal can reach the brain through other ways, and two routes have been typically characterized: the neural and the humoral routes.

In the *neural route*, cytokines activate peripheral afferent nerve fibers including the vagus nerve, which transmit cytokine signals to specific brain nuclei, such as the nucleus of the solitary tract, which then serves as a relay station to other brain nuclei (Hansen et al., 1998).

In the *humoral route*, cytokines access directly the brain, either through leaky regions in the BBB, or through the binding of cytokines to saturable transport molecules on endothelial cells that comprise the BBB: e.g. transport molecules for IL-1α, IL-1β,TNF, and IL-6, as well as the chemokine MCP-1, have been described. (Banks, 2015)

A third and more recent pathway for inflammatory signals to reach the brain is the *cellular pathway* (M. D. Weber et al., 2017; Wohleb et al., 2015): under stress and inflammation, catecholamines induce release of monocytes from the bone marrow. Monocytes get then activated by stress associated danger signals called damage-associated molecular patterns (DAMPs) and bacteria and bacterial products such as microbe-associated molecular patterns (MAMPs) leaked from the gut (M Fleshner, 2011; Monika Fleshner, 2013). In parallel stress-activated microglia releases MCP-1 and other chemokines, which attract monocytes to brain vasculature or the brain lymphatic system. Once in the CNS, monocyte can facilitate the central inflammatory response.

1.3 Mechanism for inflammation to affect the brain

We have seen that peripheral signals can reach the brain: what happens then? How can inflammation impact brain functioning? Which are the mechanisms involved? This paragraph reviews some of the mechanisms activated in the brain in the context of elevated peripheral and central inflammation, focusing on the role of cytokines, microglia, monoamines and the HPA axis.

1.3.1 Cytokines

Cytokines as TNF, IL-1 and IL-6 at physiologic levels play decisive roles on a number of CNS processes including synaptic plasticity, learning and memory as well as mediate the response to antidepressant medications (del Rey et al., 2013).

Yet excessive levels of cytokines can cause detrimental effects on the brain: they can activate microglia, with further release of cytokines, they can alter concentrations of monoamines and glutamate metabolism, and affect the neuroendocrine systems.

1.3.2 Microglia: roles and effects of peripheral inflammation

Microglia are phagocytic myeloid cells distributed throughout the brain parenchyma, and the major source of cytokines and other inflammatory molecules in the CNS. The below box provides an overview on microglia origins and functions.

MICROGLIA: ORIGINS AND FUNCTIONS

Microglia are derived from erythromyeloid progenitors in the yolk sac, that colonize the brain during embryonic life (Kierdorf et al., 2013), and are maintained since then through a process of self-renewal (Steiner et al., 2015). Their phenotype and function vary depending on the specific brain region, and develop on the 2nd week of postnatal life (De Biase et al., 2017).

During neurodevelopment microglia produce neurotrophic factors and regulate synapsis formation and pruning, control of cell numbers, and formation and refinement of neural circuits (Frost & Schafer, 2016; Hammond et al., 2018).

In the mature healthy brain they provide the brain's first line of defense against tissue damage and infection, by removing cellular debris and apoptotic or necrotic cells through their phagocytic capacity (Crotti & Ransohoff, 2016). They also regulate a wider series of processes that are needed for CNS development and homoeostasis: they lend trophic support to neurons, modulate neuronal activity, and modify synaptic connections and plasticity, so as to be defined " synaptic partners" (Tremblay et al., 2011; Y. Wu et al., 2015).

As immunocompetent cells, they can produce an array of proinflammatory and anti-inflammatory factors, as cytokines and DAMPS. Some of these mediators, as e.g. TNF-alfa, play a critical role in synaptic plasticity (Stellwagen & Malenka, 2006), or, as IL-1, in hippocampal-dependent memory processes (Goshen et al., 2007).

With a highly ramified cell morphology and small cell soma, microglia continuously assess their surrounding microenvironment via extension, withdrawal, and reformation of long cellular processes (Nimmerjahn et al., 2005), with a housekeeping function (Fonken et al., 2018)

Microglial activation in the adult CNS is tightly controlled by endogenous signaling, and exposure to neuronal cell surface and soluble factors maintains microglia in a comparatively quiescent immunophenotype compared to other myeloid cells (Biber et al., 2007).

This tight regulation of microglia by molecular factors in the CNS likely evolved to prevent microglia from damaging brain tissue, which is less susceptible to infection, but has more limited capacity for repair and regeneration than peripheral tissue.

When microglia detect a "danger" signal, they can undergo rapid morphological and functional changes in order to phagocyte microbes and cellular debris, to migrate or proliferate to increase density in specific regions, and/or to produce and secrete inflammatory or anti-inflammatory molecules (T. L. Tay et al., 2017; Yirmiya et al., 2015). Activated microglia was classically described with shortening and extensive branching of processes, hypertrophy of the cell body, and the release of different mediators, and distinguished into an M1 phenotype that releases proinflammatory mediators, and an M2 phenotype that releases anti-inflammatory cytokines to antagonize the proinflammatory responses. (Y. Tang & Le, 2015). Activated microglia could therefore be either cytotoxic or neuroprotective, and it remains unclear whether this activation is beneficial or detrimental. (Valeria Mondelli et al., 2017). In recent years, the classification of the M1 and M2 phenotypes was challenged (Ransohoff, 2016), in favor to the hypothesis that the microglial phenotype might vary along a continuum, and that the morphological phenotype alone may not be sufficient to infer about the activation state (Peferoen et al., 2015; Ransohoff, 2016).

To study microglia activation in vivo, research has focused on putative biomarkers of microglia activation, and on radiotracers that bind to microglia in PET studies (Tronel et al., 2017). The biomarker most used has been the 18-kDa translocator protein (TSPO), increased when microglia and other brain cells are activated (Cosenza-Nashat et al., 2009). Different radiotracers of TSPO – first and second generation - and measuring techniques have been developed (Plavén-Sigray et al., 2018), even though its suitability for psychiatric conditions has lately been discussed (Notter et al., 2017; Tronel et al., 2017). Microglia activation can also be measured in post-mortem studies.

Whether *microglia are activated in some psychiatric disorders* or in subsets of psychiatric patients, is object of intense research. Some recent reviews and meta-analyses have analyzed data from in vivo – mainly PET - and post-mortem works across the diagnostic spectrum. Evidence in general is still limited and controverted. There is anyway primary evidence for activation of microglia and for neuroinflammation in ASD (Liao, Liu, et al., 2020; Liao, Yang, et al., 2020), possibly in psychotic disorders (Marques et al., 2019; Plavén-Sigray et al., 2018; Trépanier et al., 2016) and depression (Enache et al., 2019), with more inconclusive data on bipolar disorder (Giridharan et al., 2020).

Whether *peripheral inflammation can activate microglia, and whether this activation can cause psychiatric symptoms,* has also been intensively studied. Preclinical research accumulated in the past two decades suggests that microglia get activated by peripheral inflammation, and that this activation may play a role in mediating behavioral changes in systemic infections and in some psychiatric and neurodegenerative disorders. High concentrations of proinflammatory mediators released by pro-inflammatory activated microglia are potentially neurotoxic and might lead to persistent detrimental effects through bystander damage to neighboring neuron (Hoogland et al., 2015; Lemstra et al., 2007)

The most abundant and consistent data supporting this view come from animal studies. A recent systematic review on 51 animal studies, mainly on rodents, has confirmed that peripheral inflammatory stimuli, such as challenge with LPS or live bacteria, cause microglial activation (Hoogland et al., 2015). Animal studies have also shown how microglia activation can mediate the effects of systemic inflammation on mood and behavior. Wachholz et al. e.g. demonstrated that interferon-α treatment led to significant increases in depressive-like behavior, and that this is associated with increased expression of a variety of pro-inflammatory surface markers as MHC-II and CD86 on microglia in vulnerable animals (Wachholz et al., 2016).

Human studies are at the beginning. Signs for activation of microglia in context of systemic inflammation have been found in some human studies, e.g. in a post-mortem study on patients died with sepsis (Lemstra et al., 2007). Two recent studies have analyzed in-vivo effects of exogenous inflammation on TSPO activity (see box) in small groups of healthy subjects. In one work, systemic administration of LPS lead to increased binding of radiotracer by 30–60%,

accompanied by an increase in blood levels of inflammatory cytokines, vital sign changes, and sickness symptoms (Sandiego et al., 2015). The other work used stimulation with INF-α, causing a perturbation of the immune system similar in magnitude to that seen in psychiatric patients, and did not find increased PET binding (M A Nettis et al., 2020). Authors underline how the degree of microglia inflammation in psychiatric disorders may be minor versus that of classical neuroinflammatory disorders, where the technique is sensitive (such as e.g. multiple sclerosis, Huntington Chorea etc.). Various authors advocate for caution in interpreting TSPO binding, and auspicate for new techniques to be developed to detect possible microglia activation, and to assess its correlations with peripheral inflammation, if they exist. (M A Nettis et al., 2020; Notter & Meyer, 2017; V. H. Perry, 2018).

Thus, activation of microglia in psychiatric disorders is a putative but not yet confirmed mechanism for inflammation to cause psychopathology.

1.3.3 Monoamines and glutamate: roles and effects of peripheral inflammation

Preclinical and human studies show that cytokines alter levels of various neurotransmitters in the brain.

Inflammatory cytokines decrease dopamine availability and dopamine release (J Felger et al., 2012), possibly by reducing availability of tetrahydrobiopterin (BH4), an essential cofactor for tyrosine hydroxylase, the rate limiting enzymes that synthesize dopamine (Ebrahim Haroon et al., 2012). Basal ganglia nuclei, especially ventral striatum, and reward and motor circuits would be preferential targets. Reduced dopamine would translate in animals into decreased willingness to expend effort for reward, without reduction in the sensitivity to reward (Jennifer C. Felger et al., 2013; Vichaya et al., 2014), and in humans into anhedonia, fatigue, and psychomotor retardation (Capuron et al., 2012).

Cytokines can also reduce serotonin availability: they can shift the conversion of tryptophan from serotonin to kynurenine, by activating the enzyme indoleamine 2,3 dioxygenase (IDO) (Dantzer et al., 2008), reduce availability of BH4, cofactor also for serotonin synthesis (Ebrahim Haroon et al., 2012), and by increasing expression and function of the serotonin transporter (SERT), by activation of mitogen-activated protein kinase (MAPK) pathways, specifically p38 MAPK. (Zhu et al., 2010). Such increases in SERT activity and MAPK are paralleled by depressive-like behavior in both rats

and rhesus monkeys (reviewed in (A. H. Miller et al., 2013). Inhibition of SERT and increase in serotonin availability is a primary mechanism of action of conventional antidepressants: thus the capacity of inflammatory cytokines to increase SERT while reducing serotonin synthesis, may undermine the effect of SSRIs to treat mood and anxiety disorders, consistent with the observation that inflammation is associated with treatment resistance (Ebrahim Haroon et al., 2018).

There is also evidence for inflammation to influence glutamate metabolism. Excess or altered glutamate transmission has been implied in various psychiatric symptoms, e.g. in first-episode psychosis (Kaminski et al., 2021), bipolar disorders (Gigante et al., 2012), or depression (Moriguchi et al., 2019). The antidepressant effects of ketamine, a Glu antagonist, also support alterations in glutamatergic transmission (McGirr et al., 2015). Preclinical and human works suggest that cytokines increases glutamate availability especially in basal ganglia and dorsal anterior cingulate cortex (dACC): they alter function of astrocytes and microglia, increasing glutamate release and compromising its reuptake and clearance. At the same time, cytokines can increase levels of quinolinic acid (QUIN), a powerful NMDAR agonist that can potentiate glutamate toxicity on postsynaptic NMDA receptors. (all reviewed in (Ebrahim Haroon & Miller, 2016)). Human studies using proton magnetic resonance spectroscopy (MRS) with exogenous and endogenous inflammation, have shown that increased inflammation correlated with increased Glu levels in basal ganglia, and that Glu levels correlated with reduced motivation and psychomotor slowing (E. Haroon et al., 2016; Ebrahim Haroon et al., 2014).

Cytokines can as well alter neuroplasticity by decreasing expression of the brain-derived neuroprotective hormone BDNF (Calabrese et al., 2014).

1.3.4 HPA axis: effects of inflammation

Inflammation has also potent effects on neuroendocrine systems and on the hypothalamus pituitary axis (HPA) in particular. In case of acute infection or injury, inflammatory cytokines as IFN, TNF-α and IL-6 up-regulate HPA activity and cortisol levels, with the purpose of activating stress response (Beishuizen & Thijs, 2003). Chronic inflammation though can lead to chronic hypercortisolemia (Tsoli & Kaltsas, 2000) and can reduce the synthesis, function and sensitivity of the glucocorticoid receptor (GR) in the hypothalamus and pituitary gland. This may result in

disruption of the negative feedback within the HPA axis (T. W. W. Pace & Miller, 2009), with continued synthesis of corticotropin releasing hormone (CRH) and sustained activation of the HPA-axis (CL Raison et al., 2003; Cytokine-Effects on Glucocorticoid Receptor Function: Relevance to Glucocorticoid Resistance and the Pathophysiology and Treatment of Major Depression, 2007). Increased cortisol can affect brain functions in several ways: it can alter memory and executive functions controlled by hippocampus and the medial PFC, regions that express high levels of glucocorticoid receptors; it can change expression of key genes which influence brain development, e.g. reduce BDNF; it can influence levels of neurotransmitters as dopamine and glutamate with possible risk for respectively positive psychotic and negative symptoms; and in general can induce sleep disturbances, anxiety and psychomotor changes (reviewed in (Pruessner et al., 2017; Wolkowitz et al., 2009)). This process can become self-perpetuating, as chronically elevated glucocorticoids can activate microglia and then stimulate neuroinflammation (Frank et al., 2013; Nair & Bonneau, 2006).

Of note, disruption of the HPA axis is well described across psychiatric diagnoses: meta-analytic evidence has reported increased cortisol levels (Borges et al., 2013; Chaumette et al., 2016; Girshkin et al., 2014; Hubbard & Miller, 2019; Stetler & Miller, 2011), blunted cortisol response to stress (Borges et al., 2013; Burke et al., 2005; Girshkin et al., 2014), attenuated cortisol awakening response (CAR) (Berger et al., 2016) and increased pituitary volume (Nordholm et al., 2013; T. S. Saunders et al., 2019) in mood and psychotic disorders, also in children (Lopez-Duran et al., 2009), as well as decreased cortisol levels in PTSD (Schumacher et al., 2019). At the same time it is important to note that these associations do not prove causality in themselves, as it is also possible that the psychiatric symptoms can trigger HPA activity (Belvederi Murri et al., 2012), or that these HPA axis abnormalities are an epiphenomenon, e.g. a manifestation of global physiological dysregulation, or secondary to medication effects or substance use (Cullen et al., 2020)

1.3.5 Conclusions about effects of peripheral inflammation on the brain

In synthesis, preclinical and clinical evidence have described mechanisms through which peripheral inflammation can access the brain and influence neural processes relevant for psychiatric symptoms across diagnoses, providing strong support for a possible causal association.

1.4 Maternal Immune Activation and Lupus pregnancies: effects on neurodevelopment

Besides inflammation along the lifetime, research indicates that also maternal inflammation during pregnancy can be determinant for future mental health of offspring.

Mounting evidence indicates that prenatal conditions in general are determinant for future health, and that maternal physical and mental health during pregnancy can influence fetal development and adult health of offspring.

Different kind of stressors during pregnancy have shown consistent association with suboptimal development in offspring and higher risk for mental and physical adverse outcomes later in life. Stressors include infections, autoimmune diseases, stress, suboptimal diet, obesity: all conditions that have in common elevated inflammation and, more generally, maternal immune activation (MIA) (reviewed in (Han et al., 2021)).

This field is particularly relevant to this doctoral research, which analyzes offspring of women with SLE, thus at risk for both physical and mental challenges under pregnancies.

This paragraph will review the evidence about the effects of MIA on offspring mental and physical health and the mechanisms implied, and describe the specific case of Lupus pregnancies.

The separate box on fetal brain development and the connectome gives an overview about typical neurodevelopment and the measures of connectivity, that are of increasing use in neurosciences.

DEVELOPMENT OF FETAL BRAIN AND THE CONNECTOME

Fetal brain development: Human brain development begins early in gestation and follows an orchestrated series of events including processes such as proliferation, migration, and differentiation (Cowan, 1979). Cell migration initiates during the first trimester. When neurons reach their final destination, they arborize and branch in an attempt to establish appropriate connections (Sidman & Rakic, 1973). Synaptogenesis commences during the fourth month, and neural circuits begin to organize (Kostovic et al., 2002). By the end of the second trimester, 200 billion neurons have been produced. In the last trimester the fetal brain forms secondary and tertiary gyri and exhibits neuronal differentiation, dendritic arborization, axonal elongation, synapse formation (that accelerates to a rate of 40,000 synapse per minute), collateralization, and myelination. (J. P. Bourgeois, 1997; Jean Pierre Bourgeois et al., 1994). During the fetal period the majority of genes are expressed in the human brain, with an approximately twofold greater gene expression compared with the adult (Johnson et al., 2009). Mid- to late-second trimester marks the genesis of the macroscale connectome (Collin et al., 2014).

The connectome:

The connectome can be defined as the complete, point-to-point spatial connectivity of neural pathways in the brain(Toga et al., 2012), the capacity of neurons to create, adapt, and disconnect networks between themselves (Buckholtz & Meyer-Lindenberg, 2012). While local groups of neurons perform specialized tasks, their functional integration is necessary to perform even simple behaviors. Connectivity makes this orchestration possible. . The connectome is developing along the lifetime, but the most active periods of development are the fetal period and the first two years of life. Mid- to late-second trimester marks the genesis of the macroscale connectome (Collin et al., 2014), when thalamo-cortical, cortico-cortical, callosal-cortical, and cortico-spinal connections begin to form. This period is marked by vulnerability to injury from numerous environmental sources, as oxygen deprivation, chemical exposure, infection, stress (E. P. Davis et al., 2018; A. Di Martino et al., 2014).

By start of adolescence, gross functional network community structure and interaction properties are in place. Adolescence provides critical refinements in integration of information processing and coordination between regions. (A. Di Martino et al., 2014). Network architecture is known though to mature across the lifespan, including during late adulthood (Hafkemeijer et al., 2014).

Such complex integration between regions could provide many opportunities for failure, and in fact alterations in circuit-level connectivity may have a more pronounced impact on behavior and psychopathology, than disruptions in regional activity alone (Buckholtz & Meyer-Lindenberg, 2012). The notion that major forms of mental illness, such as schizophrenia, are essentially disorders of dysconnectivity has a long history. Such ‘‘disconnection hypotheses’’ motivated in fact the beginnings of investigation in the area (Friston, 1998).

Studies of connectivity have now shed new insight on brain function in healthy and pathological conditions, and on etiopathogenesis of mental illness, by studying effects on brain circuits of exposure to possible modifying factors (fx environmental, genetic etc.) (Buckholtz & Meyer-Lindenberg, 2012).

Connectivity can be described structurally, by anatomical networks, and functionally.

Anatomical or structural connectivity shows connections between brain regions and can be studied by diffusion-weighted imaging (dMRI). dMRI assesses the diffusion of water along axons, permitting visualization of axonal pathways and white matter tracts. It returns a measure of Fractional Anisotropy (FA), the degree to which water diffuses along the axon and a measure of axonal integrity: high values of FA suggest more highly organized, strongly myelinated tracts (Mori & Zhang, 2006).

Functional connectivity informs about functional coupling between neural regions: it can be assessed by functional MRI (f-MRI), that obtains data of metabolic activity in different brain regions through repetitive measures, taken at rest (resting state connectivity), or during a cognitive task (task-based connectivity) (Friston, 2011).

Studies of connectivity in healthy subjects have revealed specific network mechanisms that underlie diverse aspects of cognitive, affective, motivational, and social functioning. Functions as attention, working memory, and cognitive control appear related to connectivity between lateral frontal, dorsal cingulate, and dorsal parietal cortices. Vigilance and arousal responses to biologically salient stimuli seem regulated by a corticolimbic circuit comprising the amygdala, medial prefrontal cortex and lateral prefrontal cortex. Reward, motivation and decision-making have been related to connectivity between striatum and prefrontal cortex. (reviewed in (Buckholtz & Meyer-Lindenberg, 2012)).

Likewise, connectivity analyses in pathological conditions have shown disruptions in the above circuits across diagnoses and in relation to symptoms: atypical connectivity within circuits coordinating executive functions have been described across various disorders that share executive difficulties (schizophrenia, major depression, ADHD, substance abuse), and changes within circuit coupling striatal with prefrontal cortex are observed in many disorders characterized by impaired motivation, impulse control and decision making (schizophrenia, depression, OCD, substance abuse) (Buckholtz & Meyer-Lindenberg, 2012).

Lately, connectivity studies have started studying effects of in-utero and early exposures on new-born or infant development

1.4.1 Effects of MIA on neurodevelopment

This paragraph will review epidemiological, preclinical and prospective studies indicating how MIA can alter development in offspring, and describe the main mechanisms implied.

1.4.1.1 Epidemiological evidence about impacts of MIA on neurodevelopment

Mounting evidence is showing that several maternal conditions characterized by elevated inflammation during pregnancy associate with increased risk for different psychiatric disorders in offspring.

Several population based studies have e.g. shown associations between maternal autoimmune disorders (AD) during pregnancy and increased risk in offspring for ASD (see (S. wei Chen et al., 2016) for a meta-analysis), ADHD (Instanes et al., 2017) and preliminarily for Tourette Syndrome/Tics disorder (Mataix-Cols et al., 2018). Some studies that compare maternal and paternal history of AD, find higher associations with maternal data, supporting a role of exposure to maternal environment during pregnancy (Atladóttir et al., 2009; Croen et al., 2019; Mataix-Cols et al., 2018).

Maternal infections in pregnancy have also been linked to suboptimal development in offspring, with increased risk for psychotic disorders ((G M Khandaker et al., 2013) for a review) and ASD ((Jiang et al., 2016; Tioleco et al., 2021) for meta-analyses), but also major affective disorders (Machón et al., 1997), any mental disorder (Lydholm et al., 2019) and also other CNS disorders ((Knuesel et al., 2014) for a review). Findings across these studies converge in suggesting that it is the maternal inflammatory response to the infectious agent, and not the presence of any *specific* agent, that is linked to the effects observed in offspring (Estes & McAllister, 2016; Furman et al., 2019; Knuesel et al., 2014; Ratnayake et al., 2013; Tioleco et al., 2021).

Also direct measures of maternal immune activation as cytokines and CRP have been associated with adverse outcomes in offspring in numerous large nested case-control studies.

Various inflammatory markers measured prospectively during pregnancy have been found elevated in mothers whose children had later developed mental disorders, especially within developmental and psychotic spectrum. Meta-analytic evidence has shown that higher CRP and IL-8, and lower IL-10 (an anti-inflammatory cytokine) in mothers associate with schizophrenia in offspring (J. Zhang et al., 2018).

Other associations have also been described, at times with discordant results.

Higher maternal CRP has been associated with higher (A. S. Brown et al., 2014), lower (Zerbo et al., 2016) and no change (Koks et al., 2016) in risk for ASD/ASD traits in offspring, with a recent meta-analysis finding no significant association (Nadeem et al., 2020).

Higher TNF-α, IL-1β, and IL-6 in early pregnancy associated with schizophrenia in one large longitudinal study (Allswede et al., 2020), but various nested case-control studies from the New England Family Study show different results: higher IL-6 related with schizophrenia in males only (Goldstein et al., 2014), lower TNF-α associated with increased risk for schizophrenia in females (Goldstein et al., 2014), and higher TNF-α associated with reduced risk of major depression in offspring (S. E. Gilman et al., 2016).

Higher IL-1α and IL-6 have also been associated with ASD with intellectual disability (K. L. Jones et al., 2017). More inconsistent evidence has been found for affective disorders (Cheslack-Postava et al., 2017; S. E. Gilman et al., 2016), where larger studies are invoked.

Maternal concentrations of IL-6 during pregnancy are considered particularly crucial for human fetal brain development (J. M. Rasmussen et al., 2019), and elevated IL-6 is frequent among women with conditions associated with increased risk for neurodevelopmental and other psychiatric disorders in the offspring: obesity ((Y.-M. Li et al., 2015) for a meta-analysis), infections, high psychosocial stress (Coussons-Read et al., 2005) and autoimmune diseases as SLE (Tsokos, 2011; Évelyne Vinet et al., 2015).

Besides inflammatory markers, another potential agent of MIA effects on fetus could be maternal antibodies against fetal brain, that during pregnancy could theoretically access the fetal brain through an immature blood–brain barrier (BBB).

Maternal antibodies that recognize proteins in the developing fetal brain are thought to lead to a subphenotype of ASD that has been termed maternal autoantibody related (MAR) (reviewed in (Karen L. Jones & Van de Water, 2019)).

Mothers of children with ASD have in fact a higher prevalence of antibodies reacting against rat embryonic and human fetal brain antigens, which presence associate with behavioral regression in children (Singer et al., 2008). The same reactivity is found in women with autoimmune disorders as SLE or rheumatoid arthritis (Brimberg et al., 2013), and maternal antibodies acting against (fetal) NMDA-receptor have been implied in the higher incidence of neurodevelopmental

disorders of offspring of women with SLE (É Vinet et al., 2014; Évelyne Vinet et al., 2015), as discussed further on.

This evidence about effects of MIA is supported by a recent systematic review of 32 meta-analysis and 26 other studies looking at relation between several maternal states all associated with inflammation in pregnancy, and common neurodevelopmental disorders in offspring (Han et al., 2021). Authors conclude that autoimmune diseases, infections, obesity, pre-eclampsia, stress, and depression during pregnancy are risk factors for both ASD and ADHD. Furthermore, diabetes mellitus and pollution are risk factors for ASD; smoking, asthma and low SES are risk factors for ADHD; and autoimmune disease, low SES and depression are risk factors for Tourette syndrome.

1.4.1.2 Preclinical evidence about impacts of MIA on neurodevelopment

Experimental studies in animal models confirm that MIA can disrupt early neurodevelopment in offspring. These models consist in triggering the maternal immune system during fetal development using various immunogens, and then registering changes in offspring's behavior. (Meyer et al., 2009). Triggers can be various: cytokines, lipopolysaccharide (LPS), a gram-negative bacterial cell wall component that mimics a bacterial infection, polyriboinosinic polyribocytidylic acid (poly I:C), a synthetic double stranded RNA analog that mimics a viral infection, or antibodies with reactivity against fetal brain antigens, extracted e.g. from women with offspring with ASD. Exposed offspring show alterations that parallel some findings described in schizophrenia and ASD in humans: altered cognitive and social behavior, impaired sensorimotor gating, and increased anxiety; altered cell migration, dendrite development, synaptic structure and function, microglial function (reviewed in e.g. (Estes & McAllister, 2016; Guma et al., 2019; Gumusoglu & Stevens, 2019; Reisinger et al., 2015)) and hyperproliferation of neural stem cells and brain overgrowth (Le Belle et al., 2014).

Here again the functional and structural alterations do not seem to depend on specific immune activating agents, but rather on the inflammatory condition: certain cytokines, such as IL-6, have been identified as key players (Bergdolt & Dunaevsky, 2019; Gumusoglu & Stevens, 2019; S. E. P. P. Smith et al., 2007; W.-L. Wu et al., 2017). Rodent models involving e.g. direct administration of

IL-6 in the pregnant dam have shown that IL-6 is both sufficient and necessary to induce MIA-associated social and behavioral deficits (S. E. P. P. Smith et al., 2007).

Maternal antibodies have shown to alter fetal brain development and cause long-term impairment of brain function also in animal models. Studies have used antibodies with brain reactivity extracted from mothers of subjects with ASD, or from women with SLE, and also pre-pregnancy immunization with peptides in order to create brain-reactive antibodies present throughout gestation (revised in (Gata-Garcia & Diamond, 2019). Several works show how in utero exposure to maternal brain-reactive antibodies is sufficient to permanently alter brain anatomy and cause aberrant cognition or behavior mimicking certain neurodevelopmental disorders as ASD and schizophrenia. (Gata-Garcia & Diamond, 2019)
For example, mice exposed to antibodies cross-reactive for brain antigens (against NMDA-Receptor) generate pups that show histological abnormalities and develop behavioral impairments when adults, in a dose-dependent manner. They present increased neocortical cell death as fetuses, and disorganization of the neocortical architecture with decreases in neocortical neuron size and in the neocortex thickness as adults. Behavioral changes affect tasks that depend on the neocortex, as impaired extinction of fear and reduced exploration of novel object (J. Y. Lee et al., 2009) or hyperactivity, lower anxiety, and impaired sensorimotor gating (Jurek et al., 2019). Also Rhesus monkeys exposed in first two trimesters to IgG isolated from women whose offspring had ASD, showed accelerated growth in total brain volume (TBV) between 3 and 6 months of life, and increased frontal and occipital lobe volume, driven by WM volume expansion, at 1 and 2 years of life (Bauman et al., 2013). These finding parallel the cortical overgrowth in frontal lobe and other regions commonly observed in the first 2 years of life of ASD children (J. K. Lee et al., 2020; Schumann et al., 2010). Asymptomatic mothers may thus harbor low-level pathogenic human antibodies that are transferred through the placenta, causing neurotoxic effects on neonatal development (Jurek et al., 2019).

1.4.1.3 Prospective evidence about impacts of MIA on specific outcomes/phenotypes

Some reviewers suggest that prenatal exposure to inflammatory adversity may be viewed as a general vulnerability factor for developmental disturbances, that shapes increased susceptibility to

the effects of postnatal stressors ("a second hit"), rather than being a disease-specific risk factor (Graham et al., 2018). They suggest psychiatric outcomes in offspring to be deconstructed into their essential psychopathological and neuropathological components (Alan S. Brown & Meyer, 2018).

In this line prospective studies are beginning to emerge, that follow dyads of mother-child and relate repeated measures of maternal parameters with specific outcomes in children.

The group of Heim, Buss and Entringer has analyzed the effect of maternal chronic systemic low-grade inflammation, assessed by mean of three repeated measures of IL-6 across pregnancy, on offspring development, by studying functional and structural MRI shortly after birth and working memory and impulse control at 2 years of age. They found that higher average maternal IL-6 concentration in pregnancy associated with larger right amygdala volume; that IL-6 associated with lower working memory (Rudolph et al., 2018) and lower impulse control at 24-months-of-age, with amygdala mediating the effects of IL-6 on impulse control (Graham et al., 2018). IL-6 levels associated also with higher rsFC within multiple large-scale functional systems, in particular the salience (SAL), subcortical (SUB) and dorsal attention (DAN) systems, to such an extent that IL-6 could be estimated using machine learning on the basis of these connectivity patterns (Rudolph et al., 2018). These networks are important for supporting normal social, emotional and cognitive development, as they have relevance for various neuropsychiatric disorders including ADHD, schizophrenia and autism (V Menon, 2015; Sporns, 2014). In a more recent work (J. M. Rasmussen et al., 2019), the group analyzed prospective relations between maternal IL-6 levels and *structural connectivity* within the uncinate fasciculus (UF), the main fiber tract of the frontolimbic circuitry, a circuitry critical for socioemotional and cognitive development. The UF connects the anterior temporal lobe to the orbitofrontal cortex via limbic regions (e.g. amygdala) and provides a direct structural link between higher-order cognition and emotional regulation. Reduced integrity of the UF has been linked to a range of neurodevelopmental and psychiatric disorders (reviewed in (J. M. Rasmussen et al., 2019)). Connectivity was assessed by fractional anisotropy (FA) shortly after birth and at 12-months age. Higher maternal IL-6 across pregnancy associated with lower UF FA at newborn, and with higher rate of FA increase across the first year of life, resulting in a null association between maternal IL-6 and UF FA at 12-mo age. Maternal IL-6 was also inversely associated with Bayley cognitive development scores at 12-mo age after adjustment for postnatal

caregiving, and this association was mediated by FA growth across the first year of postnatal life. Authors posit that the accelerated postnatal growth may be compensatory, and/or reflective of a general postnatal overgrowth pattern, analogous to that seen in ASD, where prenatal inflammation is also a risk factor (Zielinski et al., 2014). The relation between accelerated change in UF FA and poorer cognitive development at 12-mo age suggests furthermore that this catch-up growth may not be beneficial, hinting that the dynamic processes of brain development may be more important for the establishment of later behavioral phenotypes, than the outcome at a certain time points, and thus underlying the importance of longitudinal studies (J. M. Rasmussen et al., 2019).

The association between maternal IL-6 and increased neonatal rsFC in the salience network has been replicated by another group (Spann et al., 2018). In this work, though, increased IL-6 and CRP in the third trimester correlated positively also with measures of cognitive development at 14 months, in domains that include attention, sensorimotor integration, and early executive functions.

Other works suggest similar mixed patterns: higher 2nd and 3rd trimester levels of TNF-α correlated with lower IQ and visual-motor cognitive scores at age 7 years, while higher IL-8 levels correlated with better performance on tactile recognition and drawing skills, in a sample of over 1,300 participants from the New England Family Study (Ghassabian et al., 2018). Also a prospective pre-birth cohort study, the Newborn Epigenetic Study (N=246), studying effects of different maternal cytokines measures at a single time-point between 1st and 2nd trimester, found that higher IL-12 and IL-17A correlated with higher cognitive and executive functioning at a mean age of 4,5 years (SD=1.1), while higher IL-1β correlated with lower cognitive scores, and IL-8 was positively associated with verbal abilities and negatively associated with child spatial abilities (Dozmorov et al., 2018). (Of note, experimental studies in mice suggest that IL-12 activates recovery and neurogenesis, and has a protective role on brain development and functioning (Yaguchi et al., 2008)).

A recent longitudinal study on 418 mother-child dyads studied relation between maternal systemic, low-grade chronic inflammation and number of areas of child neurodevelopmental delay up to 10.8 years of age (Girchenko et al., 2020). They took repeated measures of two inflammation markers with long half-lives: high-sensitivity CRP (hsCRP) and glycoprotein acetyls, a novel

systemic biomarker, representing the abundance of circulating glycated proteins, and suggestive of a prolonged low-grade inflammation (Ritchie et al., 2015). They found that higher maternal inflammation was associated with higher number of areas of child neurodevelopmental delay and mediated the effects on neurodevelopment of any prenatal environmental adversity, such as maternal overweight/obesity, diabetes, hypertension, and mood and anxiety disorders.

1.4.1.4 Effects of MIA on neurodevelopment - conclusions

From these data various observations arise.

Researchers agree in observing that MIA is associated with short- and long-term influences on offspring brain development and functioning (Dozmorov et al., 2018; Ghassabian et al., 2018; Lu et al., 2018; J. M. Rasmussen et al., 2019)

The differences reported in the directions of associations between maternal immune molecules and offspring neuropsychiatric outcomes, suggests that the impact of cytokines may be brain-region and brain-function specific (Ghassabian et al., 2018).

Differences may also result from methodological differences between the studies, as variation in the studied set of biomarkers, small sample sizes, or reliance on a single vs multiple measurement points (Girchenko et al., 2020).

Some authors note how some of the alterations may be adaptive: higher correlations found e.g. between IL-6/CRP and activity in certain brain networks - as the salience one – as well as higher scores in some early cognitive functions (Rudolph et al., 2018; Spann et al., 2018) may give survival advantage, if the pre- and postnatal environments match together. If heightened maternal inflammation during pregnancy signals a more adverse or dangerous environment, then heightened vigilance and reactivity would be protective for the child, and shaping basis for resilience. (Graham et al., 2018; Spann et al., 2018; Wadhwa et al., 2009). Similar responses are described in some animal studies, where neonatal bacterial infection in rats can lead to a protection against induced depressive-like behaviors in adulthood (Bilbo et al., 2008).

These data may also be in line with the mismatch hypothesis, that suggests that an individual is programmed by his/her early life environment to be suited to a similar environment later in life, and that disorders arise when the two environments actually don’t match (Santarelli et al., 2014).

1.4.1.5 Mechanisms implied in MIA effects: animal and human data

How can maternal immune activation reach the fetus, and then impact its development? Evidence suggests a role of cytokines, antibodies and microbiome, among other mechanisms.

Transfer of cytokines ad antibodies

Even though animal studies suggest that at least some maternal cytokines can pass through the placenta and enter fetal circulation, whether cytokines in humans directly cross the placenta is not known (Estes & McAllister, 2016; Rakers et al., 2017). Human studies on TNF-α suggest minimal (Zaretsky et al., 2004) or no transfer (R. Aaltonen et al., 2005) through at termin-placenta, but also indicate that TNF-α can alter the inflammatory secretion profile of the placenta. This would lead to increased levels of pro-inflammatory cytokines in the fetal compartment (Siwetz et al., 2016), and to changes in the fetal gene expression. (Abdallah et al., 2012; Ashdown et al., 2006; Jonakait, 2007; Lazarides et al., 2019; Parker-Athill & Tan, 2010).

As to maternal antibodies, IgGs get transferred at high concentrations from around midgestation, culminating in circulating IgG levels in the newborn that exceed those in maternal circulation, due to active transport across the placenta (Garty et al., 1994). Maternal antibodies have at then free access to the fetal brain in early pregnancy, because the fetal blood–brain barrier (BBB) begins to form around the second trimester, and is not mature until the postnatal period (B. Diamond et al., 2009).

Furthermore, inflammation can damage the fetal blood brain barrier, thus facilitating transfer of inflammatory mediators and antibodies to CNS (Knuesel et al., 2014; Stolp & Dziegielewska, 2009).

Animal studies suggest also that MIA can induce persistent immune alterations in offspring: increased cell-mediated immunity (Zager et al., 2013), hyperresponsive CD4+ T cells, and decreased levels of regulatory T cells (E Y Hsiao et al., 2012).

In humans, it is not yet clear whether serum and brain levels of cytokines correlate in fetal life. Yet, animal studies show that an inflammatory stimulus in pregnant mice increases the levels of a broad range of cytokines in the fetal brain within few hours, (Arrode-Brusés & Brusés, 2012; Meyer et al., 2006) and that many of these cytokines remain generally increased at birth and in the adult brain (Garay et al., 2013).

Within the CNS, MIA animal models have induced in offspring *hypomyelination,* and widespread connectivity anomalies that are maintained in adult life (Makinodan et al., 2008), c*hanges in gene transcription,* e.g. reduced expression of reelin, a protein that regulates radial migration of cortical principal neurons, reduced also in brain tissue of patients with schizophrenia (reviewed in (Knuesel et al., 2014)), or upregulation of brain protein crystallin, also found increased in brain of patients with schizophrenia or ASD (Martins-de-Souza, 2010; Pickett, 2001). Such changes could be linked to epigenetic changes, as some first studies suggest (Connor et al., 2012; B. Tang et al., 2013). MIA models *increase MHCI levels on neurons* in offspring (Coiro et al., 2015): MHCI inhibit synapse formation and pruning (reviewed in (Estes & McAllister, 2016)), and its increase results in reduced ability of newborn neurons to form synapses (Elmer et al., 2013), and thus in changes in cortical connectivity and behaviors (Knuesel et al., 2014). MIA can also induce *microglia priming:* permanent changes in microglia, suggestive of an activated and pro-inflammatory phenotype, and still evident in adulthood (Giovanoli et al., 2013; Juckel et al., 2011).
Cytokines are thought to mediate these effects of MIA (Estes & McAllister, 2016). IL-6 in particular plays a requisite role in fetal brain development (Burns et al., 1993; S. E. P. P. Smith et al., 2007), and inappropriately elevated levels may produce perturbations in cellular survival, proliferation and differentiation, axonal growth and synaptogenesis (Boulanger, 2009; Deverman & Patterson, 2009; Mehler & Kessler, 1997; Zhao & Schwartz, 1998). Rodent models involving direct administration of IL-6 in the pregnant dam have e.g. demonstrated that IL-6 is both sufficient and necessary to induce MIA-associated social and behavioral deficits (S. E. P. P. Smith et al., 2007).

Pre-clinical research is also testing the *two-hit hypothesis*, i.e. whether pre- and perinatal insults can have a synergistic effect with later insults, with synergy mediated by microglial priming. The first studies in this line show that following a prenatal or neonatal inflammatory exposure, a second hit - hypoxic–ischemic damage, peri-pubertal social stress, or postnatal inflammatory challenge - resulted in a significantly heightened inflammatory response, including expression of several cytokines and chemokines, increased numbers of morphologically hyperreactive microglia, and decreased numbers of reparative microglia. The resulting phenotypes were varied, including schizophrenia-like behavioral abnormalities (Giovanoli et al., 2013), promotion of protein aggregation and cognitive deficits (Krstic et al., 2012), or severe cerebral infarcts (Stridh, 2013).

In humans, the two-hit hypothesis has been developed initially for schizophrenia: of note, the first epidemiological confirmation is appearing: a large cohort prospective study, following nearly 100,000 individuals born in Denmark 1980-1998 from 1995 through 2013, found that exposure to prenatal infections and peripubertal trauma interacted in synergy to increase risk for schizophrenia in males (Debost et al., 2017).

Microbiome and the gut-immune-brain axis: The gut may also play an important role in explaining the consequences of MIA on behavior. Animal models of ASD suggest that MIA alters microbiota signatures and gastrointestinal permeability in offspring (Elaine Y Hsiao et al., 2013), and that restoring a more typical microbiome by treating MIA offspring with Bacteroides fragilis restores peripheral immune homeostasis and ameliorates several aberrant behaviors (Elaine Y Hsiao et al., 2013). The fetal gut is colonized by maternal microbiota at birth, and this colonization primes the developing immune system (Estes & McAllister, 2016) as well as influences brain development. Microbiome "constantly controls maturation and function of microglia in the CNS" (Erny et al., 2015), and differential microbial colonization in early life may also influence the developing serotonergic system (O'Mahony et al., 2015).
Besides, influence of maternal microbiota would start already in utero, when maternal microbial molecules can penetrate the placental barrier and start influencing fetal development long before birth (Ganal-Vonarburg et al., 2020).

1.4.2 Effects of MIA on Physical health

Evidence is also indicating that MIA may affect offspring *physical* health, increasing risk for metabolic and inflammatory disorders, and also measures of general health as telomere length.

MIA may affect offspring risk for obesity during childhood, suggest some studies. Some works have found associations between higher maternal inflammation in pregnancy and higher fat mass or obesity in children: higher CRP in mid pregnancy with adiposity in mid-childhood (Gaillard et al., 2016), higher average maternal IL-1β, IL-8, IL-6, and IL-10 with lower BMI at birth but higher BMI during childhood (Ghassabian et al., 2020), higher TNF-α with higher BMI in girls at 6 months (Donnelly et al., 2020) and in infancy (Ghassabian et al., 2020), and lower median IL-4 and IL-13

(anti-inflammatory cytokines in adipose tissue) with higher risk for overweight development up to 3 y.o. age (Englich et al., 2017).
Results are not univocal, as other works find no associations – e.g maternal measures of hsCRP, TNF-α, IL-1β and IL-6 did not correlate with higher BMI or other markers for metabolic syndrome in offspring at 20 y.o. age in a Danish study (Danielsen et al., 2014).
In animal models, induced maternal inflammation associates with increased adiposity and insuline resistance in offspring (Nilsson et al., 2001; Wei et al., 2007). Mechanisms are not well understood yet, but may partly coincide with those implied in risk for obesity after maternal obesity (Barker, 1995; Parisi et al., 2021) and/or after fetal growth restriction and low birth weight (P. D. Gluckman et al., 2008). Effects of cytokines on placenta function, regulation of the HPA axis (Ghassabian et al., 2020), epigenetic factors, induction of insulin resistance (Gaillard et al., 2016) have been involved. One hypothesis is that fetoplacental adaptions and fetal epigenetic reprogramming may occur, that initially aim to preserve pregnancy and fetal maturation, in the presence of an inadequate nutrient supply from the mother. Adaptations would though persists into post-natal life, when nutritional conditions get normalized, and then would not be functional anymore (the mismatch hypothesis), but may increase the susceptibility to future noncommunicable disease (Macpherson et al., 2017; Parisi et al., 2021).

MIA may also shape a pro-inflammatory phenotype in offspring, that could persist through 2nd generation (Furman et al., 2019; Parisi et al., 2021). Animal models of maternal inflammation can induce a proinflammatory macrophage phenotype and enhanced IL-β production in adult offspring (Kirsten et al., 2013), and associate with exaggerated inflammatory cytokine responses in two generations of progeny, without further insults (R. C. M. C. Adams & Smith, 2020; R. C. M. Adams & Smith, 2019). Offspring would thus develop elevated risk for chronic systemic inflammation in childhood and adulthood, and therefore be more likely to suffer from a wide variety of inflammation-related health problems, including obesity, CVD, cancer, besides the over mentioned neuropsychiatric alterations (Furman et al., 2019).

There also indications for that MIA may have “programming” effects on the development and initial setting of the telomere system, and by that, of the future general health.

Telomeres are complexes of DNA and proteins (shelterins) that form the protective caps at the ends of the eukaryotic chromosomes. The play a crucial role in genome integrity and chromosomal stability, protecting against senescence and cellular aging (Karlseder, 2009; Oeseburg et al., 2010). They shorten with each cell division and thus constitute an indicator for cellular aging processes, but can be also elongated through the enzyme telomerase (Oeseburg et al., 2010). Shortened telomere length has been linked to higher risk for age-related diseases as cardiovascular disease, type 2 diabetes, cancer ((M. J. J. D'Mello et al., 2015; Haycock et al., 2014; Ma et al., 2011; Mons et al., 2017) for meta-analyses), as well as mental disorders (Xuemei Li et al., 2017; Schutte & Malouff, 2015), and mortality (Rode et al., 2015). Telomere length (TL) at any given age during life is a joint function of the initial/newborn TL, and of telomere attrition rate over time (Aviv, 2008), and animal studies indicate that the newborn TL and the attrition in early life have a greater influence on subsequent health outcomes, than TL and attrition later in life (Lazarides et al., 2019). MIA may contribute to newborn TL.

Adult mice exposed to a prolonged pro-inflammatory state in utero exhibited shorter telomeres in adulthood, than their unexposed counterparts (B. Liu et al., 2016).

In humans, a prospective work from the Entringer, Buss and Heim group, showed that higher maternal inflammatory state measured as ratio between a proinflammatory and an anti-inflammatory cytokine, TNF- α and IL-10, was significantly associated with shorter newborn TL, with a 10% difference in newborn TL in offspring of women in the upper compared to lower quartile of the TNF-α/IL-10 ratio (Lazarides et al., 2019). This supports the growing recognition that intrauterine conditions during gestation may have "programming" effects on the development and initial setting of the telomere system, and thus of the future general health.

1.4.3 Conclusions - effects of MIA on offspring psychophysical health

Maternal immune activation during pregnancy, therefore, configures as a common pathway mediating the effects of a diverse set of inflammation-related states and conditions during pregnancy, on offspring neurodevelopment and mental and physical health outcomes (Knuesel et al., 2014; J. M. Rasmussen et al., 2019)

1.4.4 Lupus pregnancies and offspring: a model of MIA

Among MIA models, are pregnancies in women with Systemic lupus erythematosus (SLE). SLE is an autoimmune disease of unknown etiology, characterized by the presence of autoantibodies directed against multiple self-antigens including DNA, and affecting several systems. It has a striking 9:1 female predominance and peaks during childbearing years. Arthritis and skin disease are the most frequent manifestations, but involvement of the lungs, kidneys and central nervous system accounts for most of the morbidity and mortality attributed to it (Cervera et al., 2003; Jacobsen & Jacobsen S Ullman, P J, S, 1999). Neuropsychiatric symptoms include e.g. cognitive dysfunction, mood and anxiety disorders, psychosis, acute confusional state and headache, and are grouped under the label Neuropsychiatric Lupus (NPSLE) (J. G. Hanly, 2004). Primary NPSLE - i.e. due to SLE and not to its consequences or treatment - is attributed to vascular abnormalities, autoantibodies and inflammatory mediators, that both would access the CNS by passive transfer from the circulation through increased permeability of the blood–brain barrier and, independently, be produced intrathecally (reviewed in (John G Hanly, 2014)).
Elevated cytokines are described in SLE patients, where they influence pathogenesis and clinical presentation. Cytokines in SLE are involved in cardiopulmonary, cutaneous, and renal affection, by acting both on immune cells and on local cells, as the endothelial cells (G. S. Dean et al., 2000). IL-6 in particular is markedly elevated in affected patients and stimulates autoantibody production (Tsokos, 2011). CSF levels of IL-6, IL-8 and IL-10 correlate with NPLSE disease activity (reviewed in (T Yoshio et al., 2016)).

Pregnancies in women with SLE represent therefore one relevant model of MIA (É Vinet et al., 2014), and the first retrospective studies carried out in SLE-offspring suggested higher incidence of neurodevelopmental disorders as well as learning disabilities (Lahita, 1988; McAllister et al., 1997; Neri et al., 2004; Urowitz et al., 2008). A recent review has confirmed that maternal SLE is associated with learning disabilities (specifically dyslexia), ASD, attention deficit and probably speech problems in offspring (Yousef Yengej et al., 2017). Maternal inflammatory mediators and antibodies have been implied. At the same time, other factors may impact on the development of SLE-offspring, as maternal medication use during pregnancy, or an inflammatory response in the fetus or later the child. Furthermore, these pathways could overlap. (Instanes et al., 2017).

1.4.4.1 Autoantibodies in NPSLE

Different autoantibodies have been described to have a pathogenic role in NPSLE.

Anti-phospholipid antibodies (aPL) induce a procoagulant state, causing thrombosis within vessels of different calibers and consequent cerebral ischemia (Musial et al., 2012). They associate with focal manifestations as stroke and seizure disorders, but also with cognitive impairment, even in the absence of stroke. (John G. Hanly et al., 1999; Love & Santoro, 1990; S. Menon et al., 1999). A possible direct pathogenic effect of aPL is suggested by their intrathecal production in patients with NPSLE (Martinez-Cordero et al., 1997) and their modulation of neuronal cell function in vitro (J. Chapman et al., 1999).

Anti-ribosomal P antibodies have been associated with NPSLE in two meta-analysis (Choi et al., 2020) and are found specific for psychotic symptoms in some, but not all, studies (Briani et al., 2009; Karassa et al., 2005).

Another line of research has focused on a subset of anti-dsDNA antibodies, that can cross-react with the NMDA receptor. They can be identified by their binding a peptide sequence DWEYS/DWDYS, found in the extracellular domain of the receptor, and are thought to have neurotoxic properties (see specific section). Clinical studies indicate that 40–50% of SLE patients carry autoantibodies (AAbs) with such reactivity (Fragoso-Loyo et al., 2008; J G Hanly et al., 2006; Husebye et al., 2005; Lapteva et al., 2006; Omdal et al., 2005; Steup-Beekman et al., 2007; Taku Yoshio et al., 2006), and a recent meta-analysis has confirmed their association with neuropsychiatric symptoms in SLE (S. H. Tay et al., 2017).

----------separate picture ----------

1.4.4.2 The Anti-GluN2/anti-DWEYS antibodies in SLE

These antibodies have been discovered by the group of prof. Betty Diamond while studying possible treatments for a mice model of renal Lupus.

In renal Lupus anti-DNA antibodies deposit in the kidneys of lupus patients and cause glomerulonephritis, by cross reacting with some renal tissue antigens and thus causing damage (reviewed in (Gaynor et al., 1997)). Investigators wanted to study whether antibody-binding to renal antigens could be prevented by using surrogate antigens, that could compete for pathogenic antibodies. They looked for possible peptides reacting with the R4A antibody, a nephritogenic monoclonal IgG anti-dsDNA antibody (Shefner et al., 1991). By using peptide display phage libraries, they found a distinct consensus motif present in most of the selected phage: D/E-W-D/E-Y-S/G. The DWEYS peptide bound the antibody at the same site as ds-DNA did, and its exogenous administration inhibited R4A deposition in the kidney (Gaynor et al., 1997), and lead to production of anti-dsDNA antibodies.

A protein database search found that the D/E-W-D/E-Y-S/G consensus sequence was found in some bacterial antigens but also in the extracellular, ligand-binding domain of mouse and human NMDA (N-methyl-D-aspartate) receptors GluN2A and GluN2B subunits (DeGiorgio et al., 2001). Given the importance of NMDA-R for both murine and human brain development and function, investigators argued that antibody reactivity with GluN2A or GluN2B could be a plausible candidate mechanism to mediate some of the CNS disturbances observed in Neurolupus. (DeGiorgio et al., 2001; Volpe, 1997). The R4A antibodies could in fact bind murine GluN2 in vitro, and mediated neuronal death both in vitro, when added to cultures of fetal brain cells, and in vivo, when directly injected into a mouse brain. Neuronal loss was mediated by apoptosis, and by activity on the NMDA-R receptor (DeGiorgio et al., 2001).

SLE patients had also antibodies with the same reactivity and properties: they bound dsDNA, and when injected into mice hippocampi, caused hippocampal neuronal loss through action on NMDA-R, where NMDAR antagonists could protect neurons from damage (DeGiorgio et al., 2001).

Such antibodies could also be found in the CSF of a patient with NP-SLE (DeGiorgio et al., 2001), and could elicit cognitive impairment in mice, if the human serum was given intravenously

together with lipopolysaccharide to compromise the BBB integrity. Brain histopathology showed hippocampal neuron damage, and behavioral testing revealed hippocampus-dependent memory impairment (Kowal et al., 2006). Other murine models from the same group confirmed a causal relationship between exposure of fetal and adult brain to these antibodies, and impairments in cognition and behavior (B. Diamond et al., 2009; Huerta et al., 2006; Kowal et al., 2004; J. Y. Lee et al., 2009). Presence in serum of these antibodies was not sufficient to cause alterations, but a breach in the BBB triggered by inflammation or brain immaturity was necessary.

These antibodies appeared not to be agonists of the NMDAR, but positive modulators of receptor function, that at low concentration increase the size of NMDAR-mediated excitatory postsynaptic potentials, whereas at high concentration, promote excitotoxicity through enhanced mitochondrial permeability transition (Faust et al., 2010). Such graded action may mirror the condition of NPSLE patients, in which transient changes may reflect synaptic effects, whereas permanent damage may reflect neurotoxicity and neuronal death. (Faust et al., 2010)

In mouse models, the acute phase of excitotoxic neuron loss is followed by persistent alteration in neuronal integrity, with reductions in dendritic processes and spines, and spatial memory impairment. These latter changes become evident only after the antibodies are no longer detectable in the brain (E. H. Chang et al., 2015), and would be mediated by activated microglia and C1 complement fraction (Nestor et al., 2018). Microglia could be activated by mediators secreted by activated or apoptotic neurons and by deposition of immune complexes DNA-Ab. (Nestor et al., 2018)

In a very recent work, these Abs confirm as positive allosteric modulators on NMDARs, with greater effect on NMDARs containing GluN2A- subunits, than those with exclusively GluN2B subunits. (Chan et al., 2020)

In parallel, various other groups of research have investigated presence and role of antibodies with such reactivity in SLE patients, and possible association with NPSLE symptoms.

The first clinical studies have found that:

- 30-60% of SLE patients carry antibodies with such reactivity in serum (Fragoso-Loyo et al., 2008; J G Hanly et al., 2006; Husebye et al., 2005; Lapteva et al., 2006; Omdal et al., 2005; Steup-Beekman et al., 2007; Taku Yoshio et al., 2006), and/or in CSF (Arinuma et al., 2008; Fragoso-Loyo et al., 2008; Hirohata et al., 2014; Taku Yoshio et al., 2006). Not all studies

compare SLE patients with HC, but some confirm higher serum titers for SLE patients than HC (Husebye et al., 2005; Omdal et al., 2005; Steup-Beekman et al., 2007; S. H. Tay et al., 2017)

- Correlation between serum and CSF titers is found in some (Taku Yoshio et al., 2006) but not all studies (Fragoso-Loyo et al., 2008). Different permeability in the BBB or intrathecal synthesis of antibodies may explain lack of correlation. (Hirohata et al., 2014; Kowal et al., 2004)
- Associations between serum titers and NPSLE symptoms are quite inconsistent: some works suggested association with depression (Lapteva et al., 2006; Omdal et al., 2005), cognitive dysfunction – decreased short-time memory and learning (Omdal et al., 2005), impairment in spatial cognition (E. H. Chang et al., 2015) – and NPSLE in general (Gono et al., 2011), while others do not find any association (Fragoso-Loyo et al., 2008; J G Hanly et al., 2006; John G. Hanly et al., 2015; M. J. Harrison et al., 2006; Husebye et al., 2005; Kozora et al., 2010)
- Associations between CSF titers and neuropsychiatric symptoms have been more consistently reported: higher titers of these antibodies in patients with central neuropsychiatric symptoms, vs. those SLE patients without neuropsychiatric symptoms, or vs. healthy controls (Arinuma et al., 2008; Fragoso-Loyo et al., 2008; J. Wang et al., 2014), association of antibodies with acute confusional state (Hirohata et al., 2014) and reduced hippocampal gray matter (Lauvsnes et al., 2014).

A meta-analysis from 2017 (S. H. Tay et al., 2017) on over 2,200 SLE patients, 500 healthy controls (HC) and nearly 100 disease controls (DC), has found higher prevalence of anti-GluN2A/B Abs both in SLE patients vs. HC and vs. DC, and in NPSLE patients vs SLE patients without NP symptoms. Serum anti-GluN2A/B antibodies were not specifically associated with any NP syndrome. Authors concluded that anti-GluN2A/B antibodies may have the potential to be biomarkers to diagnose NP syndromes and monitor disease progression in SLE.

Critiques to the model/Limitations:

Critical questions crossing this work have been whether anti-GluN2A/B are pathogenic or epiphenomenal (Pavlovic et al., 2010; S. H. Tay et al., 2017), whether they belong to anti-DNA antibodies, and whether they indeed bind NMDA-R in vivo.

- Some works have investigated whether these anti-DWEYS antibodies correlate with anti-dsDNA antibodies, of which they should be a subset. Several studies don't find such a correlation (Gono et al., 2011; Husebye et al., 2005; Omdal et al., 2005; Taku Yoshio et al., 2006). While this can be explained by the sheer fact of anti-DWEYS being only a subset of all anti-dsDNA antibodies (Gono et al., 2011; Taku Yoshio et al., 2006), some authors hypothesize that these antibodies are "distinct from anti-dsDNA autoantibodies, which are the hallmark of SLE" (Husebye et al., 2005).
- Another point of debate has been whether reactivity against the DWEYS peptide really equals reactivity against in vivo, native NMDA: "peptide reactivity does not necessarily imply receptor-binding activity" (Omdal et al., 2005). A paper published in October 2020 questions this assumption (Varley et al., 2020). The study analyzes sera and CSF of 35 SLE patients, of whom 15 with NPSLE, using the same method applied to detect antibodies in the anti-NMDA-receptor encephalitis, a clinically distinctive form of encephalitis, with prominent neuropsychiatric features, and consistently associated with serum and CSF autoantibodies against the native extracellular domain of the NMDAR NR1 subunit. (Josep Dalmau et al., 2008; Irani et al., 2010). The study tested whether patients' anti-DWEYS antibodies bound to live mammalian cells with surface expressed NR1/2A or NR1/2B heteromers (HEK293T cells), and to the array of native surface proteins expressed on live rodent primary hippocampal cultures.

Authors did find higher levels of anti-GluN2/anti-DWEYS IgG in serum of SLE patients versus HC and DC, and in CSF of NPSLE patients vs non-NPSLE patients. Yet, when testing the binding of the patients serum/CSF samples to HEK293T cells, or to murine live hippocampal neurons, no binding was found. The same occurred for the G11 recombinant monoclonal antibody, isolated from patients with SLE, and earlier on reported to bind to NMDAR (E. H. Chang et al., 2015). Authors conclude for "absence of auto-antibodies directed against conformationally active neuronal surface targets, in both the plasma and CSF of patients with NPSLE", and that "the brain disease associated with SLE is likely to have pathological drivers other than neuronal surface autoantibodies" (Varley et al., 2020)

----------final picture dweys----------

1.5 Comorbidity and interplay between somatic and psychiatric conditions

Besides being described in psychiatric conditions, an inflammatory state represents the shared ground of several multifactorial diseases, as chronic rheumatic disorders, type 2 diabetes, cardiovascular and neurodegenerative diseases, inflammatory bowel diseases, obesity, cancer, asthma, and ageing (Kotas & Medzhitov, 2015; Scrivo et al., 2011).

In the recent years, several works have described comorbidity between these chronic diseases and psychiatric disorders throughout the life span. Longitudinal and register studies have also shown that somatic and psychiatric diseases are risk factors for each other, suggesting mutual influences or shared causal factors.

This paragraph will review this epidemiological evidence in adult and children populations.

1.5.1 Adult studies:

Cardiometabolic risk: Meta-analyses and reviews of longitudinal studies have shown that depression and anxiety disorders are associated with an increased incidence of cardiovascular (CV) disease, and with worse prognosis after CV events have emerged(Batelaan et al., 2016; De Hert et al., 2018; Harshfield et al., 2020; Nicholson et al., 2006). The association is partly independently from lifestyle factors (Penninx, 2017) and bidirectional, with higher prevalence of depression in patients with CV disease (De Hert et al., 2018; Doyle et al., 2015; Meijer et al., 2013). Potential mechanisms are dysregulation in biological systems as the autonomic, HPA-axis, and immune-inflammatory, triggered by the psychiatric condition and influencing CV health, as well as shared underlying factors as childhood stressors, personality traits and genetic pleiotropy (one gene affecting multiple traits) independently affecting CV and psychopathological risk. (Carney & Freedland, 2017; Penninx, 2017; Vaccarino et al., 2020)

Schizophrenia and bipolar disorder are well known to associate with metabolic syndrome and other cardiovascular (CV) risk factors (De Hert et al., 2009; Fleischhacker et al., 2008), which contribute to the shorter life expectancy. Even if these associations have traditionally been attributed to long-term medical treatment and chronic illness, two recent meta-analysis show that in subjects with schizophrenia glucose homeostasis is altered already from illness onset, suggesting that schizophrenia and type 2 diabetes might share intrinsic inflammatory disease pathways. (B. I. Perry et al., 2016; Pillinger et al., 2017)

Autoimmune and allergic diseases:

Recent meta-analyses have shown overall positive association between autoimmune (AI) diseases and depressive/anxiety (Siegmann et al., 2018), bipolar (M. Chen et al., 2021) and psychotic disorders (Cullen et al., 2019). Evidence for associations of autoimmunity with ADHD (M. H. Chen et al., 2017) and ASD is growing (see the children section for reviews), and there is evidence also for association of AI disorders with eating disorders (Raevuori et al., 2014), obsessive–compulsive disorder and Tourette's/chronic tic disorders (D. Martino et al., 2020; Mataix-Cols et al., 2018; Pérez-Vigil et al., 2016)

Prospective ad population studies have shown the associations are bidirectional. Autoimmune diseases and infections increase risk of subsequent mood (Benros et al., 2013; Eaton et al., 2010; Euesden et al., 2017) and psychotic disorders (Benros et al., 2011; Cullen et al., 2019; Eaton et al., 2010) and OCD (L. Y. Wang et al., 2019), but the opposite is also valid: depression (N. W. Andersson et al., 2015; Euesden et al., 2017; Roberts et al., 2018), schizophrenia and related psychosis (Benros, Pedersen, et al., 2014), PTSD and psychosocial trauma (Roberts et al., 2017) increase risk of subsequent autoimmune diseases.

Similar trends are described for allergic conditions: Several large population studies describe association between atopic dermatitis and depression, anxiety, ADHD and suicidality (reviewed in (Kage et al., 2020; Sandhu et al., 2019)), and between allergies and TS and ADHD (reviewed in (D. Martino et al., 2020)) . Asthma and panic disorders have shown mutual bidirectional associations in longitudinal studies (Hasler et al., 2005). Atopic disorders have recently also shown association with psychotic symptoms, both cross-sectionally (Begemann et al., 2019) and longitudinally, with atopies correlating with increased incidence of subsequent psychotic disorders (Pedersen et al., 2012).

1.5.2 Children studies:

Mounting research in children and adolescents describes higher risk for several medical conditions in subjects with a psychiatric diagnosis. Some works are already cited in the previous adult section, as including populations of all ages.

A very recent umbrella review has found that children with ASD have increased risk for autoimmune disorders, atopy, and obesity (Rydzewska et al., 2021). Research in ADHD has mostly focused on allergies, and a recent umbrella review (Kim et al., 2020) confirms childhood atopic diseases to be strongly associated with ADHD.

Even though most works focusing on young population concern ASD and ADHD, data on other diagnoses are emerging. A recent Swedish population study on over 50,000 children aged 3-18 has shown that anxiety and affective disorders associated with diabetes type 1, obesity, and atopic disorders, and that psychotic disorders associated with asthma (Agnafors et al., 2019). Association between children anxiety ad asthma is also confirmed by a meta-analysis (Dudeney et al., 2017). Excess of immune and allergic conditions is also described in young subjects with OCD and tics (H. F. Jones et al., 2021; Westwell-Roper et al., 2019; Yuce et al., 2014).

Most works are cross-sectional, so limited data are available about directions of associations. To date there is some evidence about immune and allergic disorders increasing risk of subsequent psychiatric disorders: a personal history of autoimmune diseases – particularly arthritis juvenilis, autoimmune thyroiditis and diabetes type 1 - was associated with increased incidence of ADHD in a longitudinal Danish Register Study (Philip Rising Nielsen et al., 2017), and childhood atopic disorders associated with increased incidence of subsequent childhood psychotic disorders (Golam M. Khandaker, Zammit, et al., 2014), ADHD and ASD (M. H. Chen et al., 2014).

1.5.3 Family studies:

Several works have highlighted familial association between AI and psychiatric disorders.

There is meta-analytic evidence for association of family history of AI diseases (in particular hypothyroidism, type 1 diabetes, rheumatoid arthritis, and psoriasis) with increased risk for ASD in children(S. Wu et al., 2015).

Population-based studies and systematic reviews show associations between family history for AI diseases and ADHD (Instanes et al., 2017; Xinjun Li et al., 2019; Philip Rising Nielsen et al., 2017), OCD and TS/tic disorders (H. F. Jones et al., 2021; Mataix-Cols et al., 2018; Pérez-Vigil et al., 2016), psychosis (Eaton et al., 2010; Jeppesen & Benros, 2019), and also the opposite, that a family history of psychosis associates with increased risk for AI disease (Benros, Pedersen, et al., 2014). ADHD is also associated with increased risk for atopy in siblings (T.-H. H. Chang et al., 2019).

Some of the studies analyze only maternal condition, but most extend to all relatives, and find also elevated associations of AI diagnoses in fathers and siblings of psychiatric patients. The patterns of associations, generally higher in 1st than in 2nd degree relatives, and in mothers than in fathers, is compatible with shared genetic and environmental factors, and with possible additional mother-

specific factors, such as placental transmission (e.g. (H. F. Jones et al., 2021; Mataix-Cols et al., 2018)).

1.6 The role of Infections

Infections may represent another immune insult. The hypothesis that infections can cause mental illness has been reported since 1896, with bacterial (Noll, 2007) and later on viral (Torrey et al., 2006) infections suspected to cause schizophrenia. At the end of last century Streptococcal infections were implied in acute onset of tics ad OCD within the discussed PANDAS ('Paediatric Autoimmune Disease associated with Streptococcal Infection') syndrome (Swedo et al., 1998). Evidence for associations of psychiatric disorders with previous infections has since mounted up. Works come primarily from Scandinavian register studies. Hospital treated infections throughout the lifetime increase risk for subsequent psychotic (Benros et al., 2011; O. Köhler et al., 2016) and mood disorders (Benros et al., 2013; O. Köhler et al., 2016), irrespective of the site of infection, and in a dose-response relationship with the number of infections. Furthermore, infections interact in synergy with diagnosis of AI disorders. More recent works and children studies confirm these associations also for infections treated in primary care (Blomström et al., 2014; O. Köhler et al., 2016) and extend associations to the full diagnostic spectrum, with increased risks also for anxiety, ADHD, OCD, tic disorders, ASD, personality and behavior disorders, and mental retardation (Ole Köhler-Forsberg et al., 2019). The risk appears increased with more severe and bacterial infections (Philip R. Nielsen et al., 2014) and with use of antibiotics (Ole Köhler-Forsberg et al., 2019; Lavebratt et al., 2019) and not of antivirals and antimycotics, and though in some works the risk was higher with time proximity of the infection (Benros et al., 2011, 2013; Ole Köhler-Forsberg et al., 2019), it was still present more than 10-15 years after the last prescription of anti-infective agents (Benros et al., 2011; O. Köhler et al., 2016). Also throat infections in children, especially streptococcal but also non-streptococcal, increased incidence of all mental disorders, and in particular OCD, tics, mood and personality disorders, ADHD (Orlovska et al., 2017). In general risk estimates were attenuated – though still valid – after siblings analysis, that accounts for genetic, familial, and socioeconomic factors (Ole Köhler-Forsberg et al., 2019). Authors make shared considerations. Data suggest that infective processes and/or antibiotic drugs may contribute to the etiology of a wide range of mental disorders: infections may trigger the immune system and damage the BBB, and antibiotics may affect the microbiome and the gut-brain communication. (Benros & Mortensen, 2020; Blomström et al., 2014; Ole Köhler-Forsberg et al., 2019; Lavebratt et al., 2019; D. Martino et al., 2020). Yet, data do not prove causality: they may

also indicate that individuals who will later develop psychiatric disorders might be more susceptible or vulnerable to infections, because of genetic or environmental factors (Benros & Mortensen, 2020; Blomström et al., 2014; Ole Köhler-Forsberg et al., 2019; Lydholm et al., 2019; D. Martino et al., 2020).

1.7 Inflammation as the common soil for the chronic diseases

The observations that significant associations between psychiatric disorders and autoimmune disorders exist for most AI diseases and not a few specific ones (Benros et al., 2011, 2013), that those between psychiatric disorders and infections do not depend on one specific infectious agent or site of infection (Benros et al., 2011, 2013), and the observed comorbidities between psychiatric and CVD and other chronic disorders, have made some authors posit that part of the associations between psychiatric and somatic conditions may be mediated by inflammation. Inflammation would be the "common soil" or pathway for chronic somatic and psychiatric disorders. (Benros, Eaton, et al., 2014; Penninx, 2017; Scrivo et al., 2011)

1.8 The role of stress on health and inflammation

Comorbidity between somatic and psychiatric disorders have also been suggesting shared causal factors. If inflammation is the common soil, are there shared triggers? Psychosocial stress along lifetime may be one of them. Mounting work from the past decades gives support for a role of prenatal, early life and later stress in shaping lifelong health.

Several works have collected epidemiological and experimental evidence for that hypothesis, and describing mechanisms implied. Chronic inflammation appears to be a hallmark across these conditions, and one potential mechanism for stress to be embedded.

This paragraph reviews evidence about the influences on health and inflammation of psychosocial adversities, including prenatal maternal stress, psychosocial stress in early life and stress in adolescence and adulthood.

1.8.1 Prenatal maternal stress: a MIA model

Recent reviews of epidemiological and case-control studies have confirmed that maternal stress in pregnancy affects offspring neuro- and cognitive development, and associates with negative affectivity, difficult temperament and psychiatric disorders (Van den Bergh et al., 2017), and neurodevelopmental disorders in particular (Manzari et al., 2019).

Meta-analyses have also shown associations with physical outcomes, as asthma, allergic (Flanigan et al., 2018; Van De Loo et al., 2016) and atopic disorders (N. W. Andersson et al., 2016).

Implied biological systems are the same described in the general MIA model: changes in immune system and microglia, in HPA axis, Autonomic Nervous System, in gut microbiome, in telomere biology, with a possible mediation by epigenetic changes (reviewed in (Cao-Lei et al., 2016; Van den Bergh et al., 2017).

A large body of clinical and preclinical research suggests that maternal inflammation would be one mediator of the consequences of maternal psychosocial stress (reviewed in (Hantsoo et al., 2019)). In rodents, stress can increase inflammation peripherally and at the placenta, and induces behavioral dysregulation in offspring, showing causal links (Bronson & Bale, 2014; Mueller & Bale, 2008). In humans, maternal stress associates with elevated peripheral IL-6, IL-8 and TNF-α during pregnancy (Niklas W. Andersson et al., 2016; Blackmore et al., 2011; Coussons-Read et al., 2012; Stephen E Gilman et al., 2017; Walsh et al., 2016; R. J. Wright et al., 2010). As seen above in MIA

section, these three proinflammatory cytokines mediated relationships between MIA and offspring outcomes in clinical studies (Coussons-Read et al., 2012; Graham et al., 2018; G. E. Miller et al., 2017; J. M. Rasmussen et al., 2019; Rudolph et al., 2017).

Prenatal stress configures therefore as one model of MIA, leading to the same consequences that MIA can have.

1.8.2 Psychosocial stress in early life

Psychosocial stress in the early years of life have shown to have lingering influence on physical and mental health, leading to increased rates of morbidity and mortality from chronic diseases of aging and to increased risk for psychiatric disorders.

Early life stress includes difficulties that fall outside children normative experiences in developed countries (e.g. maltreatment), and that are prolonged in time (e.g. recurring conflict between parents, or a lack of material resources due to poverty). Stressors of acute duration generally do not make lasting imprints on physiology, unless they bear lasting consequences (Dickerson & Kemeny, 2004; Segerstrom & Miller, 2004).

The most investigated adverse childhood experiences (ACE) include childhood neglect, physical, sexual, and emotional abuse, witnessing domestic violence, bullying, parental death, low socio-economic status (SES). Yet, also more trivial stressors as e.g. parental divorce have shown important consequences.

Meta-analytic and population studies have confirmed consequences of ACE on mental and physical health.

Recent meta-analyses have shown that over one third of psychosis cases (Varese et al., 2012), and over one-half of global depression and anxiety cases (M. Li et al., 2016) are potentially attributable to ACE, and that ACE are associated with two- to three-fold increased risk for both suicidality and suicidal attempts in adults, with higher risk in case of complex childhood abuse (Angelakis et al., 2019). Studies underline also the impact of more silent and common childhood adversities on future mental health. In a meta-analysis studying the relation of depression with each type of ACE, psychological abuse presented the strongest association with depression, followed by neglect and physical abuse. Authors evidenced the impact of more “silent” forms of maltreatment, other than physical and sexual abuse, on later depression (Infurna et al., 2016). Populations studies suggest

that also stressors that are more common and trivial than overt abuse, such as parental divorce, relate to lifetime psychopathology independently of, and in synergy with, other childhood adversity (Afifi et al., 2009).

Parallelly, evidence has accumulated for ACE increasing risk for later physical illness. A meta-analysis on over 48,000 subjects found that childhood neglect, physical, sexual, and emotional abuse, were associated with an increased risk of negative physical health outcomes in adulthood, so that individuals maltreated as children, had outcomes more severe or more common by almost a half standard deviation, than individuals not-exposed to maltreatment. Neurological and musculoskeletal problems yielded the largest effect sizes, followed by respiratory problems, cardiovascular disease, gastrointestinal and metabolic disorders. (Wegman & Stetler, 2009)

Another recent meta-analysis on over 240,000 subjects found significant effects of cumulative childhood adversity on adult cardiometabolic disease (Jakubowski et al., 2018).

Increased risk for autoimmune diseases is also described: the Adverse Childhood Experiences (ACE) study, a large retrospective cohort study on over 17,000 subjects in a metropolitan area, found that ACE increased risk for later autoimmune (and in particular rheumatic) diseases (Dube et al., 2009); and The Nurses' Health Study II, a prospective cohort study of 67,516 US female nurses enrolled in 1989 and followed with biennial questionnaires, recently found that childhood physical and emotional abuse significantly increased risk of Lupus, making authors conclude that exposure to childhood adversity may contribute to Lupus development (C. H. Feldman et al., 2019).

Effects of low SES have also been investigated as a single, independent risk factor: low SES increases risk for CVD by 20-40% after adjusting for adult SES (reviewed in (Bruna Galobardes, Smith, et al., 2006)), and was associated to higher mortality risk from all causes, cardiovascular, coronary heart disease, stroke, lung and stomach cancer, and respiratory disease in the Glasgow longitudinal study cohort on approximately 10,000 university students (Bruna Galobardes, Davey Smith, et al., 2006).

These data suggests that many adult somatic diseases should be viewed as developmental disorders that begin early in life, facilitated by early adversities (Shonkoff et al., 2011).

Some studies suggest a dose-response effect on both mental (Afifi et al., 2009; Edwards et al., 2003) and physical (Anda et al., 2009; Dong et al., 2004) outcomes. A recent meta-analysis on 37 studies with a total of over 250,000 participants, estimated health risk for individuals exposed to at least 4 ACEs. It confirmed that having multiple ACEs is a major risk factor for various conditions, with weak associations (OR <2) for physical inactivity, overweight or obesity, and diabetes; moderate associations (ORs 2-3) for smoking, heavy alcohol use, poor self-rated health, cancer, heart disease, and respiratory disease, strong associations (ORs 3-6) for sexual risk taking, mental ill health, and problematic alcohol use, and strongest ones (ORs >7) for problematic drug use and interpersonal and self-directed violence. (Hughes et al., 2017)

Effects visible from childhood: The effects of ACE on health might become evident already from childhood. A recent review on 35 longitudinal studies found that exposure to childhood adversity is associated with delays in cognitive development, asthma, infection, somatic complaints, and sleep disruption. Maternal mental health issues were associated with elevated cortisol levels, and maltreatment was associated with blunted cortisol levels in childhood. Furthermore, exposure to childhood adversity was associated with alterations of immune and inflammatory response and stress-related accelerated telomere erosion.(Oh et al., 2018)

The role of inflammation: Several studies have looked at and found associations between psychosocial stress in early life and subsequent higher inflammation. Meta-analyses and systematic reviews confirm that history of childhood adversities associates with increased inflammation markers in adult life: CRP, fibrinogen, and inflammatory cytokines as interleukin IL-1β, IL-6, and TNF-α (Baumeister et al., 2016; Coelho et al., 2014; Deighton et al., 2018; Lanius, 2014). In Baumeister's meta-analysis individuals with a history of childhood trauma showed an average CRP increase of 0.84 mg/l, or a mean CRP value of 3.5mg/l, above the threshold of 3 mg/l acknowledged as risk factor for future heart attack, stroke and development of diabetes (Ridker, 2003).
These works include adversities as 'Child Maltreatment', 'Childhood Trauma', 'Early Life Stress', 'Psychological Stress', 'Emotional Stress', 'Child Abuse' and 'Child Neglect'. Even a more silent adversity as social isolation would associate with later inflammation: a large longitudinal study on

7,462 participants of the National Child Development Study in Great Britain, found that socially isolated children (7—11 yrs) had higher levels of C-reactive protein in mid-life (44 yrs). In addition, children who were socially isolated tended to have lower subsequent educational attainment, to be in a less advantaged social class in adulthood, to be more psychologically distressed across adulthood and to be obese and smoke. All these factors partially explained the association between childhood social isolation and CRP, that however remained statistically significant after considering all mediators simultaneously (Lacey et al., 2014).
Similar findings came from the Dunedin cohort: childhood social isolation was associated with cardiovascular risk factors at age 26 (Caspi et al., 2006), and with a 60% increased risk of a CRP value >3 mg/L at age 32 (Danese et al., 2009).
Lower SES in childhood associates also with increased inflammation in adulthood in two recent meta-analyses, with effects though strongly attenuated/no longer significant when adjusting for BMI (R. S. Liu et al., 2017) or for adult SES (Milaniak & Jaffee, 2019) , suggesting a possible influence of childhood SES on health risk behaviors (Milaniak & Jaffee, 2019).

Various authors posit that inflammatory activation as a consequence of childhood trauma is a subtle effect, and likely one mechanism underlying risk of health problems in survivors of childhood adversities (Baumeister et al., 2016; Lanius, 2014). In this light, Shonkoff suggests that many adult diseases could be viewed as developmental disorders that begin early in life, and are associated with increased inflammation (Shonkoff et al., 2011).

An open question is whether higher inflammation is present already from childhood. Evidence is not conclusive. A recent meta-analysis has analyzed association between early life adversity exposure and circulating markers of inflammation in children and adolescents, namely CRP and IL-6 (Kate R. Kuhlman et al., 2019). Associations for both markers were small and nonsignificant when subjected to meta-analysis, although comparable in magnitude to the effects observed in adult samples. Yet, most studies that analyzed stimulated production of inflammatory cytokines in vitro, found association between early life adversity and exaggerated production of cytokines in vitro. Authors conclude that evidence supporting an association between early life adversity and

inflammation in pediatric samples is still limited and heterogeneous, and advocate for more research.

1.8.3 Stress in adolescence and adulthood

Besides stress in early life, also psychosocial stressors in adolescence and adulthood associate with health consequences and elevated levels of inflammatory activity, according to a vast body of research. Such effects have been detected for both acute and chronic forms of life stress, and are particularly strong for social stressors involving conflict, threat, isolation, and rejection (Hostinar et al., 2015; Slavich & Irwin, 2014).

Stressful experiences in adulthood, especially when severe and chronic (e.g. low SES, familial caregiving, job strain, social isolation, low income), are associated with poorer overall health status and higher prevalence of conditions as cardiovascular disease, diabetes and overall mortality (Braveman et al., 2010; Holt-Lunstad et al., 2010; Kivimaki & Steptoe, 2018; Pejtersen et al., 2015; Pollitt et al., 2005).

Adults confronting chronic stressors also display higher levels of inflammatory biomarkers. Correlational studies indicate that social isolation, lack of social support, interpersonal conflict, interpersonal loss are associated with higher IL-6 and CRP (reviewed in (Kiecolt-Glaser, Gouin, et al., 2010)).

Longitudinal studies show that different adversities - job stress, life events, caregiver stress, bereavement, and loneliness – induce increasing in IL-6, TNF-α, CRP, and also NF-kappaβ (a key pro-inflammatory transcription factor) and other inflammatory markers as soluble intercellular adhesion molecule-1 (sICAM-1) and endothelin-1 (ET-1) (reviewed in (Hänsel et al., 2010; Kiecolt-Glaser, Gouin, et al., 2010; Seiler et al., 2020).

Limiting to works that analyze adolescents and young adults, suggests that the same processes occur in this subgroup: negative social interactions involving friends, peers, teachers, or family members in daily life are associated with elevations in several markers of inflammatory activity, including CRP, IL-6, and a soluble receptor for TNF-α (Chiang et al., 2012; Fuligni et al., 2009; Marin et al., 2009), as higher mRNA for both NF-κB and I-κB (M. L. M. Murphy et al., 2013).

Low socioeconomic position and non-white race are also associated with elevated CRP levels among adults also after adjustment for confounders ((Nazmi & Victora, 2007) for a meta-analysis).

Acute stressors can also induce transient increase in inflammatory markers. A meta-analysis on studies measuring inflammatory reactions to exposure to laboratory challenge, found increased circulating IL-6, IL-1β, IL-10 and TNF-α, not CRP, and increased in-vitro stimulated IL-1β, TNF-α and marginally IL-6 (Marsland et al., 2017). Preliminary works suggest that acute stress increases also gene expression, i.e. RNA, both of cytokines and of other pro and anti-inflammatory markers, as e.g. NF-κB and its inhibitor IκBα (Kuebler et al., 2015; McInnis et al., 2015). There is also meta-analytic evidence for increase in some salivary cytokines after acute stress (Szabo et al., 2020). Less recent data are available on naturalistic acute stressors, that possibly have a stronger impact on endocrine and immune system, than laboratory ones (Rohleder et al., 2007). In the seminal meta-analysis from Segerstrom and Miller (Segerstrom & Miller, 2004) acute naturalist stressors associated with changes in cytokines, as decrease in IFNγ and increase in IL-6 and IL-10, interpreted as a shift away from cellular immunity (Th1) and toward humoral immunity (Th2).

1.8.4 Stress: conclusions from epidemiological evidence

This vast literature suggests that early-life and adulthood stress is associated with elevated risk of both mental and physical health problems, and that systemic low-grade inflammation may be a pathway linking adversity with morbidity and mortality. (Lanius, 2014)

1.9 Mechanisms for stress to affect health

How can stress can get embedded “under the skin” and induce inflammation and disease? Which are the processes in play?

Rich work in the past two decades has described specific biological mechanisms, reviewed in this paragraph. Stress can affect the hypothalamic-pituitary-adrenal axis (HPA-axis), the Sympathetic Nervous System (SNS), the immune system (IS), the function of microglia and other brain cells, the development of neural regions and networks, epigenetic programming, telomere length, the microbiome.

1.9.1 Stress and the HPA axis

Functions of the HPA axis

The purpose of the HPA-axis is to promote adaptation to environmental stress and maintain homeostasis. Activation of limbic system due to threat activates the paraventricular nucleus (PVN) of the hypothalamus, that secretes corticotropin releasing hormone (CRH) and vasopressin (AVP) to the anterior pituitary gland, which in response secretes adrenocorticotropin hormone (ACTH). ACTH stimulates the adrenal gland to increase production and release of cortisol. Much of circulating cortisol is immediately bound to cortisol binding globulin. The bound fraction of the hormone has limited biologic activity. In its unbound form, cortisol is lipid soluble, and enters all cells of the body and binds to glucocorticoids receptors (GRs), which reside mainly in the cell body. Once bound, the hormone-receptor complex translocates into the cell nucleus and interacts with glucocorticoid responsive elements placed in the promotor regions of numerous genes, regulating up to 20% of the genome (Doom & Gunnar, 2015; M R Gunnar et al., 2015).

Cortisol is essential for the maintenance, duration, and downregulation of the stress response. (Kate Ryan Kuhlman et al., 2017). Also proinflammatory cytokines, as IL-1, IL-6, and TNF are potent stimulators of CRH and of HPA axis (CL Raison et al., 2003).

GRs are expressed in nearly all nucleated cells, and their effects differ by cell type.

One critical function of glucocorticoids (GC) is to down-regulate inflammation (Stark et al., 2001). Binding of GRs in immune cells reduces cytokine production (Silverman et al., 2005), and increases

production of anti-inflammatory factors as inhibitor of nF-kb (CL Raison et al., 2003). Yet, GC action on immune cells is more complex than purely anti-inflammatory: GC promote the expression of various genes involved in the inflammatory cascade (as e.g. TLR2, TLR4, NLRP3) (Busillo & Cidlowski, 2013) as well as the expression of several cytokine receptors, including the receptors for TNF, IL-1, IL-6 and IFNγ (Wiegers & Reul, 1998). Such changes would render cells more sensitive and reactive to potentially harmful stimuli as DAMPs, PAMPs and inflammatory cytokines. Increases in circulating GC concentrations triggered by physiological or other stressors may thus serve as a systemic warning system against potential insults (Cain & Cidlowski, 2017). Besides, the same stimuli that up-regulate the HPA axis and increase cortisol production, down-regulate the sensitivity of GRs on immune cells, thus reducing the extent to which cortisol can inhibit inflammation (Stark et al., 2001).
Some authors suggest that GC physiology on immune system follows a biphasic dose–response curve, such that they have immunosuppressive effects at high concentrations, and immunostimulatory effects at low concentrations, as e.g. seen with a chronically hyperactivated HPA axis. This immunostimulatory function would allow for the rapid detection of potential dangers and promote the induction of a rapid inflammatory response upon tissue insult. (Cain & Cidlowski, 2017; Munck & Náray-Fejes-Tóth, 1992; Sapolsky et al., 2000).

GC act also on brain cells, where they bind both GC and mineralcorticoid receptors (MRs), which, in the brain, regulate many of the non-stress actions of GC. GR have the lowest affinity and thus in the brain are only bound as GC rises into stress levels and at the peak of the diurnal rhythm.
In the brain GC exert their negative feedback action on HPA axis*,* and act on a range of other brain structures involved in cognitive, emotional and behavioral processes, as hippocampus, amygdala, and prefrontal regions (reviewed in (Rohleder et al., 2010)). GC enhance memory consolidation but impair long-term memory retrieval and working memory (Rohleder et al., 2010) and impact on neural systems associated with arousal, reward, fear/threat, and loss (Adam et al., 2017).

In a typical stress response, cortisol levels increase sharply following the onset of a stressor, reaching their peak after about 20–25 minutes before slowly decreasing back to baseline levels. However, because the genomic effects of cortisol can take minutes to hours to come to fruition,

the impact of cortisol on the brain and body are experienced long after cortisol has returned to baseline (Joëls & de Kloet, 2017).

GC also follows a diurnal pattern that contributes to our circadian rhythm (Gunnar et al., 2015). Serum cortisol increases sharply upon waking, with a peak 30–45 minutes after wake-up termed the cortisol awakening response (CAR). Following this initial peak, cortisol decreases throughout the day, reaching the lowest levels 30 min after the start of sleep. (Doom & Gunnar, 2015).

There are multiple pathways that activate GC production: systemic stressors activate the HPA through brainstem pathways, while emotional and cognitive stressors operate through limbic pathways, where the amygdala plays a critical activating role (Joëls & Baram, 2009).

Termination of response operates at the level of the hypothalamus and pituitary, and also extra-hypothalamically, involving the hippocampus and regions of the prefrontal cortex.

The multiple pathways to activate and terminate the HPA response mean that GC responses depend on the specific stressor and are also influenced by the individual's prior exposure to threat and his experiences of control and coping. (Reilly & Gunnar, 2019)

Several dysregulations of the HPA are possible: changes in response to an acute stressor, with exaggerated or blunted responses, alterations in the feedback system, with delayed recovery time after a stressor, or changes in basal levels and circadian rhythms. (Kate Ryan Kuhlman et al., 2017)

Influence of stress on the HPA axis and consequences for inflammation

There is evidence suggesting that stress along lifetime induces lasting changes in HPA activity, with both hyperactive and blunted responses described (reviewed in (Agorastos et al., 2019)). Studies indicate that the effects depend on the *type* of stressor, the *time when* it happened, its *duration*, and the *time interval from* when it happened. (Kate Ryan Kuhlman et al., 2017; G. E. Miller et al., 2007).

Early life and adolescence appear especially important periods for shaping HPA reactivity. There is evidence for that stress-mediating systems, like the HPA axis, are being organized early in life (Danese & McEwen, 2012), and that adversities happening during those sensitive periods shape these systems, which then respond differently from those of unexposed individuals (Reilly & Gunnar, 2019).

Stress in early life may lead to both heightening or blunted cortisol responses in later childhood and adulthood (reviewed in (Kate Ryan Kuhlman et al., 2017)). Prospective and meta-analytic work suggest that early stressors associated with threat/harshness, especially when recent, may lead to HPA hyperactivity (Doom et al., 2020; Fogelman & Canli, 2018), and those associated with deprivation/neglect, lead to hypoactivity (Doom et al., 2020; Reilly & Gunnar, 2019). It is also suggested that these patterns may emerge sequentially during development, with hypercortisolism preceding hypocortisolism (Bernard et al., 2017; Trickett et al., 2010).
Works on institutionalized children suggests that these changes can be partially reversed by placing children in high quality foster care in an early age and avoiding further excessive stressors (DePasquale et al., 2018; Fisher et al., 2007; McLaughlin et al., 2015; Wade et al., 2020).
Adolescence is a period of transition from a naturally hypo- to a naturally hyper-reactive HPA, and some works suggest that this transition also may offer the possibility of restoring a normal HPA (Kate Ryan Kuhlman et al., 2017).

Exposure to stress *in adulthood* would have similar effects on the brain and behavior, of exposure in childhood and adolescence: in case of chronic stress, meta-analysis suggests that an initial hyper-response is followed by a blunted response also in adults (G. E. Miller et al., 2007).
Yet, effects of adult exposure appear reversible in case of time-limited stress: they usually disappear after cessation of the stressor (Lupien et al., 2009).
During adolescence stress would have more important effects on the HPA axis than a similar stress exposure during adulthood, with effects that can incubate until adulthood, at which time they will become apparent (Lupien et al., 2009).
Another common finding after stressful experiences in all ages is a flat diurnal cortisol slope (reviewed in (Kate Ryan Kuhlman et al., 2017; G. E. Miller et al., 2007), described even after early adversities of low degree (Kuras et al., 2017).

The link with inflammation. There is good evidence for that the described changes in HPA following early life or chronic stress associate with and contribute to higher inflammation. A recent meta-analysis (Adam et al., 2017) has described a significant association between flatter

diurnal cortisol slopes and poorer health, with largest effect size for immune/inflammatory outcomes. The association was significant also when the meta-analysis was limited to prospective studies, thus supporting that a flattered cortisol curve may have a causal role on subsequent inflammation and other health outcomes.

A vast literature has also described how dysregulated cortisol levels, whether abnormally low or chronically high, can impair control of inflammatory responses (CL Raison et al., 2003; Sapolsky et al., 2000).

In synthesis, glucocorticoids appear important contributors to the altered immune function and increased inflammation associated with chronic stress (Dhabhar, 2002; Dhabhar et al., 2012).

1.9.2 Stress and the Autonomous Nervous System

The Autonomic Nervous System (ANS), and an imbalance between the Sympathetic (SNS) and the Parasympathetic Nervous System, are also putative mediators between stress exposure and later inflammation.

Stress activates the *SNS*, increasing release of catecholamines in blood and target organs, as bone marrows and spleen. Preclinical studies have shown that SNS activation releases monocytes from bone marrow, and that when stress is prolonged or repeated, hematopoiesis shifts towards production of monocytes, that acquire an inflammatory signature (M. D. Weber et al., 2017). Such monocytes would traffic into the CNS, where they would activate neural stress circuitry (Wohleb et al., 2013) and propagate inflammation to microglia (V. Mondelli & Vernon, 2019; M. D. Weber et al., 2017). Some authors posit that these effects could be more accentuated when stress occurs in early life, as it then could prime microglia and render them more vulnerable to further hits (V. Mondelli & Vernon, 2019).

Up-regulation of the SNS is typically accompanied by down-regulation of the parasympathetic arm (*PNS*), and reduced PNS activity has been associated with increased inflammation (Haensel et al., 2008). Decreased vagal tone and heart rate variability (HRV) have been associated with increase in inflammation, proinflammatory cytokines and acute-phase proteins, besides increased cardiovascular morbidity, overnight urinary cortisol, fasting glucose and hemoglobin A1c levels (reviewed in (Thayer & Sternberg, 2006).

Changes in Autonomic Nervous Systems would therefore create mechanisms that bridge stress with the observed increases in both central and peripheral inflammatory markers (V. Mondelli & Vernon, 2019).

1.9.3 Stress and the Immune System – the role of Monocytes

Some studies indicate that stress can shape over-reactive innate immune cells, that would then produce higher amounts of cytokines and thus create inflammation.

When occurring in early life, stress could prime monocytes and macrophages to respond aggressively to pathogen-associated and danger-associated molecular patterns, and render them less sensitive to glucocorticoid inhibition (G. E. Miller, Chen, et al., 2011; Rook et al., 2014). This pro-inflammatory tendency would first be detectable at intracellular and cellular levels, when looking at gene expression or in vitro stimulation. Elevation of circulating inflammatory markers instead may become evident only later in life, after repeated activation of these primed cells, or manifesting as exaggerated proinflammatory responses to external stimuli (reviewed in (Kate Ryan Kuhlman et al., 2017)).

Children from lower SES families e.g. produce larger volumes of inflammatory cytokines when their cells are stimulated ex vivo with microbial products (Azad et al., 2012; R. J. Wright et al., 2010), and this sensitization remains evident in adulthood (G. E. Miller et al., 2009). Monocytes of low-SES adolescents are also relatively insensitive to inhibition by glucocorticoids (Schreier et al., 2014).

Youth reared in harsh family climates show similar patterns. In longitudinal work, adolescents from harsh families showed over 18 months an increasingly proinflammatory phenotype, with progressively larger ex vivo cytokine responses to lipopolysaccharide (LPS), and declining glucocorticoid sensitivity over time; in ex vivo studies, cortisol became progressively less effective at suppressing LPS-evoked cytokine production (G. E. Miller & Chen, 2010). Such insensitivity to glucocorticoids may be adaptive during acute threats but if sustained would facilitate low-grade chronic inflammation (Slopen et al., 2013).

The priming mechanisms are still being established but likely involve some combination of direct influences, e.g. through pollutants, and indirect influences mediated through hormonal products

of the SNS and the HPA (Nusslock & Miller, 2016). Early stress would e.g. increase the sympathetic innervation of the peripheral stress response systems, and of bone marrow within it. This would enable a rapid and robust response to later acute stress, and the rapid release into circulation of the immature, proinflammatory and glucocorticoid resistant monocytes described (Kate Ryan Kuhlman et al., 2017).

Also acute stress through sympathetic outflow promotes hematopoietic stem cells to differentiate into a glucocorticoid-resistant and primed myeloid lineage immune cell, with activated immune gene transcription (Irwin & Cole, 2011; M. D. Weber et al., 2017)

These activated macrophages have also been involved in the 'cellular pathway', another way by which peripheral inflammation can reach the brain besides cytokine signaling (C D'Mello et al., 2009; A. H. Miller & Raison, 2016). Chemokines as MCP-1 and cytokines as IL-1β, TNF-α, IL-6 produced by activated microglia, would attract monocytes towards the brain vasculature (Charlotte D'Mello et al., 2009), and upregulate adhesion molecules on endothelial cells, facilitating capturing of monocytes towards the brain parenchyma, where they would contribute to neuroiflammation (M. D. Weber et al., 2017) (see also §1.10 for an integrating model).

1.9.4 Effects of stress on brain cells and network development

Stress impacts also on brain cells and circuits. Preclinical evidence suggests that chronic stress affects all brain cells: microglia get activated and primed and generate neuroinflammation, astrocytes show reduced branching and impaired capacity to modulate synaptic environments, pyramidal neurons display decreased synaptic number and activity as well as reduced process branching, with impaired top-down regulation of other brain areas with their projections, oligodendrocytes show reduced capacity for myelination, which further impairs the potential for neuronal signal transduction, and increases susceptibility of neurons to damage (Kaul et al., 2021). Here again, cells and networks would be especially vulnerable in periods of rapid development, as early life and adolescence, where effects of stress may shape lasting consequences across the life-course (Kaul et al., 2021), and cells and circuits would become more sensitive to subsequent stressors (Daskalakis et al., 2013). When stressors occur for first time in adulthood, they may have less persistent consequences, with an easier return to homeostasis when stressors are removed (Kaul et al., 2021).

Among consequences of early and chronic stress are persistent impairments in prefrontal, limbic and hippocampal circuits (McLaughlin et al., 2016; K. E. Smith & Pollak, 2020), altered functional connectivity in circuits related to processing of emotion and reward (Herzberg & Gunnar, 2020) , and imbalance between the excitatory and inhibitory systems, in favor of excessive inhibitory tone (Page & Coutellier, 2019).

As a common mechanism, various works propose that neuroinflammation is at the center of dysregulation after stress exposure (Baumeister et al., 2016; Danese et al., 2008; A. H. Miller & Raison, 2016; V. Mondelli & Vernon, 2019)

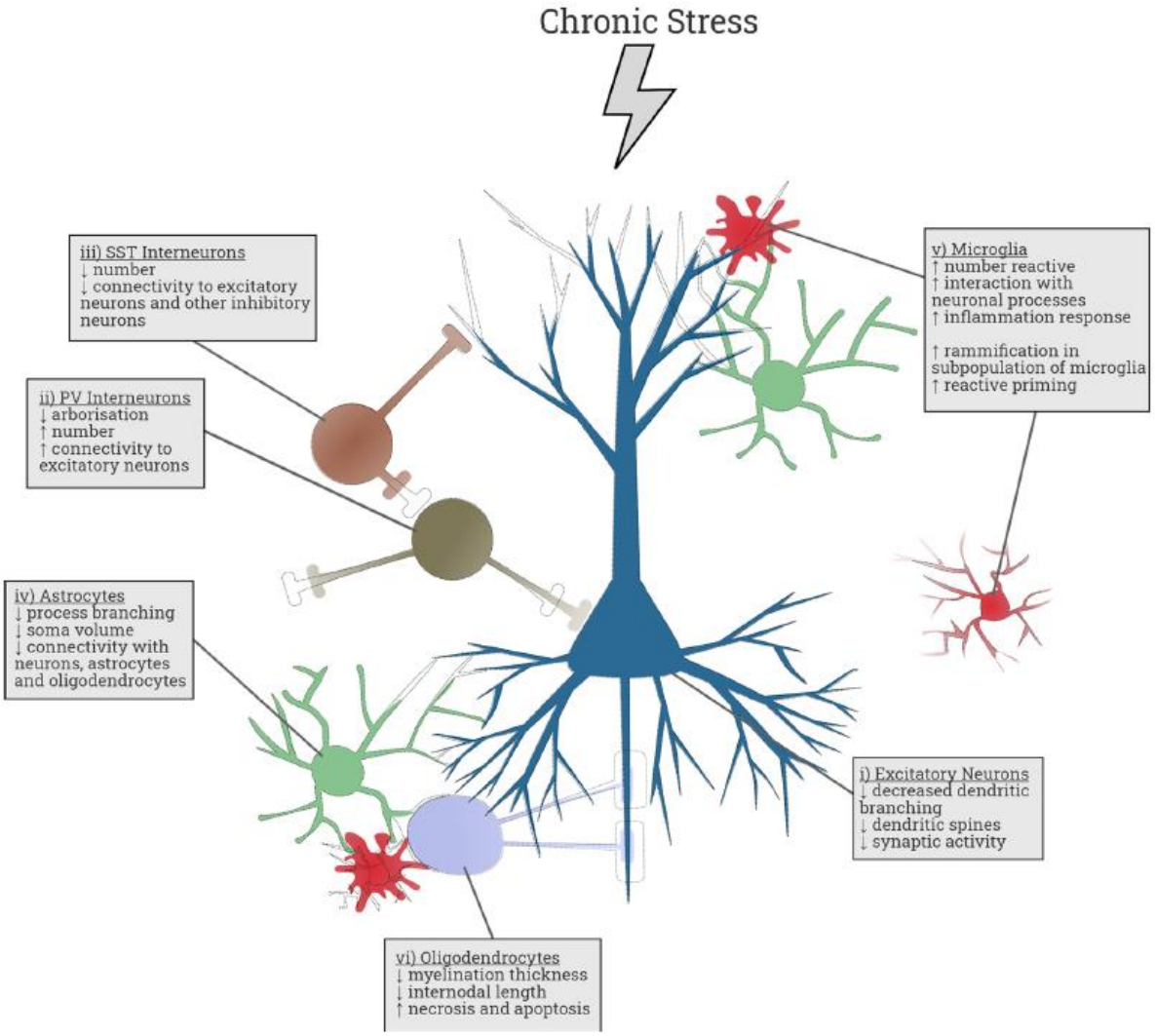

Figure 2 - from (Kaul et al., 2021)
Model of cellular impacts of stress based off of evidence from the prefrontal cortex. Stress-induced changes are highlighted by the dotted outline. In control, non-stressed individuals, excitatory and inhibitory balance is maintained through attenuation of inhibitory and excitatory neurons. Glia provide important and diverse

roles and form a closely communicative and tightly coordinated network which maintains homeostatic control. Following severe psychological stress, broad structural and functional consequences are seen across cellular networks (highlighted by dotted outlines). Changes to morphology are seen after several different stress exposures but are most substantial in stress-susceptible individuals, during key neurodevelopmental stages (e.g. early-life). Chronic dysregulation of cell-to-cell communication due to cell morphology changes can contribute to the development of cognitive and emotional impairments, which are hallmark symptoms of psychiatric disorders. Specifically: i) Excitatory (pyramidal) neurons display decreased synaptic number and activity as well as reduced process branching, impairing top-down regulation of other brain areas with their projections, as well as integrative capacity of the PFC; ii) Although parvalbumin (PV)- expressing interneurons display decreased branching, they maintain increased number and connectivity with excitatory neurons, dampening the capacity for topdown control of the prefrontal cortex (PFC); iii) Somatostatin (SST)-expressing interneurons display decreased branching and also reduced connectivity with neurons and other interneurons, promoting greater inhibitory actions; iv) Astrocytes display impaired capacity to modulate synaptic environments, further impairing neuronal function and can also impair the function of other glia, such as oligodendrocytes; v) Chronic neuroinflammation caused by increased reactivity and potential reactive capacity of microglia, in conjunction with increased interaction with other cells, contributes to impairments seen in other cellular populations. A population of microglia are also hyper-ramified following stress; vi) Reduced myelination via oligodendrocyte changes further impairs the potential for neuronal signal transduction, as well increases susceptibility of neurons to damage. This may be due to both direct effects of stress on oligodendrocytes as well an impairment of astrocytes and microglia which are important to oligodendrocyte maintenance.

Interplay between monocytes, microglia and neurons: preclinical studies from Godbout group & implications

In studying effects of stress on cell types, it is important the series of preclinical experiments by Godbout and colleagues, that shade light on the intertwined roles of monocytes, microglia and neurons after repeated exposure to stress (D. B. McKim et al., 2018; Daniel B McKim et al., 2016; M. Weber et al., 2017; M. D. Weber et al., 2019; Wohleb et al., 2015).

Investigators exposed rats first to repeated social defeat (RSD), a preclinical model of stress that causes persistent anxiety-like behavior, and 24 days after that, to a subthreshold stressor, i.e., a stimulus that does not trigger such behavior in naïve mice. They eliminated microglia at different timepoints and allowed them to repopulate. Animals were considered *sensitized* to stress, if they experienced anxiety after the subthreshold restimulation.

Results showed that: anxiety-like behavior triggered by RSD is dependent on recruitment of inflammatory monocytes from the spleen to brain regions associated with fear circuitry; that sympathetic nervous system drives production and release of monocytes, while microglia and chemokines drive their recruitment. These inflammatory monocytes are characterized by glucocorticoid insensitivity, elevated expression of receptors for pathogen-associated molecular patterns, and higher expression of proinflammatory cytokines as IL1-b, and this latter is required for induction of anxiety-like behavior.

RSD induced also stress sensitization, where recurrence of anxiety was again dependent on monocytes, and presence of microglia necessary for their recruitment. Microglia did get primed after RSD – showing sustained increased expression of several immune-related genes, and activation of pathways as IL-1b, IFN-gamma, also 24 days after RSD – but priming was not necessary for sensitization to manifest, as sensitization manifested also with repopulated microglia. This made researchers posit that there should be other CNS components involved in stress sensitization besides microglia. They investigated neurons, finding that after the second stimulus neurons in regions involved with fear and threat appraisal showed increased activity in a well-characterized marker of neuronal plasticity: pCREB (phosphorylated cAMP-responsive element-binding protein). They concluded that this may indicate *neuronal sensitization*, i.e. a sensitized neuronal reaction to acute stress after previous RSD. These sensitized neurons may in turn cause microglial activation.

The group also analyzed what happened when the 2nd insult was a subthreshold peripheral immune challenge instead. They found that a prolonged sickness response happened only in RSD-sensitized mice, where it was mediated by microglia priming, and prevented by microglia replacement, without involvement of neuronal activation.

Authors concluded that in case of a 2nd stressor of psychological nature, communication would go from neuronal to immune system, and in case of a 2nd stressor of immunological nature, communication would go from immune system to the brain (D. B. McKim et al., 2018; M. D. Weber et al., 2019; Wohleb et al., 2011, 2012, 2014).

If the same mechanisms apply to humans, prolonged/intensive stress in vulnerable development windows would sensitize neurons, microglia and macrophages, rendering the organism more vulnerable to subsequent psychosocial or immunological stressors. A second insult acting on the SNS could trigger anxiety-like responses, while one acting as an immunological challenge, could trigger amplified depressive-like responses.

Such a sensitization would be in line with the two-hit hypothesis of mental illness, that posits that insults during early life sensitizes the Immune System and microglial cells in particular, rendering the organism over-reactive to later stressors. This exaggerated elevation of microglial reactivity to stress in late adolescence or adulthood, would lead to brain changes that underlie the development of some mental disorder (Calcia et al., 2016; Hickie et al., 2009)

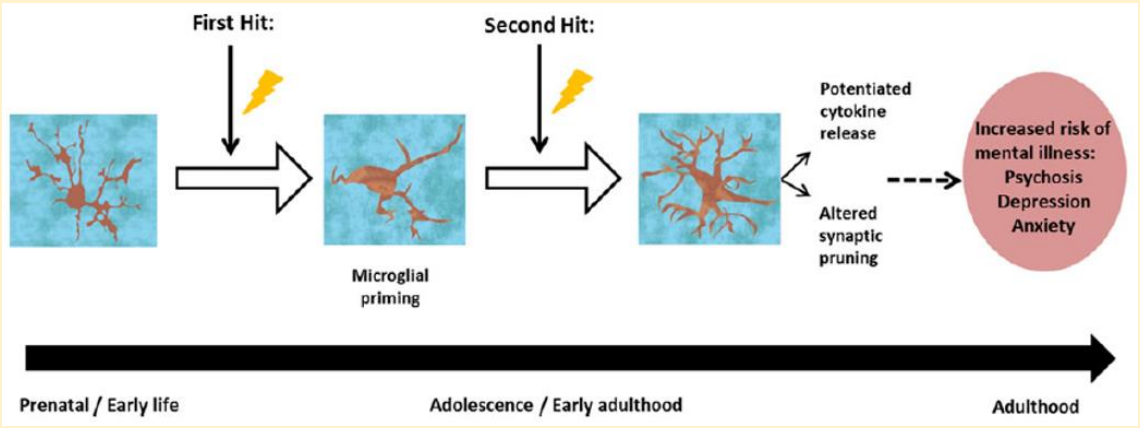

Figure 3: . From (Calcia et al., 2016)

The 'two-hit' hypothesis: exposure to prenatal/early-life stress (lightning bolt) may act to prime microglia within the CNS so that a subsequent challenge later in life, either in adolescence or adulthood invokes a potentiated microglial response, leading to an increased risk of developing a mental illness

1.9.5 Stress and telomere length

Telomere length is an emerging marker of biological age and oxidative stress, with shorter length being associated with accelerated biological aging, premature cell death and increased morbidity and mortality from age-related diseases (M. J. J. D'Mello et al., 2015; Shalev et al., 2013). There is increasing evidence that stress accelerates the erosion of telomeres from very early in life and possibly even influences the initial setting of telomere length.

Recent review and meta-analyses show that stress in childhood associates with shorter telomere length (TL) in children (Coimbra et al., 2017) and in adults exposed to childhood stressors (Hanssen et al., 2017; Z. Li et al., 2017). Also long lasting exposure to chronic stress in adults associates with shorter TL in reviews and longitudinal studies (Meier et al., 2019; Oliveira et al., 2016).

TL reflects the history of oxidative stress and chronic inflammation, and there is preclinical evidence that telomere dysfunction can affect metabolic and mitochondrial function (Sahin et al., 2011). Shorter telomere length could thus contribute to mediating the long-term biological impact of stress on health.

1.9.6 Stress and microbiome

The microbiome is an integral part of human physiology, and recent studies have shown that changes in the gut microbiota can modulate gastrointestinal physiology, immune and microglia function, and behavior (Erny et al., 2015; Rudzki & Maes, 2020; Vuong & Hsiao, 2017), so much that the term Microbiota-Gut-Immune-Glia (MGIG)-Axis has been coined (Rudzki & Maes, 2020)r. Stress of various kinds can increase permeability of the intestinal barrier, leading to subsequent inflammation, and risk for psychiatric and autoimmune diseases (Rudzki & Szulc, 2018). Implied mechanisms are: transfer of non-pathogenic commensal bacteria and derived microbial-associated molecular patterns (MAMPs) from the gut into the peripheral circulation, where they contribute to systemic inflammation; food-derived antigens with neurotransmitter (e.g. exorphins) or immunogenic (e.g. gluten) properties, and possible cross-reaction with brain antigens (reviewed in (Rudzki & Szulc, 2018).

1.9.7 Stress and timing. The three main hypotheses: stress generation, stress sensitization, and stress accumulation

Some of the key questions researchers have faced have been: are there sensitivity windows where stress and insults can be more harmful, that is, are the effects of stress in early life qualitatively different than effects later in life? And if so, how does that happen? Does stress in early life impact on later lifestyle habits? Does it alter regulating systems that are under shaping in the early development? Or is it just a matter of global amount of stress?

Three competing, or rather, complementary models describe the lifelong effects of stress and inflammation on health: the stress generation, the early life stress sensitization, and the stress accumulation model (Hostinar et al., 2015).

In *stress generation models*, childhood adversity is a risk factor for later inflammation because it correlates with, or generates, adult stress. It is this later exposure that largely explains any variance associated with childhood adversity (Hammen, 1991). This effect can unfold in various ways.

One way is *environmental continuity*, where low socioeconomic status (SES) in early life associates with lower adult SES, lower educational attainment and social positioning, and these would partly mediate the relation between low early SES with higher mortality (B. Galobardes et al., 2008). Childhood stressful experiences can also influence one's mental approach to life, shaping a lasting vulnerability to stress. Early adversities can shape *cognitive biases* towards threat, where threatening stimuli are allocated more attentional resources (Shackman et al., 2007), and even ambiguous stimuli are interpreted as dangerous (Edith Chen et al., 2009), increasing risk for anxiety and stress over the lifespan. Early adversities can also impair development of *self-regulation skills* (Blair & Raver, 2012) and of *abilities for getting support* from close others in adulthood (Fagundes et al., 2011), reducing thus capacity to cope with stress. Trauma in childhood increases *likelihood of being re-exposed* to traumatic events in adolescence or adulthood, by continued exposure to violent environments or by affecting the survivors' behavioral, emotional and cognitive patterns (Widom et al., 2008).

All these influences together increase the odds that childhood adversity can directly or indirectly generate adult stress.

In *stress accumulation models*, childhood and adult stressors have independent and *additive associations* with health and inflammation later in life. It is the accumulation of adversity over time that explains gradients in health, based on total stress exposure, without interactive or multiplicative effects (G. W. Evans et al., 2013; G. W. Evans & Kim, 2010). Low SES along life can promote exposure to multiple stressors and tax many physiological systems, leading to *cumulative "wear and tear"* on the organism, accelerated aging and ultimately to heterogeneous disease processes (G. W. Evans et al., 2013; Seeman et al., 2010). This model fits some outcomes: a review found that total exposure to low SES and negative experiences across any life stages was related to poorer outcomes and was a stronger predictor on adult cardiovascular outcomes than either adult or childhood SES (Pollitt et al., 2005). Linear dose-response relationships were also found between the number of adversities experienced before age 18, and the prevalence in adulthood of some health conditions - as obesity or number of comorbid psychiatric disorders - but not others as stroke or cancer (Anda et al., 2006; Felitti et al., 1998).

Early-life stress sensitization models predict instead *synergistic effects* between early and later stressors. Stressors occurring early in development would be particularly harmful, as they act during periods of heightened plasticity and structural or functional maturation of many organs and systems. A biological "programming" would occur, that permanently shapes the organism's physiology, in a way that amplifies vulnerability to later disease. This approach roots in the Fetal Origins Hypothesis (Barker, 1998) and its descendent the Developmental Origins of Health and Disease (DOHaD) hypothesis (P. D. Gluckman et al., 2008; Wadhwa et al., 2009) (see §1.10.1). As described above, there is emerging evidence that early-life stress can shape the functioning of various physiological systems - HPA axis, autonomic nervous system, Immune system with hyperactive monocytes and microglia - and brain circuits, with lifelong consequences for inflammation and psychophysical health (M. Gunnar & Quevedo, 2007; Lupien et al., 2009; G. E. Miller, Chen, et al., 2011).

1.10 The theoretical models, from the DOHaD and beyond.

The evidence summarized above, suggests that stress and inflammation shape lifelong mental and physical health, and contribute to chronic diseases.

Even though most of research has been carried out in specific areas, there have been efforts to gather the observations coming from the diverse fields, and to develop unifying models that transversally explain how stress can affect health.

This paragraph will summarize the main approaches research has taken, and some of the models emerged, with special focus on psychiatric conditions.

1.10.1 The Developmental Origins of Health and Disease hypothesis (DOHaD)

The DOHaD Hypothesis is a theory resting on the stress-sensitization hypothesis. It posits that during sensitive windows of fetal and early development, the environment can exert lasting influences on health and well-being, and shape individual risk for chronic illness over the lifespan (Wadhwa et al., 2009). It roots in the Fetal Origins Hypothesis or Barker's hypothesis: during periods of rapid fetal development or change, the organism would be particularly susceptible to environmental influences, and these effects would have persisting consequences for health and disease risk across the life span (Barker, 1998)

Looking at epidemiological data, Barker observed how ischemic heart disease in adult life correlated with low birth weight and adverse intrauterine factors, rather than postnatal variables. He reviewed also how fetal undernutrition at different stages of gestation can promote adaptations in concentrations of placental and fetal hormone, and lead to different metabolic abnormalities in adulthood. He proposed then that "undernutrition during gestation reprograms the relationship between glucose and insulin and between growth hormone and IGF [insulin-like growth factor]", which permanently changes the body's structure, function and metabolism and increases risk for coronary heart disease in later life. (Barker et al., 1993)

From those beginnings, interest in development expanded to recognize "the broader scope of developmental cues", extending from the oocyte to the infant and beyond, and the concept

formed that the “early life environment has widespread consequences for later health” (Barker, 2007).
The DOHaD society was established (https://dohadsoc.org/) with its own journal, the Journal of the Developmental Origins of Health and Disease.

The initial focus on nutrition broadened to include effects of other factors and other time-windows (P. D. Gluckman & Hanson, 2006). The impact on offspring development of factors as stress, mental health, inflammation, infections, and epigenetic factors both in utero (maternal factors) and during early life, has been object of intense investigation in the past 15 years. The need for extending research to paternal factors has recently been advocated for (Sharp et al., 2019)

1.10.2 Integrative models within neurosciences

More specifically within neurosciences, some unifying models are taking shape. This paragraph will focus on three of the most cited ones, that integrate each other: the *Neuroimmune Network Hypothesis, the Social Signal Transduction Theory of Depression,* and the models proposed by Mondelli and Pariante group, with particular focus on microglia and the SNS.
All models attribute special relevance to stressors occurring early in developmental life, i.e. prenatal, infancy, childhood and adolescence, as does the DOHaD hypothesis. Yet, the models have a general validity, and would still hold even if the case was, that the effects of adversity were rather short-lived, and if proximal measures of adversity were more predictive of inflammation and inflammatory outcomes than early life stressors (Kate Ryan Kuhlman et al., 2017)

The Neuroimmune Network Hypothesis – lifelong effects of early stress

Gregory Miller’s group from Northwestern University, has proposed the Neuroimmune Network Hypothesis, a model that synthesizes the information about the multiple impacts of stress in early life on psychophysical health, and about the role inflammation plays in that (Hostinar et al., 2018; Nusslock & Miller, 2016).

Authors posit that there are multiple bidirectional pathways between the immune system and brain circuits, and that early stress amplifies this crosstalk, leading to processes that self-sustain chronic inflammation and its consequences.

They summon evidence on how early stress sensitizes a) the cortico-amygdala network, in way that heightens vigilance for, and reactions to, threatening stimuli, and b) monocytes, that get primed and mount exaggerated responses to new insults. This generates low-grade inflammation, that spreads to the brain where activates microglia and increases cytokines in CNS. This traffic from immune system to the brain would accentuate threat-related processes in the cortico-amygdala circuit, attenuate reward-related processes in the cortico-basal ganglia circuit, inducing "sickness behaviors" like anhedonia, sleep dysregulation, and fatigue, and dampen executive processes related to control functions and linked to regions of the prefrontal cortex (Hostinar et al., 2018; Nusslock & Miller, 2016). This impairment in emotional ad executive functions would then facilitate self-medicating behaviors, like smoking, drug use, and consumption of high-fat and high-sugar diet, which in turn would further enhance inflammation. Such concerted dynamics would accelerate the pathogenesis of emotional and physical health problems.

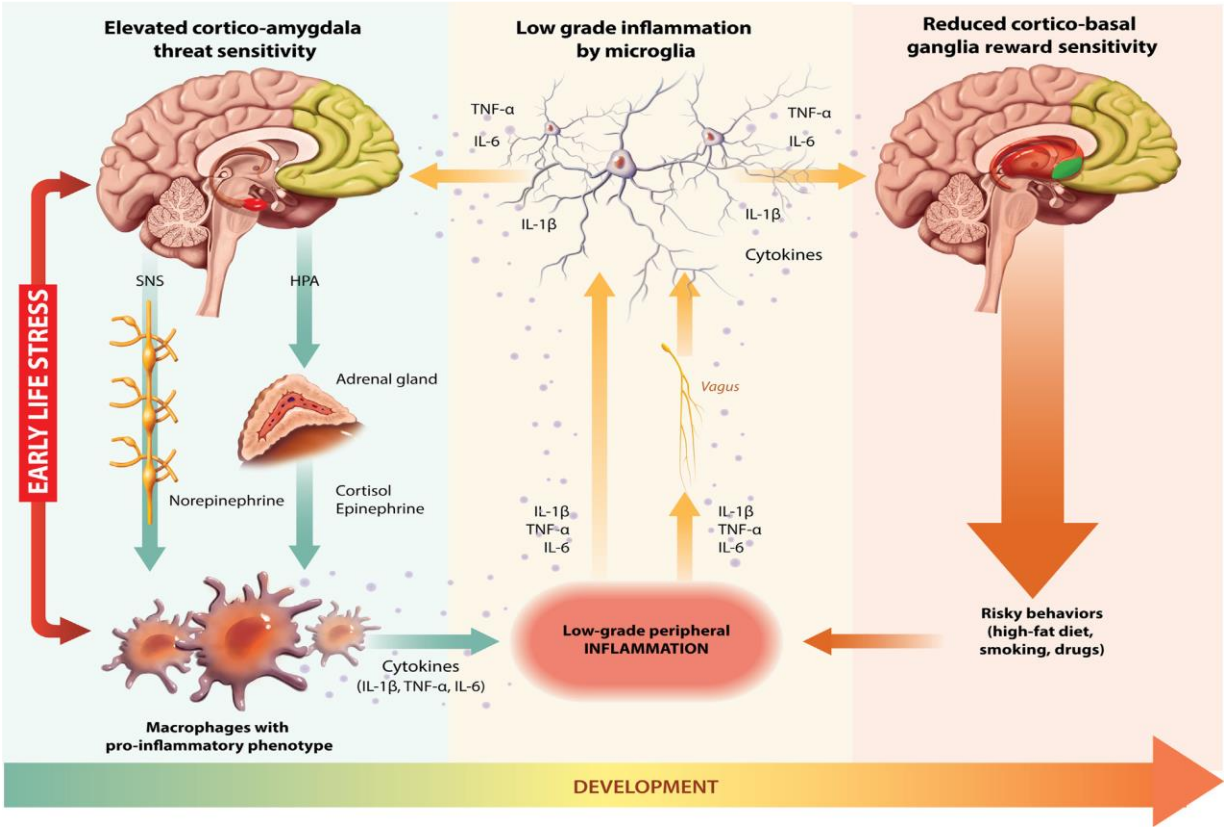

Figure 4. From (Hostinar et al., 2018)
Depiction of the neuroimmune network hypothesis. The cortico-amygdala neural circuit supports vigilance for and responses to threatening stimuli. This circuit includes the amygdala, a limbic region which has been implicated in emotion perception, learning and responding, and the prefrontal cortex, which participates in emotion-regulatory processes by exerting inhibitory top-down control over the amygdala and other limbic regions (Callaghan & Tottenham, 2016). The cortico-basal ganglia circuit supports reward processing and involves projections from midbrain nuclei (e.g., substantia nigra) to subcortical areas within the basal ganglia (e.g., ventral striatum) and cortical target regions (e.g., orbitomedial frontal cortex). Dopamine is the neurotransmitter most directly involved in reward processing within this circuit, playing a central role in incentive motivation, reward-based learning, and motor control (Haber & Knutson, 2009). Abbreviations: HPA = hypothalamic-pituitary-adrenocortical; IL-1β = interleukin-1β; IL-6 = interleukin-6; SNS = sympathetic nervous system; TNF-α = tumor necrosis factor-alpha.

The Social Signal Transduction Theory of Depression

The model proposed by George Slavich and Michael Irwin, University of California, while describing the same mechanisms and mediators already mentioned, puts a special emphasis on a developmental perspective, and on the importance of interpersonal social stressors in activating inflammatory responses and leading to psychiatric symptoms (Slavich & Irwin, 2014).
They note how historically, mounting a high innate inflammatory response to physical threats was protective, as it facilitated recovery from wounding and infections. Nowadays, this same system would be activated by contemporary social threats, that can lead to increased inflammation and the related depressive symptoms (sad mood, anhedonia, fatigue, psychomotor retardation, and social-behavioral withdrawal).

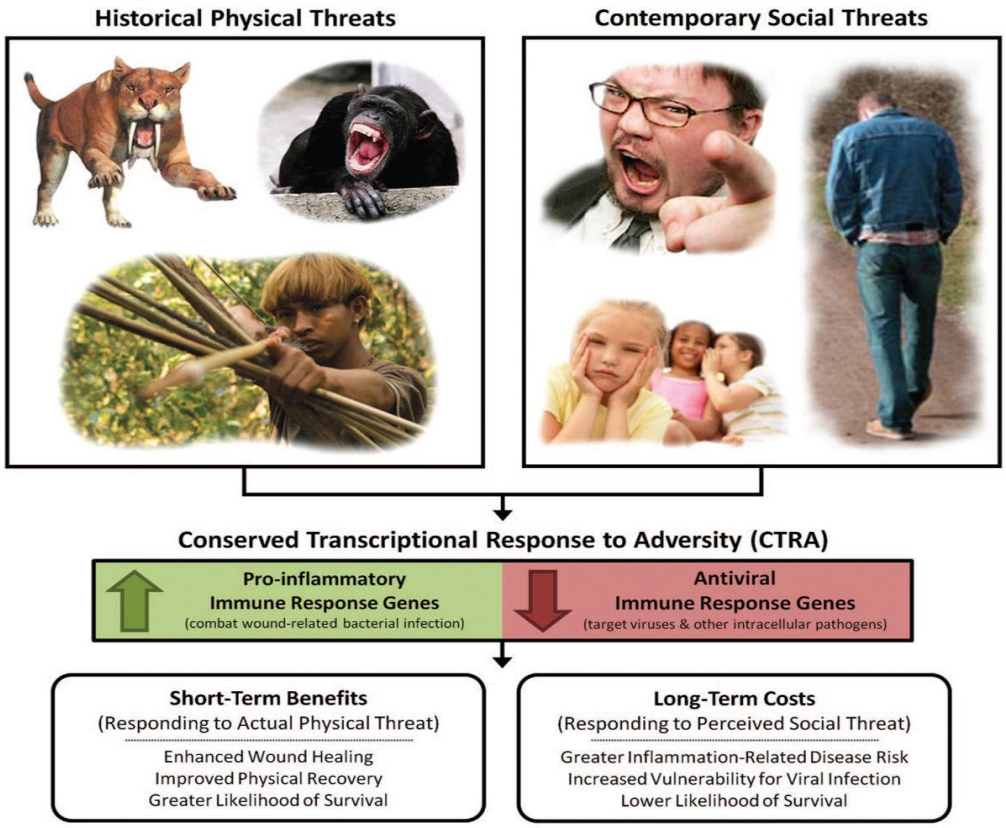

Figure 5 – from (Slavich & Irwin, 2014)
The innate immune system developed to counter physical threats from predatory animals and hostile conspecifics that dominated our ancestral environment. Exposure to these threats activates a Conserved transcriptional response to adversity (CTRA, that involves up-regulation of proinflammatory immune response genes, which combat extracellular pathogens and wound-related bacterial infections, and down-regulation of antiviral immune response genes, which target intracellular pathogens such as viruses. This redeployment of the leukocyte basal transcriptome is adaptive in the context of actual physical threat because it enhances wound healing and recovery from injury and infection. The CTRA can also be activated by modern day social, symbolic, anticipated, and imagined threats, however, leading to increased risk for several inflammation-related conditions, including depression.

Grounding their observation on results from experimental studies using exogenous inflammation and laboratory experiences of social exclusion (Eisenberger, 2012a, 2012b; Eisenberger et al., 2009; Slavich et al., 2010), they argument how social threat can activate brain regions that process experiences related to negative affect and rejection, as the anterior insula and the dACC. These in turn would influence downstream regions as hypothalamus and brainstem, with direct control on HPA axis and SNS, and increase in peripheral inflammation, producing the correlated depressive and anxiety symptoms. Increased inflammation can in turn can enhance neural sensitivity to social rejection: activity in pain-related neural systems and systemic inflammation may thus potentiate

each other, especially in case of repeated or prolonged stressors, and install a recursive loop that leads to increases sensitivity to stressful stimuli, and to self-sustained higher inflammation and risk for depression.

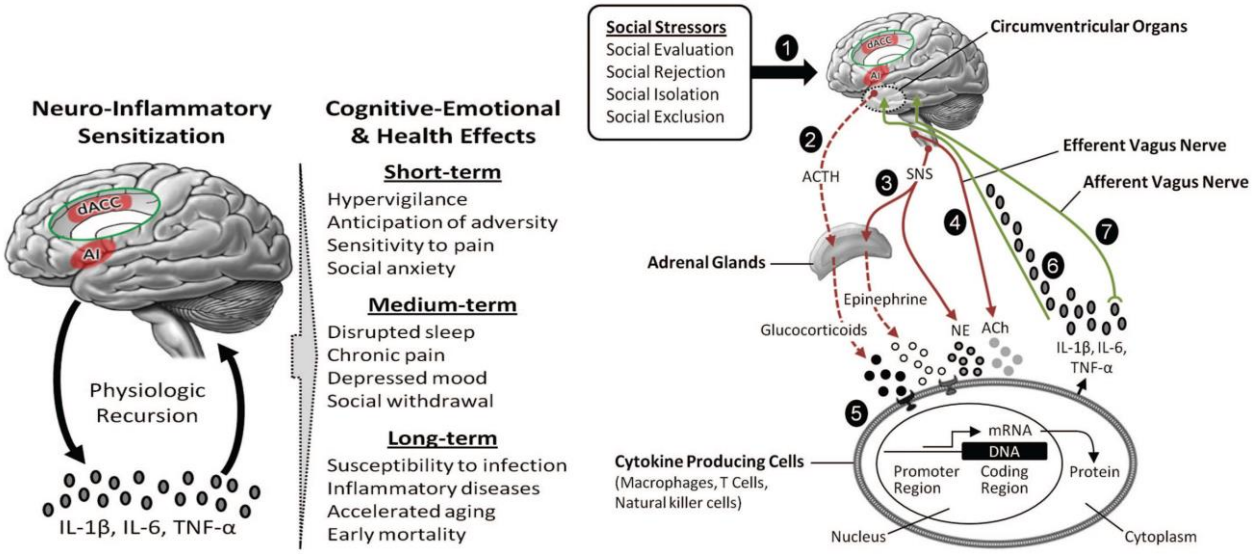

Figure 6 – from (Slavich & Irwin, 2014)
Neuro-inflammatory sensitization to adversity. Bidirectional links between the brain and periphery allow the brain to regulate inflammatory activity, and inflammatory activity to in turn influence neural processes in the brain. This dynamic is initiated by experiences of early life stress or chronic adversity, which promote a proinflammatory skewing of the leukocyte basal transcriptome (i.e., the conserved transcriptional response to adversity [CTRA]) that feeds back on pain-related neural systems to perpetuate subjective perceptions of threat. Brain regions involved in this process include the anterior insula (AI) and dorsal anterior cingulate cortex (dACC, shown in the insert). As a result of this physiologic recursion, experiences of social environmental adversity can become biologically embedded and sustain perceptions of threat for months or years after the original social-environmental impetus has passed. The consequences of these dynamics are multifold and start with increased hypervigilance, chronic anticipation of adversity, sensitivity to pain, and symptoms of social anxiety. As activation of the CTRA persists, somatic and affective symptoms of depression may develop. Finally, after years of sustained engagement, these dynamics may confer increased risk for inflammation-related disorders, infection, accelerated biological aging, and early mortality

They propose that the dynamic can be initiated by experiences of early life stress (sensitization) or chronic adversity (accumulation), which lead to a proinflammatory skewing of the leukocyte basal transcriptome, increase in cytokines and feedback to pain-related neural systems, thus sustain the subjective perceptions of threat. They underline how the system can also be initiated by purely symbolic, anticipated, or imagined threats, and maintained also after the threat has passed, especially if the system has become sensitized by sustained exposures. At the end, these

dynamics may confer increased risk for inflammation-related disorders, infection, accelerated biological aging, and early mortality, as also proposed by Miller's model.
The expression "social signal transduction" refers namely to how experiences of the external social environment can be "transduced" into the internal biological environment.

Models for clustering of stress, inflammation, psychopathology and treatment resistance

Research from King's College and the Maudsley Institute, from Mondelli and Pariante group, focusses on role of stress, microglia and systemic inflammation, in a subset of psychopathology. Drawing from preclinical studies (see e.g. work from Godbout group in box §1.9.4) and human data, they propose that neuroinflammation, and more specifically the activation of microglia, might play a role in the more severe states of psychiatric disorders (Valeria Mondelli et al., 2017; Maria Antonietta Nettis et al., 2020). Such activation would not be specific for any particular diagnostic category, but rather associate with previous stress, peripheral inflammation, and resistance to treatment (as e.g. reported in (Chamberlain et al., 2019; Ebrahim Haroon et al., 2018; Valeria Mondelli et al., 2015; Strawbridge et al., 2015)), with a particular relevance for the role of the SNS, that innervates the bone marrow and shifts to production of proinflammatory macrophages (V. Mondelli & Vernon, 2019)

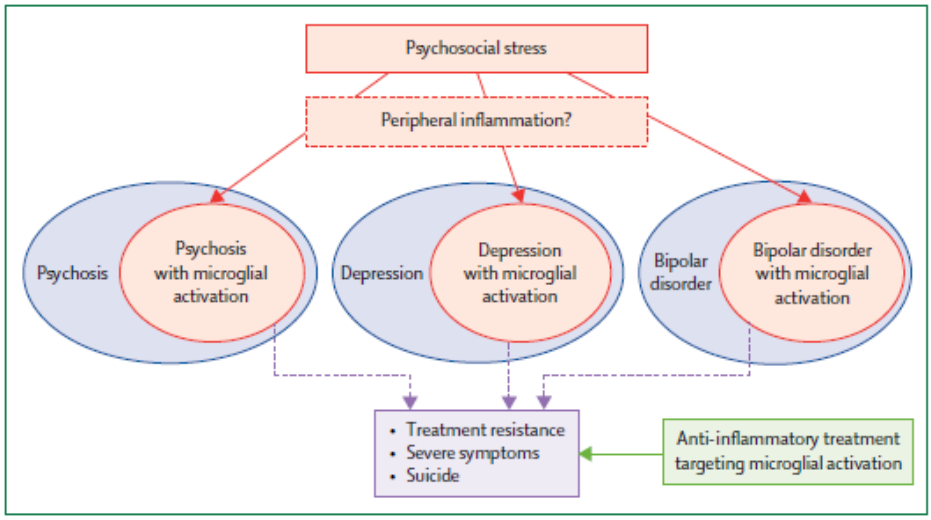

Figure 7: from (Valeria Mondelli et al., 2017)
Proposed model of how psychosocial stress can increase microglial activation in a subsample of patients with psychiatric disorders across different diagnostic categories, possibly through increased peripheral inflammation. The model proposes that patients with increased microglial activation have severe—rather than mild or moderate—psychiatric disorders, and include patients who are more resistant to treatment. Anti-inflammatory treatment targeting microglial activation could specifically be more effective in patients who present increased microglial activation

1.11 A transdiagnostic approach in psychopathology

This introduction has gathered evidence about role of inflammation and stress across the psychiatric diagnostic spectrum. In the original work presented later, we chose also a transdiagnostic approach.

This paragraph reviews the rationale for adopting transdiagnostic approaches in psychiatric research and clinical activity, and the main models that are emerging.

1.11.1 Support for a transdiagnostic approach in psychopathology

Supports for a transdiagnostic approach come from several sources and lines of investigation. Large population studies have shown pervasive comorbidity within mental disorders throughout the lifetime, with chances of getting an additional diagnosis after the first one reaching 45%-54% in some community surveys (Kessler et al., 2005; McGrath et al., 2020; Plana-Ripoll et al., 2019). Comorbidity extends across all domains of psychopathology, and appears bidirectional across domains (McGrath et al., 2020; Plana-Ripoll et al., 2019). Moreover, single psychiatric diagnoses appear also unstable along time, shifting between different successive internalizing, externalizing, and thought disorders (Caspi et al., 2020). This posits some challenges for research, especially in cross-sectional designs and case-control studies, that enroll patients on the basis of the current disorder in their mental disorder life history, unaware of other past and future disorders. (Caspi et al., 2020)

Also genetic studies have shown how genetic risk for psychiatric disorders is pleiotropic, conferring liability to broad dimensions of symptomatically related disorders such as schizophrenia, major depression and bipolar disorder (Consortium et al., 2013; Network and Pathway Analysis Subgroup of the Psychiatric Genomics Consortium et al., 2015).

A recent meta-analysis by the Cross-Disorder Group of the Psychiatric Genomics Consortium has confirmed and extended on these findings (P. H. Lee et al., 2019). It included studies on genome-wide single nucleotide polymorphism (SNP) for eight neuropsychiatric disorders: bipolar disorder (BD), major depression (MD), schizophrenia (SCZ), autism spectrum disorder (ASD), anorexia nervosa (AN), OCD, ADHD, and Tourette Syndrome (TS), with a sample of 232,964 cases and 494,162 controls. Authors found significant genetic correlations between most disorders, with the

highest associations between SCZ and BIP, followed by OCD and AN. They identified also three clusters of genetically-related disorders: one comprising mood and psychotic disorders, one with disorders characterized by compulsive behaviors (AN, OCD and TS), and a third comprising two early-onset neurodevelopmental disorders (ASD and ADHD) and one disorder each from the first two clusters (TS and MD).
They confirmed also a substantial pleiotropy (i.e. one gene influencing two or more seemingly unrelated phenotypic traits), with 109 out of the 146 detected SNPs, affecting two or more disorders, of which 23 loci affecting four or more disorders. When looking at functions and expressions of these highly pleiotropic loci (e.g. DCC, RBFOX1, BRAF, and KDM7A), researchers found that they are genes involved in early neurodevelopmental pathways including neurogenesis, regulation of nervous system development, and neuron differentiation, with expression peaking in the second trimester and remaining overexpressed throughout the lifespan. Authors posit that these genes confer relatively broad liability to psychiatric disorders by acting on early neurodevelopment and the establishment of brain circuitry, and that the final phenotype may depend on "additional sets of common and rare loci and environmental factors, possibly mediated by epigenetic effects".
This evidence remarks again a lack of correspondence between genetic mappings and clinical nosology instantiated in DSM or ICD, while highlighting the importance of early development.

Mounting evidence is indicating that psychopathological phenomena have a dimensional nature, and lie on a continuum with normal-range functioning (Kotov et al., 2017). Various authors suggest that that the notion of discrete, categorical mental disorders is so far removed from biological reality that it actually impedes clinically useful scientific discovery, and is responsible for the sluggish pace of advances in psychiatric research (Buckholtz & Meyer-Lindenberg, 2012; Cuthbert & Insel, 2013; Gould & Gottesman, 2006; Hyman, 2010).
Alternative dimensional models are emerging.

1.11.2 The Research Domain Criteria

The Research Domain Criteria (RDoC), (https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/) is a project launched in 2009 by the National Institute of Mental Health (NIMH). It

assumes that mental illnesses are disorders of brain circuits and aims at providing an evolving platform where researchers can organize accumulating data on relationships between brain and behavior, and genomic discoveries in human and non-human studies (Cuthbert & Insel, 2013; T. Insel et al., 2010).

It identifies six major domains of human functioning: negative valence systems, positive valence systems, cognitive systems, social processes, arousal/regulatory systems and sensorimotor systems. Each domain contains several constructs, i.e. behavioral elements that comprise different aspects of the domain overall range of functions. Constructs are studied along a span of functioning from normal to abnormal, using several different classes of variables including genetic, physiological, behavioral, and self-report assessments. The influence of environmental and developmental context is also accounted for. Domains and constructs are evolving depending on new findings from the research community.

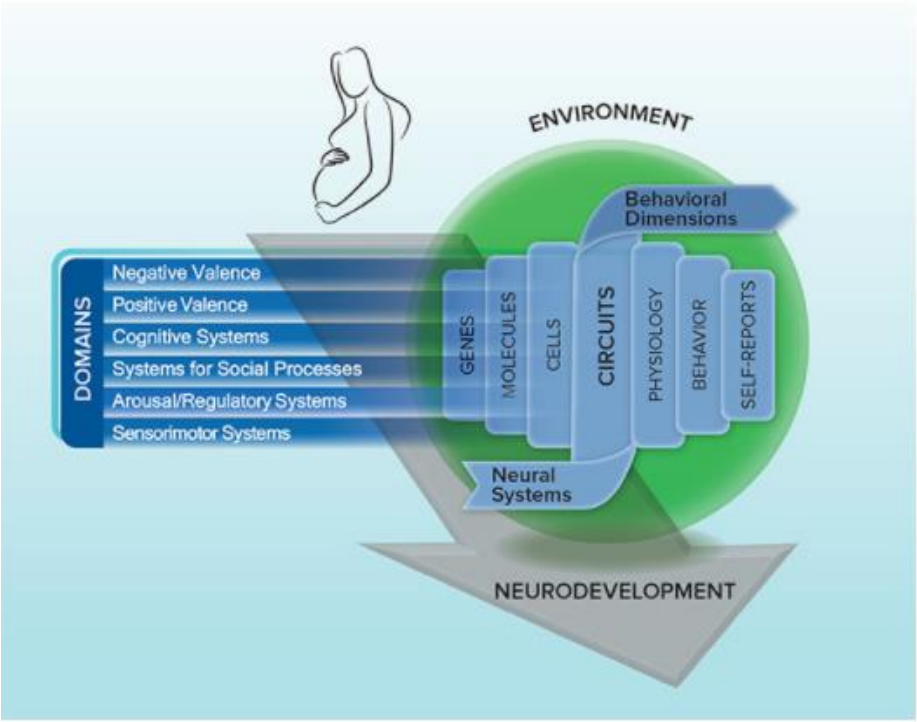

Figure 8 - The Research Domain Criteria Matrix (From https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/about-rdoc)

Table 2 Research domain criteria, October 2012 (constructs are listed within each domain)

Negative valence domain	Positive valence systems	Cognitive systems	Systems for social processes	Arousal/modulatory systems
Acute threat ('fear')	Approach motivation	Attention	Affiliation and attachment	Arousal
Potential threat ('anxiety')	Initial responsiveness to reward	Perception	Social communication	Biological rhythms
Sustained threat	Sustained responsiveness to reward	Working memory	Perception and understanding of self	Sleep-wake
Loss	Reward learning	Declarative memory	Perception and understanding of others	
Frustrative nonreward	Habit	Language behavior		
		Cognitive (effortful) control		

Figure 9: from (Cuthbert & Insel, 2013)
Example of domains and constructs per October 2012

Despite currently functioning as a framework for research, the ultimate goal of RDoC is to provide "precision medicine for psychiatry", and define a diagnostic system based on a deep understanding of the biological and psychosocial basis of psychiatric conditions, than can generate tailored recommendations for interventions that can "manage, cure and prevent mental disorders in the largest possible number of individuals" (T. R. Insel, 2014).

1.11.3 The Hierarchical Taxonomy of Psychopathology

Another dimensional system under development is *The Hierarchical Taxonomy of Psychopathology (HiTOP)* (Kotov et al., 2017). HiTOP focusses on clinical manifestations. By use of factor analysis - a statistical procedure that groups variables based on the pattern of their interrelations – carried out on multiple data sets with a combined sample size of over 100,000, it groups symptoms that covariate into a multilevel classification, such that symptoms that closely correlate are assigned to the same dimension, and symptoms that are unrelated get assigned to different dimensions. From bottom up, HiTOP identifies individual symptoms, components/traits, syndromes, subfactors, spectra, and a single general factor of psychopathology, as shown in Figure below. Each variable is dimensional and spans from normative to pathological ranges, so that any individual can be described by the system, also those with subthreshold symptoms or unusual symptom profiles.

HiTOP does not support itself on a dedicated measurement instrument, but proposes use of different existing instruments, some self-reported, some informant-reported, and some administered by an interviewer.

The classification is an ongoing project under ongoing revision, with some work e.g. suggesting that a neurodevelopmental spectrum should be included (Karcher et al., 2021).

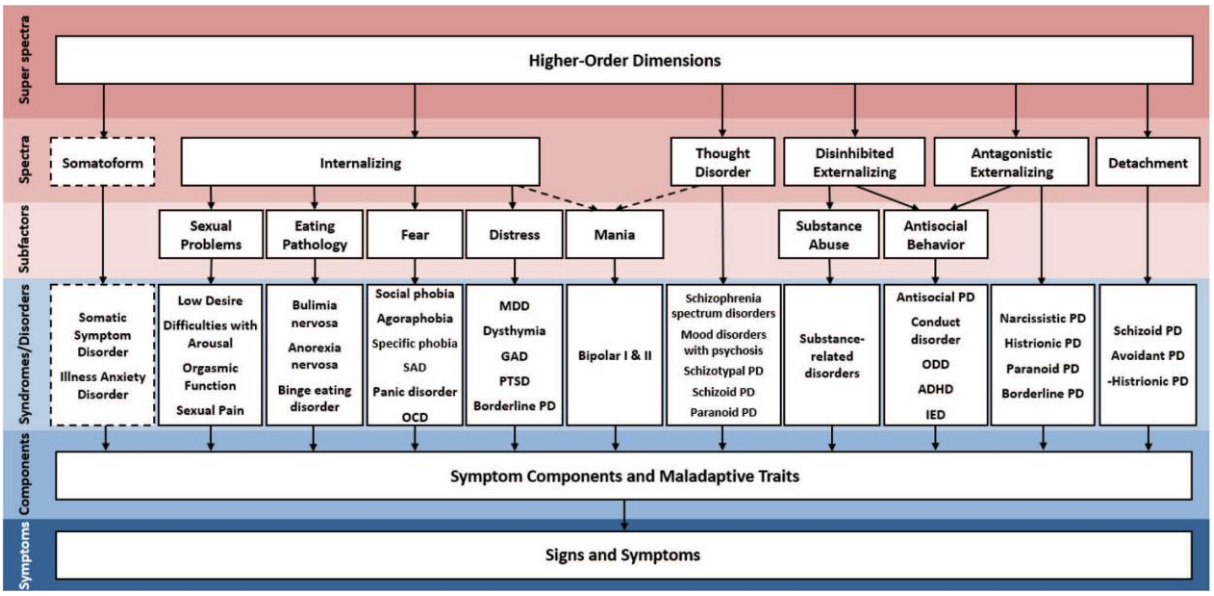

Figure 10. From (Kotov et al., 2017)
Spectra of the Hierarchical Taxonomy of Psychopathology. *Note:* Dashed lines indicate elements of the model that were included on provisional basis and require more study. Disorders with most prominent cross-loadings are listed in multiple places. Minus sign indicates negative association between histrionic personality and detachment spectrum.

The ultimate target of a new classification should be to provide a tool for researchers and clinicians, that is more useful than traditional categorical taxonomies. Evidence supports that HiTOP qualifies for that: spectra map on genetic and environmental risk factors more accurately than categorical diagnoses. HiTOP dimensions may also tight more closely to neurobiological measures, as “empirically derived dimensions offer greater informational value and specificity” (Kotov et al., 2017; Latzman et al., 2020).

Neuroscience research using dimensional constructs consistent with HiTOP is beginning to provide consistent results. For example at spectra level, disruption in fronto-amygdala connectivity emerged as a transdiagnostic neural signature of internalizing psychopathology ((Marusak et al., 2016) for a meta-analysis). At symptom level, another study found that the *distress* and the *fear*

subfactors had different relation pattern to external stimuli, with distress associating with blunted neural reactivity to all stimuli, and fear with enhanced reactivity to negative stimuli specifically (Nelson et al., 2015). Another work found that the checking symptom component across various disorders within the internalizing spectrum was specifically associated with enhanced neural reactivity to errors (Weinberg et al., 2015).
Authors defend also how a quantitative dimensional taxonomy can better describe illness course and specific functional impairments than categories, permitting targeted interventions. (Kotov et al., 2017; Latzman et al., 2020)
A recent work from the HiTOP Utility Workgroup (Kotov et al., 2020) reviews evidence regarding the two spectra under the psychosis superspectrum: *thought disorder* and *detachment.* Authors confirm validity of the two spectra against nine criteria: behavior genetics, molecular genetics, environmental risk factors, cognitive and emotional processing abnormalities, neural substrates, biomarkers, childhood temperament antecedents, illness course, and treatment response

HiTOP and RDoC approach nosology from different perspective, but can inform and integrate each other, and may advance toward one another to produce a unified system (Patrick & Hajcak, 2016). The clinical phenotypes described by HiTOP could inform the RDoC framework about key clinical dimensions that need to be considered.

1.11.4 Symptom-focused models: the Symptom Network Modelling and the Cambridge Model

Other models of psychopathology pose the focus strictly on final symptoms, arguing that empirical research should work at that level rather than on syndromes: the Symptom Network Modelling (SNWM) and the Cambridge Model (Wilshire et al., 2021).

The SNWM approach (Borsboom, 2017) posits that symptoms have a causal relations among each other and with external factors, and that once a network of symptoms gets established above a certain severity threshold, it becomes self-sustaining and “is” the disorder. In other words, symptoms are not necessarily consequences of underlying disorders, but components of the emerging causal network, which itself constitutes the mental illness. The approach distinguishes also *central symptoms* – that associate with a large number of other symptoms and can play a

central role in the development of a network of problems – and *bridge symptoms* – that associate with more than one symptom network, possibly representing a common endpoint.
For example, disrupted sleep can be a central symptoms, as it may in turn lead to fatigue, poor concentration, memory problems, loss of enjoyment, impaired work performance, and, ultimately, reduced self-esteem.
The ultimate aim of the SNWM approach is to uncover causal relationships, and researchers suggest that identifying and targeting the most central symptoms may offer novel therapeutic strategies (Fried et al., 2017). SNWM critics object, that patterns of associations do not provide direct evidence regarding causal relationships, and question that the SNWP does not address the question of what constitutes a symptom, but largely adopts those defined in DMS-V, thus not necessarily coherent constructs (Wilshire et al., 2021).

The *Cambridge Model* has also its focus on symptoms, though from a stance that merges philosophy with neurosciences. It developed within the Cambridge School, a group of researchers interested in the history and epistemology of psychiatry, gathered around prof. G.E. Berrios. It stands on the idea that mental symptoms are not mere facts, that can be directly described as such, but rather, they are primordial experiences that get interpreted by the individual depending on his/her personal, social, and cultural schemas, and then co-constructed and negotiated in the therapeutic relationship (Marková & Berrios, 2012). E.g. the same experience can be formulated as a hallucination or a delusion depending on the questions the clinician poses (German E., 2013). Different causal processes can lead to the same type of symptom experience, and conversely, similar causal processes can lead to very different symptom experiences. The objective of the Cambridge model is to develop rich descriptions of symptoms that consider the biological, psychological, and cultural factors that shape them, in order to choose the most adapted managing approach, e.g. biological vs psychological.
Reviewers observe that the model provides a rich framework for understanding how symptoms are formed and reported and has value in generating new lines of research. At the same time it gives little guidance to researchers, about how to identify and measure the multitude of factors that shape the symptom experience (Wilshire et al., 2021).

1.11.5 Connectomics: the Human Connectome Programs and Neural Circuit Taxonomies

As a bridge between RDoc, that looks for biological substrates for psychopathological domains, and HiTOP, that aims at disentangling symptom nature, is the research studying brain networks and their functions in health and pathology: Connectomics, a field concerned with mapping the neural elements and inter-connections that constitute the brain (Fornito & Bullmore, 2015).
In the past decades, the brain has increasingly been considered as a system, organized in networks which underlie the different brain functions. Each network consists of a distinct set of cortical and subcortical areas linked by temporally synchronous neural activity (Vinod Menon, 2011). Mental illnesses are becoming considered disorders of brain circuits, rather than of brain regions (T. Insel et al., 2010), and various authors advocate for new taxonomies, which relate clinical features to distinct types of neural circuit dysfunction, and cut across traditional diagnostic boundaries (Vinod Menon, 2011; Williams, 2016).
Some authors even propose a dimensional ‘‘common symptom, common circuit’’ model of psychopathology, where risk factors for mental illness would produce alterations in brain circuit function in a manner that is cognitive and symptom domain-specific, but disorder-general (Buckholtz & Meyer-Lindenberg, 2012).

Connectivity can be *structural,* looking at anatomical structures, *functional*, looking at dependance between two regions, or *effective* – referring to the causal influence that one region exerts to another. Structural connectivity can be measured by DWI (diffusion-weighed image), while functional and effective connectivity can be measured by fMRI, but also by electro-and/or magneto-encephalography, which compensates for the minor spatial resolution, by offering a richer representation of temporal dynamics (Fornito & Bullmore, 2015).

Great investments have been made to map the neural pathways that underlie brain functions both in normative conditions and in neuropsychiatric disorders. In 2009 NIH launched the Human Connectome Project (HCP), that looked at normative functioning: it analyzed structural and functional connectivity on 1200 healthy adults aged 22 to 35, and produced maps of neural fibers crisscrossing the brain. Other projects have followed: Lifespan Connectome in 2015, on healthy

adults of all ages, and Disease Connectome, looking at connectomes in diverse neurological and psychiatric conditions. (Connectome Programs | Blueprint (nih.gov)).
Besides that, several independent works have investigated connectivity in diverse conditions.

Works are accumulating, that describe functional and structural supports for different mental processes, as well as changes in these across psychopathological conditions. Particular interest have gone to some large-scale networks, i.e. networks that distributed across most of the brain (Barrett & Satpute, 2013).
For example, self-referential processes such as introspection and autobiographical memory retrieval, as well as social processes as empathy, mentalizing and emotion communication, appear supported by the *default mode network* (DMN), a network mainly composed by the medial PFC (mPFC), posterior cingulate cortex (PCC), and lateral temporal cortex. (Feng et al., 2021; ME & Raichle, 2015). The DMN is also called the *resting-state network*, as reflects the connectivity observed under task-free conditions, when participants are asked to rest and reflect on their thoughts (Williams, 2016).
High level cognitive functions such as long-term planning, decision making, and the control of attention and working memory appear supported by the *central executive network* (CEN), a frontoparietal network anchored in the dorsolateral PFC (dlPFC) and posterior parietal cortex (PPC) (M. W. Cole et al., 2014; Vinod Menon, 2011). CEN is also involved in various regulatory functions of social processes, including emotion regulation, and making strategic choices taking into account the mental states of other individuals and inhibiting of one's own experience (Feng et al., 2021).
Switching between reciprocal activation and deactivation of DMN and CEN would depend on the salience network (SN) (V Menon, 2015). The SN is anchored on the anterior cingulate cortex and anterior insula, and includes two subcortical structures, key in affect and reward processing: the amygdala and the substantia nigra/ventral tegmental area. SN is crucial for salience mapping: detection of salient external stimuli and internal mental events and, through its interactions with the CEN and DMN, allocation of attentional resources for additional processing and initiation of appropriate executive control(V Menon, 2015).

SN is considered a motivation system regulating human decision-making, mainly engaged by anxiety-related information (as that aroused by negative social interaction and norm violation) and driving people to change their behaviors and internal states to align with social norms, even when this is at odds with maximizing the individual payoff (Feng et al., 2021).
Conversely, motivation towards social reward, and the positive aspects of social interactions such as mutual cooperation and altruistic giving, appear supported by the subcortical network (SCN), containing bilateral striatum (Feng et al., 2021).
Several other large-scale networks have been mapped and characterized: the cingulo-opercular (CON), dorsal attention (DAN) (M. W. Cole et al., 2013; Yeo et al., 2011) posterior multimodal (PMM), ventral multimodal (VMM), orbito-affective (ORA), language network (LAN), together with the well-known primary visual (VIS1), secondary visual (VIS2), auditory (AUD), and somatomotor (SMN) networks, to name a few (Ji et al., 2019).

In parallel with research carried out in normative conditions, work has investigated alterations in these networks both in specific diagnosis, and more recently across the spectrum.
Results indicate shared alterations across psychiatric diagnoses in networks and regions subserving cognitive, affective and motor functions, suggesting a common background from which psychopathology can develop.
The networks most often implicated are the DMN, CEN, SN and sensorimotor network (SMN).
Already in 2011 V. Menon proposed a “unifying triple network model” of psychopathology, which posits that aberrant functional organization of the SN, FPN and DMN and their dynamic interactions underlie a wide range of psychiatric disorders. Such dysfunction would result in impaired abilities to engage with and respond to changing external contexts and internal goals, that is, result in *impaired cognitive control* (Vinod Menon, 2011).
Deficits in cognitive control are in fact observed in many psychiatric disorders and have been proposed as a transdiagnostic vulnerability factor for psychopathology (Vinod Menon, 2020; Vanes & Dolan, 2021).
This hypothesis has been supported and expanded on by subsequent works. A recent meta-analysis on data for over 8,000 patients with eight disorders (anxiety, BAD, MDD, OCD, PTSD, SCZ, ADHD and ASD) and over 8,000 healthy subjects, confirmed common alterations of functional

connectivity within and between these three networks across disorders (Sha et al., 2019). Another meta-analysis looking at brain activation during cognitive control tasks, found common disruptions in patients with axis I disorders vs. healthy controls in a superordinate, "multiple demand" network, deputed to cognitive control and processing, including the CEN and interacting with the SN (McTeague et al., 2017).

The same regions and networks emerge from structural studies: three trans-diagnostic meta-analyses have found reduced grey matter volume in regions localized within these neurocognitive networks (Crossley et al., 2014; Goodkind et al., 2015; Sha et al., 2019), and showed that decrease in grey matter volume in the same areas correlated with worse cognitive performance in healthy volunteers (Goodkind et al., 2015; Sha et al., 2019), thus supporting the notion that neurocognitive networks are susceptible to gray matter loss across multiple psychiatric disorders.

Besides impairment in cognitive control, research suggests also transdiagnostic *alterations in emotional processing*. A recent meta-analysis comparing activation during emotional processing tasks in over 5,000 patients (diagnosis of schizophrenia, bipolar or unipolar depression, anxiety, and substance use) and healthy controls, found transdiagnostic disruption in regions and networks key to adaptive emotional reactivity and regulation, as the amygdala and the salience and reward networks (McTeague et al., 2020).

A third domain that is emerging as a possible hallmark of psychopathological vulnerability is the *sensorimotor area*. Meta-analytic evidence has detected hyperconnectivity between the SN and the precentral cortex in the sensorimotor network (Sha et al., 2019). This may suggest that basic sensory features of the environment have excessive influence on cognitive processing in the diseased brain, and explain the alterations found in sensory processing across a wide psychopathological profile (Javitt & Freedman, 2015; Mrad et al., 2016; Piek & Dyck, 2004)

Motor dysfunctions – e.g. motor planning, inhibition, learning, coordination, involuntary movements – have also been reported across various disorders, preceding disease onset and predicting disease progression (D. J. Dean et al., 2015; Mittal et al., 2008, 2010), and it is proposed to introduce a motor dimension into the RDoC (Walther et al., 2019).

These shared alterations in cognition, emotion and sensorimotor processing may reflect the *p factor*, a general psychopathology (or p) factor, thought to reflect individuals' susceptibility to

develop any and all forms of common psychopathologies (Caspi et al., 2014; Vanes & Dolan, 2021), also captured in the "single general factor of psychopathology" in HiTOP.
Such vulnerability to mental illness would be linked to delayed or disrupted maturation of large-scale networks and between-network connectivity throughout development, resulting in a compromised ability to integrate and switch between internally and externally focused tasks (Vanes & Dolan, 2021).
Vanes and colleagues propose a developmental model that takes into account meta-analytic evidence existing to date (Vanes & Dolan, 2021). They suggest that lower prefrontal grey matter volume is a childhood marker of vulnerability, that would sum up in adolescence with a slower maturation of myelinated white matter tracts between frontal cortex and temporo-limbic areas. This may hinder the development of stable and interconnected functional networks, which in the long run may cause structural changes in grey matter, with further impairment in communication between brain regions. These changes would form the base on which the diverse psychopathologies can build on.

Research is also emerging that describes the neural correlates of specific symptoms. Williams e.g. proposes that transdiagnostic symptoms as rumination, anxious avoidance, anhedonia, negative affective bias, lack of cognitive control etc., are grounded on dysfunction in specific network (Williams, 2016).
A recent meta-analysis on ASD has found hypofunction of DMN, likely corresponding to a weakened "mental self", i.e. a reduced capacity of reflecting on one's internal states and emotions, as well as of distinguishing between self and other (Lian & Northoff, 2021).
A large study on adolescents, the ABCD study (N=11,876) found relation with OCD scores and altered connectivity within and between the DAN and the DMN (Pagliaccio et al., 2021).

1.11.6 Conclusions about the transdiagnostic approach

Taken together, mounting evidence from both symptom-based and image-based studies converges in supporting a transdiagnostic approach, and in considering that vulnerability to psychopathology develops progressively during childhood and adolescence.

1.12 Conclusions from the introduction

The purpose of the introduction was to give an overview about current evidence on the role of inflammation and immune disturbances in psychiatric disorders, and on the link between psychiatric and somatic conditions.

It showed how inflammation and immune changes are described across the diagnostic spectrum, how inflammation can potentially produce psychiatric symptoms, how psychiatric and chronic somatic conditions often co-occur, or precede each other, and how inflammation is suggested to be a common mediator.

The introduction looked then at the role of psychosocial and other forms of stress along lifetime in starting inflammation and vulnerability to chronic diseases.

It described the mechanisms implied, and some of the theories that connect early and lifelong stress with inflammation, and these with physical and mental health. Among these theories, the first ones that appeared, the Fetal Origins Hypothesis and theory of the Developmental Origins of Health and Disease, DOHaD.

To conclude, it reviews evidence that supports a dimensional and transdiagnostic approach in psychiatric research, and potentially also in clinical activity.

This collective evidence provides a context, within which to set and understand the original research that will be discussed in the next paragraphs.

2 HYPOTHESES

The main hypothesis underlying this work is that psychopathology and immune changes are interrelated, that inflammation is a putative common mediator, and that psychosocial stress and other insults along development are putative causal factors.

We studied two groups of subjects: acute child and adolescent psychiatric inpatients, and offspring of women with Systemic Lupus Erythematosus, who have potentially been exposed to immune insults since their foetal life.

In each group we hypothesized:

Hypothesis 1: *Inflammation, immunity, stress and psychopathology*

Inflammatory and immune changes will be found in children and adolescents hospitalized for psychiatric pathology, throughout the entire diagnostic spectrum, in comparison with a group of healthy controls. These changes will be related to measures of psychosocial stress.

Hypothesis 2: *Immune status, neurocognition and psychopathology in the children of women with Systemic Lupus Erythematosus.*

Children of women with Systemic Lupus Erythematosus will show changes in neurocognition, psychopathology, and immune profiles, in comparison with a group of healthy controls. Neurocognition, psychopathology and/or immune asset may relate to stress measures.

3 AIMS

3.1 Global aim

To increase knowledge about links between inflammation, autoimmunity, psychosocial stress and psychiatric conditions, in adolescent population.

Rationale:

- Evidence coming mainly from adult studies reported common inflammatory alterations across the psychiatric diagnostic spectrum. At the same time, several researchers advocate for a transdiagnostic approach in psychiatry. On these premises, we chose to study young patients with all psychiatric diagnoses, with the idea that common alterations might be found.
- At the same time, offspring of women with SLE appear an emblematic category, when studying interplay between immune system, brain and stress. These children have both been exposed to maternal immunity (MIA) in their foetal lives, may be at high genetic risk for autoimmune dysregulations, and have potentially been exposed since birth to the psychosocial stressor of having a parent chronically ill. Moreover, an antibody isolated from women with SLE, the anti-GluN2 or anti-DWEYS, may have neurotoxic effects when reaching the brain, and has been implied in preclinical MIA models. Learning disabilities and neurodevelopmental disorders had been previously reported in this population (Marder et al., 2014; Neri et al., 2004), but no complete immune assessment had been carried out in these children, nor description of presence of this antibody.

3.2 Specific aims

1. To study the inflammatory and immune profile of acute child and adolescent psychiatric inpatients, cross-diagnostically and relation with stress measures, and compare them with a population of healthy controls. In particular, we looked at
    a. An extensive panel of cytokines (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL_10, granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon (IFN)-γ, tumor necrosis factor (TNF)-α, IFN-γ-induced protein-10 (IP-10), monocyte chemoattractant protein (MCP)-1.)
    b. White cells
    c. Various antibodies, among which those described neurotoxic in SLE patients
    d. Stress measures

2. To explore immune asset, psychopathological and neurocognitive profiles in a group of offspring of women with SLE, and compare them with a population of healthy controls. To investigate relations between immune, inflammatory, psychosocial and neuropsychological indicators. We looked at
    a. The same immunological and stress data as in point 1 (excluding MCP-1 and IP-10).
    b. Neurocognitive profiles
    c. Mother psychophysical condition and immune profile.

RESEARCH GAPS:

1. This is the first study assessing such a broad panel of markers and across diagnosis in this patient group
2. Even if changes in neurocognition already are reported in the SLE-offspring population, this is the first work that analyses these immune data in this group.

4 MATERIALS AND METHODS - SCIENTIFIC PUBLICATIONS

4.1 STUDY 1

Title:

IL-8 and the innate immunity as biomarkers in acute child and adolescent psychopathology

AIM:

To study inflammatory profile in a sample of 77 child and adolescent psychiatric inpatients, ages 8-17, and compare it to a group of 34 healthy controls, and to assess possible relations between inflammatory state, psychopathology and stress measures.

The parameters assessed are

- Inflammation/immunity: 12 cytokines (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL_10, GM-CSF, IFN-γ, TNF-α, IP-10, MCP-1, white cells count, CRP
- Stressors: measure of family structure, and parent and child-reported measures of stress in the past 12 months.

RESÚMEN EN CASTELLANO:

Objetivo:
El papel de la inflamación en la psicopatología ha recibido una gran atención durante las últimas décadas. Se ha descrito disfunción del sistema inmunológico y niveles alterados de citocinas en la mayoría de los trastornos psiquiátricos en adultos. Hay pocos datos disponibles sobre niños y adolescentes (N&A), o sobre la relación entre los niveles de citocinas y el estrés psicosocial. Este estudio investiga el perfil de las citocinas más descritas, en una muestra de pacientes infanto-juveniles hospitalizados por una condición psiquiátrica aguda que requiere hospitalización, en comparación con sujetos sanos, así como las posibles asociaciones entre los estresores psicosociales con psicopatología y/o niveles de citocinas.

Métodos:
Pacientes infanto-juveniles con un diagnóstico de trastornos afectivos, de ansiedad, adaptativos, psicóticos, obsesivo-compulsivos, tic o de Tourette se reclutaron consecutivamente en nuestra clínica entre junio de 2010 y febrero de 2012. Los controles se reclutaron de la misma área geográfica. Todos los sujetos tenían entre 8 y 17 años. Se comparan doce citocinas: interleucina (IL) -1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL_10, factor estimulante de colonias de granulocitos-macrófagos (GM-CSF), interferón (IFN))-γ, factor de necrosis tumoral (TNF)-α, proteína-10 inducida por IFN-γ (IP-10), proteína quimioatrayente de monocitos (MCP) -1. El estrés psicosocial se midió a través de la Escala de Eventos Vitales Estresantes, versiones Niño y Padres (SLES-C y SLES-P) y evaluando la integridad del núcleo familiar.

Resultados
Se reclutaron ciento once sujetos (77 pacientes hospitalizados y 34 controles sanos), de los cuales 54 eran varones (49%), con una mediana de edad (rango intercuartílico) de 16 (13,7-17,3) años. Se encontró que IL-1β, IL6, IL8, IP-10, MCP-1 y monocitos eran significativamente más altas en el grupo de pacientes ($p < 0.05$). Ajustando por el IMC, la edad, el sexo y la toma de medicamentos al ingreso, las diferencias se confirmaron para todas las citocinas excepto MCP-1. IL-8 e IL-1β también resultaron más altas en todas las subcategorías diagnósticas, con respecto al grupo control ($p < 0,05$). Las medidas de estrés resultaron más elevadas en los pacientes. Se encontró una correlación significativa entre el estrés medido por las escalas SLES y algunos marcadores inflamatorios: SLES_C con IL-1β, IL-8, MCP-1 y SLES_P con IL-1β y recuentos absolutos y relativos de monocitos (r de Spearman entre 0.219 y 0.297, $p < 0,05$).
La regresión logística identificó las siguientes variables como predictores independientes de la condición del paciente (razón de probabilidades por cuartil, valor de p): IL8 (1, 0.9, 12.1, 32.0, $p = 0.044$), IP10 (1, 14.1, 2.5, 3.7, $p = 0,044$), recuento absoluto de monocitos (1, 1,1, 6,0, 19,4, $p = 0,030$).

Conclusiones
Los resultados muestran elevación de marcadores inflamatorios propios de la inmunidad innata en pacientes psiquiátricos agudos infanto-juveniles, y sugieren un vínculo entre psicopatología, inflamación y estrés. Los marcadores inflamatorios resultan predictores del estado de paciente. Estos resultados exploratorios son coherentes con las investigaciones actuales en psiconeuroinmunología y neurodesarrollo.

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IL-8 and the innate immunity as biomarkers in acute child and adolescent psychopathology

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ABSTRACT

Objective: The role of inflammation in psychopathology has received great attention over the past decades. Immune system dysfunction and altered cytokine levels have been reported in most psychiatric disorders in adults. Few data are available regarding children and adolescents (C&A), or regarding the relationship between cytokine levels and psychosocial stress.

This study investigates the profile of the most described cytokines in a sample of C&A inpatients affected by an acute psychiatric condition requiring hospitalization, in comparison with healthy subjects, as well as possible associations between psychosocial stressors and psychopathology and/or cytokine concentrations.

Methods: Patients with a diagnosis of Affective, Anxiety, Adjustment, Psychotic, Obsessive–Compulsive, Tic or Tourette Disorders were consecutively recruited from our clinic between June 2010 and February 2012. Controls were recruited from the same geographic area. All subjects were between 8 and 17 years old. Twelve cytokines are compared: interleukin (IL)-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL.10, granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon (IFN)-γ, tumor necrosis factor (TNF)-α, IFN-γ-induced protein-10 (IP-10), monocyte chemoattractant protein (MCP)-1. Psychosocial stress was measured through the Stressful Life Events Scale, Child and Parents versions (SLES-C and SLES-P) and the evaluation of the family integrity.

Results: One hundred and eleven subjects (77C&A inpatients and 34 healthy controls), of which 54 were males (49%), with a median (interquartile range) age of 16 (13.7–17.3) years, were included in this study. IL-1β, IL6, IL8, IP-10, MCP-1 and monocytes were found to be significantly higher in the patient group ($p < 0.05$). Differences were confirmed when adjusting by BMI, age, gender and drug intake at admission for all cytokines except MCP-1. IL-8 and IL-1β were also higher throughout the different diagnostic categories, than in control group ($p < 0.05$). Stress measures were higher in patients. A significant correlation was found between stress measured by the SLES and some inflammatory markers: SLES_C with IL-1β, IL-8, MCP-1, and SLES_P with IL-1β and monocytes absolute and relative counts (Spearman's r between 0.219 and 0.297, $p < 0.05$).

Logistic regression identified the following variables as independent predictors of the patient condition, (odds ratio per quartile, *p*-value): IL8 (1, 0.9, 12.1, 32.0, $p = 0.044$), IP10 (1, 14.1, 2.5, 3.7, $p = 0.044$), monocyte absolute count (1, 1.1, 6.0, 19.4, $p = 0.030$).

Conclusions: Results show elevated inflammation markers from the innate immune system across C&A acute psychiatric diagnosis, and suggest a link between psychopathology, inflammation and stress. Inflammatory markers resulted predictors of patient status. These exploratory results are coherent with current psychoneuroimmunology and neurodevelopmental investigations.

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1. Introduction

Over the past decades there has been a great interest in the role of inflammation in psychiatric psychopathology. All major psychiatric disorders have been investigated. Recent meta-analysis have been published for schizophrenia and psychotic disorder (SCZ), bipolar disorder (BAD), major depression (MDD), post-traumatic-stress-disorder (PTSD), autism spectrum disorder (ASD) (Miller et al., 2011a; Modabbernia et al., 2013; Gray and Bloch, 2012; Masi et al., 2014; Dowlati et al., 2010) as have some revisions on PTSD (Wieck et al., 2014), and they all conclude that cytokine alterations and a pro-inflammatory state are associated with the disorder in question.

Even though studies have mostly been developed separately for each diagnosis, some findings are common. When summarizing the results across the diagnostic spectrum, it is clear that cytokines such as IL-1β, IL-6, IL-8 and TNF-α, have proven to be higher across various adult patient populations, in comparison with healthy controls (HC). An overview chart is provided in Appendix A of Supplementary information. Of note is the fact that, these cytokines are all suggestive of an inflammation pattern related to innate immunity and monocyte activity, and some authors have posited that this condition may be associated with an activation of the microglia at a central level (Bergink et al., 2014).

It may be noteworthy that most studies analysed a very restricted panel of cytokines: this can give the false impression of a very specific immune activation. To obtain a better picture of the pattern of inflammatory changes, a broad range of immune markers should be investigated and compared throughout all experimental groups.

In order to better understand correlations and possible pathogenic mechanisms, a deeper knowledge of inflammatory and cytokine states in child and adolescent (C&A) psychiatric population is of special interest. This would allow the bypass of the confounding burden of long-term treatment and physical comorbidities often found in adults, and also the optimization of signal detection, because of shorter illness duration and minor allostatic load (Mitchell and Goldstein, 2014) in these subjects.

Literature in C&A psychiatric patients, though increasing, is still limited and heterogeneous. Even though results have been somewhat inconsistent, a recent review (Mitchell and Goldstein, 2014) suggests that there would be preliminary evidence for elevated inflammatory markers also in this population, with some markers such as IL-1β and IL-6 found altered through various disorders.

The presence of common markers across psychiatric disorders is coherent both with clinical observations, and with the most recent findings in genetics and neuroscience. Inputs in favour of a cross-diagnostic approach in psychiatry come from various fields. There is accumulating evidence from genetic studies suggesting shared susceptibility across traditional diagnostic categories in psychiatry: family studies have shown how there is a cross-diagnostic familiar risk for schizophrenia, mood disorders, ASD and attention deficit and hyperactivity disorder (ADHD) (Doherty and Owen, 2014), i.e. how members of families of patients with one disorder, also have a higher risk for the other disorders. Genetic studies also evidence how the same risk-markers, like single-nucleotide-polymorphism (SNP) and copy number variants (CNVs) that have been associated with one specific disorder, can be linked to other disorders as well (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). From a clinical point of view, it is commonly experienced that many symptoms and signs overlap between disorders, and that patients often present with features of more than one disorder, which can account for the high comorbidity observed in psychiatry. This implies that at least some of the underlying biology may not be specific, or at least not at the level of current diagnoses (Doherty and Owen, 2014).

It has been discussed to what extent the overlap across diagnoses, and the lack of specific biomarkers for psychiatric disorders, has to do with a diagnostic classification system that is artificial in many aspects, and that includes patients that are highly heterogeneous (Kapur et al., 2012) under the same diagnostic group.

In the last decades, research has been focusing on new possible ways for classifying mental disorders, relating more specifically to neurobiological substrates, response to treatment, and clinical evolution. In this light also stands the Research Domain Criteria (RDoC) Project, an initiative set up by the National Institute of Mental Health, to "develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behaviour and neurobiological measures" (Insel, 2014; Doherty and Owen, 2014).

The same studies show the limits of genetics and the importance of the environment in determining epigenetic variables, and investigators speculate about how the same genetic risk factor can translate into different clinical phenotypes, or into healthy individuals, depending on the interaction with different environments. One of the environmental factors that is currently of interest is childhood trauma and stress. Accumulating evidence, in fact, suggests how adversities and trauma during childhood can be associated with the development of psychiatric disorders with an inflammatory phenotype, both during childhood and later in adulthood (Miller and Cole, 2012; Danese et al., 2008; Dennison et al., 2012).

2. Aims of the study

The current study is grounded on these premises.

As primary objectives, it aims to find possible common or specific markers of inflammation (cytokines) in a population of recently admitted, acutely ill psychiatric young inpatients. It compares the profile of the cytokines most often associated with an acute psychiatric condition, between our study population and a group of healthy subjects, in the search for transdiagnostic markers. Another dimension that has been investigated is the stress level that subjects had undergone, and the possible correlation between stress levels and inflammation parameters.

As a secondary and exploratory objective, it aims to investigate cytokine distribution across the different psychiatric diagnostic clusters.

3. Material and methods

3.1. Subjects

All patients between 8 and 17 years of age admitted to the Acute Child and Adolescent Psychiatry Inpatient Unit of Hospital Clínic of Barcelona, with a diagnosis of Affective, Anxiety, Adjustment, Psychotic, Obsessive–Compulsive, Tic or Tourette Disorders, according to DSM-IV TR Criteria, between June 2010 and February 2012, were invited to participate in the study.

Controls were healthy community subjects within the same age range, who had not received a previous psychiatric diagnosis, and should not score clinically in the psychiatric semi-structured interview (K-SADS-PL) for any psychiatric disorder, except for ADHD. They were recruited from local paediatric and family medicine practices in Hospital Clínicís referral area, among patients social network and through local advertisement. Exclusion criteria for all subjects included an IQ below 80 and an acute or chronic medical condition other than the psychiatric one, as well as regular medication intake, including anti-inflammatory drugs. This cross sectional study was approved by the Ethics Committee of the Hospital Clínic and all parents or legal guardians gave written informed consent before the study began.

3.2. Measurements

Demographic measures such as age, gender, body mass index (BMI) were taken at time of admission in patients and at interview time in controls. Family structure of the subjects was also analysed and classified into two categories: biological families that had maintained their original structure, versus families that had gone through a re-organization since the childís birth (including: parental separation, divorce, adoptions, custody under public Institutions etc.). This parameter was explored as a tentative measure of psychosocial stress, as it has been previously described how events as family disruption can promote further development of inflammation and psychiatric symptoms (Miller and Cole, 2012).

The K-SADS-PL was administered to all subjects and caregivers by a trained psychiatrist or psychologist, and psychiatric diagnosis given according to DSM-IV criteria. For the purpose of the analysis, patients were further grouped in 6 clusters, accordingly to DSM-IV grouping: Adjustment Disorders, Anxiety, Obsessive-Compulsive Disorder (OCD) & Tic disorder (TICs), Depression, Bipolar Disorder with Manic or Mix Episode (BAD), Psychosis and Schizoaffective Disorders (SZA).

Illness severity and general functioning were summarized in the GAF (Global Assessment of Functioning) scale (Axis V of DSM IV diagnosis).

Recent stress levels in subjects was assessed through the Stressful Life Events Schedule (SLES), child (SLES-C) and parent (SLES-P) versions (Williamson et al., 2003). The scales assess the presence and the emotional impact of over 80 possible stressors in the past 12 months of the subject's life, and return a score between 0 and 320. In the child and the parent version it is respectively the children themselves and their parents/guardians, who evaluate the impact of stressors on the children's lives.

Blood samples were collected with fasting, early morning extraction. Patients were sampled during the first days of admission, mainly within the first 24 h and in all cases within 96 h.

Blood analyses were performed at Core Facility of Hospital Clínic. White blood counts (WBC) were measured with automated cell counters via standard techniques. The WBC measures two components: the total number of leukocytes and the differential count. The differential count measures the percentages of each type of leukocyte (granulocytes–neutrophils, eosinophils, and basophils–lymphocytes and monocytes, as well as LUC–Large Unstained cells). Quality control is maintained by the laboratory with standard procedures. Laboratory results for each subject were accessed through the Hospital records.

Serum was obtained by centrifugation at 2000 rpm for 10 min and then kept frozen at −80° until the time of the assay (between 12 and 30 months after extraction). IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL_10, GM-CSF, IFN-γ, TNF-α were determined by a Luminex ultrasensitive kit, Invitrogen LHC6004, sensibility <1 pg/mlL, according to manufacturer's instructions. IP-10 and MCP-1 were determined by an ELISA kit Invitrogen KAC2331 and KHC1011, respectively, according to manufacturer's instructions. All samples were assayed in duplicate and compared to a standard curve. Values below the detection threshold were set to zero, and extrapolated values were accepted as valid.

3.3. Statistical analysis

Data are expressed as frequencies and% for categorical and median with percentiles 25–75 (interquartile range: IQR) for continuous variables or otherwise specified, as appropriate. Categorical data were compared using the Fisher's exact test, and continuous and ordinal data by means of the Mann–Whitney or the Kruskal–Wallis tests. A quantile regression approach was used to assess the robustness of the Univariate analysis for cytokines and monocytes in adjusted models. Correlations were assessed using the Spearman correlation. A multiple logistic regression analysis was run considering variables with a p-value < 0.1 in the univariate testing. All analyses were performed using SAS 9.2 software (SAS Institute Inc., Cary, NC, USA) or Statistical Package for Social Sciences version 20.0 (SPSS, Chicago, IL), and a level of significance was established at the two-sided 5% level. The Path Analysis described in Appendix E of Supplementary information was conducted using the Proc CALIS of SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

4. Results

4.1. Subjects

Seventy-seven consecutive inpatients from our C&A Acute Inpatient Unit, and 34 healthy controls, all aged between 8 and 17, were recruited. There were neither statistically significant nor clinically relevant differences in age, sex and BMI between the two groups.

Demographic and clinical characteristics are indicated in Table 1. Patients clustering according to diagnostic groups, and relevant clinical severity, medication and drug status at admission, are indicated in Table 2. All patients were undergoing their first hospitalization at our centre. Almost 90% of patients were not using cannabis or any other recreational drugs and about half of them (49%) were medication-naïve. Control subjects were interviewed about drug use, and one control subject declared a regular use of cannabis. Controls were not urine-screened for recreational drugs use, as it was considered that this could influence recruitment.

Results of family structure are commented further below together with stress scales.

4.2. Cytokines

Five cytokines (three interleukines and two chemokines) were significantly higher in the patients group as a whole compared to the control group: IL-1β ($p < 0.001$), IL-6 ($p = 0.004$), IL-8 ($p < 0.001$), IP-10 ($p = 0.005$) and MCP-1 ($p = 0.047$). Results are displayed on the left-hand side of Fig. 1. Differences were also confirmed when adjusting by BMI, age, gender and drugs intake at admission for all cytokines except MCP-1: IL-1β (quantile regressor for the patient effect, p-value: 0.26, $p < 0.001$), IL-6 (0.49, $p = 0.004$), IL-8 (26.77, $p < 0.001$), IP-10 (36.34, $p = 0.024$) and MCP-1 (25.27, $p = 0.199$).

Furthermore, when comparing these markers in each diagnostic cluster of patients vs the control group, IL-1β and IL8 were found to be higher than controls in all patients subgroups (Adjustment group: $p = 0.005$ and 0.034 respectively; Anxiety: $p = 0.020$ and 0.026; OCD&Tics: $p = 0.007$ and 0.001; Depression: $p < 0.001$ and <0.001; BAD: $p = 0.002$ and 0.005; Psychosis: $p = 0.006$ and 0.028), IL-6 in the Depression group ($p = 0.001$), IP-10 was higher than controls in Depression ($p = 0.021$) and OCD &Tics ($p = 0.024$) groups, and MCP-1 was higher in the Anxiety group ($p = 0.024$).

Results of the subgroup analyses are shown on the right-hand side of Fig. 1. No one of the 12 cytokines was significantly higher in the control than in the patient group, or than in any of the patients' subgroup. Some of the cytokines had concentrations close to zero-detection limit: median and interquartile range were both zero in controls for IL-1β, IL-2, IL-4, IL-5, IL-10, IFN-γ and TNF-α, and in patients for IL-5and IL-10. Furthermore, median (but not IQR) was zero in controls for IL-6 and GMCSF, and in patients for IL-2, IL-4, IFN-γ and TNF-α (see Appendix B of Supplementary information).

4.3. White cell comparison

Due to the fact that the 5 cytokines all belonged to the innate immunity and were secreted mainly by monocyte/macrophage

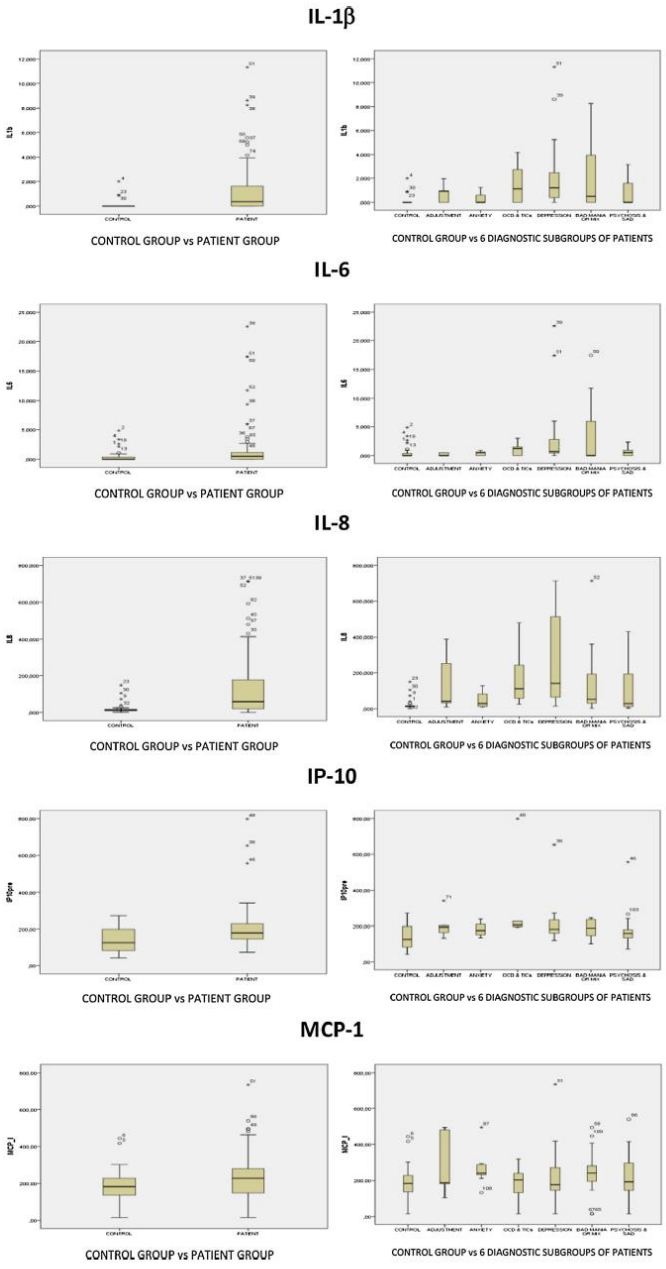

Fig. 1. Comparison of significantly different cytokines among the two groups, patients and controls. IL1b: interleukin-1beta; IL-6: interleukin-6; IL-8: interleukin-8; IP-10: Interferon gamma-induced protein 10 (CXCL10); MCP-1: monocyte chemoattractant protein (CCL2).
Interleukin; IP-10 = interferon-γ-induced protein-10, MCP-I = monocyte chemoattractant protein.

Table 1
Demographic and clinical characteristics of the study sample.

	Patient group (n = 77)	Control group (n = 34)	p
Gender			0.30
Male	40 (52%)	14 (41%)	
Female	37 (48%)	20 (59%)	
Age[a]	15.8 (13.6-17.2)	16.9 (14.5-17.6)	0.099
BMI[a]	20.2 (18.4-23.8)	20.8 (19.7-22.2)	0.419
GAF[a]	31 (15-45)	85 (85-90)	<.0001
THC positive at admission	6 (8%)	n.a.	
THC declared occasional but negative at admission	3 (4%)	n.a.	
THC declared frequent, not tested	–	1 (3%)	

[a] Median (interquartile range = IQR); BMI = body-mass index; GAF = Global Assessment of Functioningg, THC = cannabis, n.a. = not available

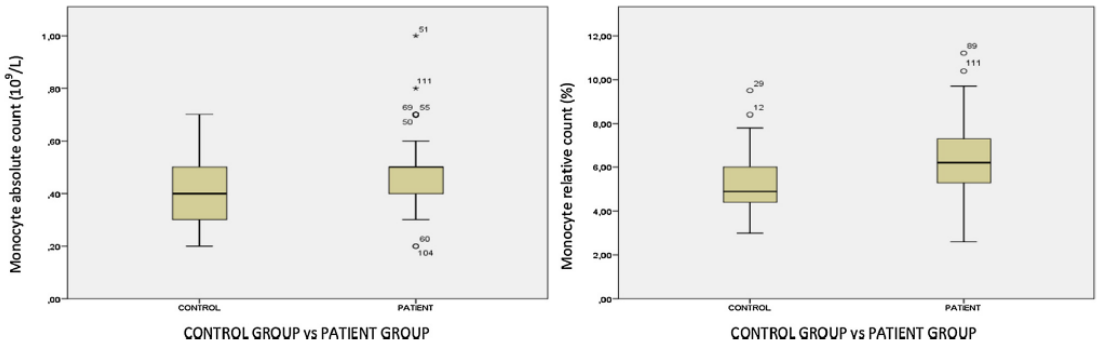

Fig. 2. Comparison of monocyte absolute blood concentrations and relative counts among the two groups.
Median (IQR) for monocyte absolute count (109/L) for control and patients: 0.40 (0.30–0.50) and 0.50 (0.40–0.50), monocyte relative count (%): 4.90 (4.40–6.00) and 6.20 (5.30–7.30), p-value < 0.001 for both variables.

cells, white cell distribution was compared between patients and controls as a secondary measure. The only cell count that was significantly different between the two groups was the monocytes, both absolute and relative count (p = 0.001 and <0.001, respectively). Differences were also confirmed when adjusting by BMI, age, gender and drugs intake at admission. To note, monocyte counts fell into the normal range (0.1–1 10^9/L absolute and 2.0–10.0% relative) for all controls and over 97% of patients. See Fig. 2.

4.4. Psychosocial stress indicators

Both Child and Parent SLE scales scored higher in the patient group. The family original structure was conserved in higher frequency among the Controls. Results and relevant significance are indicated in Table 3. There were no significant differences in SLE scale values, or in the rate of non-intact families among the six groups of patients.

Table 2
Patient grouping: clinical characteristic and medication/drug use.

DSM-IV diagnosis	*N*	*Diagnostic Cluster*	*N*	GAF[a]	Medication at admission (n)	THC positive at admission (n)
Psychosis	20	Psychosis & SZA	22	15 (15;21)	7	3
SZA	2					
Depression	18	Depression	19	40 (35;45)	11	1
Dysthymia	1					
BAD, manic or mixed episode with psychotic symptoms	8	BAD mania/mix/nos.	14	21 (15;35)	7	2
BAD–mania	3					
BAD-nos.	1					
Affective disorder nos.	1					
BAD -mixed episode	1					
OCD	6	OCD & Tics	8	43 (25;45)	8	0
Tourette/tic disorder	2					
Anxiety	6	Anxiety	9	45 (35;55)	5	0
PTSD	3					
Mixed emotion and behaviour disorder	3	Adjustment	5	35 (15;45)	2	0
Adjustment	2					
Total	77		77		40	

[a] Median (IQR); GAF = Global Assessment of Functioning; SZA = Schizoaffective disorder; BAD = bipolar affective disorder; OCD = obsessive compulsive disorder; PTSD = post-traumatic stress disorder.

Table 3
Stressful Life Events Scale Child and Parents and rates of intact families in the two groups.

	Patient group	Control group	*P*-value
SLEScale_subj[$]	39 (24–61)	14 (6–27)	<.001
SLEScale_parents[&]	36 (21–47)	11 (6–19)	<.001
Fam. original structure (%) [#]	28 (37%)	22 (67%)	0.005

Data are Median (IQRange) [$,&] or frequencies (%) [#]. Sample sizes are 54 vs 30[$], 44 and 31[&] and 76 vs 33[#] respectively for patients and controls.

4.5. Correlations between cytokines, monocytes and stress-measuring scales and indicators

Spearman's correlations were statistically significant between Child SLE scores and IL-1β ($r = 0.297$, $p = 0$ .006), IL-8 ($r = 0.224$, $p = 0.041$), MCP-1 ($r = 0.219$, $p =$ 0.045) and between Parents SLE scores and IL-1β ($r = 0.244$. $p = 0.035$), and monocyte absolute ($r =$ 0.248, $p =$ 0.032) and relative counts ($r = 0.232$, $p = 0.045$).

The SLE scales scores were significantly higher among subjects coming from families with non-conserved original structure ($p = 0.017$ and 0.002 for Child and Parents scales respectively). There was a tendency to significance for IL1-beta and IL-6 being higher in subjects with a non-conserved family original structure ($p =$ 0.054 and $p = 0.055$ respectively). To note, monocyte absolute counts correlated with IL-1β ($r = 0.219$, $p = 0$ .021), IL-6 ($r = 0.189$, $p = 0.047$) and IL-8 ($r = 0.187$, $p =$ 0.049), and monocyte relative counts with IL-1β ($r = 0.208$, $p = 0$ .028), IL-8 ($r = 0.231$, $p = 0.015$) and IP-10 ($r = 0.296$, $p =$ 0.002).

4.6. Logistic regression analysis

A multiple logistic regression analysis including all cytokines, identified IL8, IP10 and monocytes absolute count as independent predictors for patient status. When also including clinical variables (such as age, gender, stress measures), familiar disruption resulted also an independent variable, while the identified laboratory variables remained in the model with similar risk estimates (see Table 4).

An overview of quantitative results is provided in Appendix B of Supplementary information. Results for inter-group comparison of cytokine values between the different diagnostic subgroups is available on request to the authors (Appendix C of Supplementary information).

5. Discussion

This is the first study to our knowledge comparing a heterogeneous C&A psychiatric inpatient population across a large panel of cytokines. The major findings of the study can be summarized in 4 points.

IL-1β, IL-6, IL-8 MCP-1 and IP-10, as well as monocyte counts, were significantly higher in the C&A inpatient population. In particular, IL8 and IL1beta seemed to have a special sensibility for the psychiatric acute inpatient status, being higher throughout the psychiatric diagnosis.

The multiple regression analysis identified IL8, IP10 and monocytes – as well as familiar disruption – as independent predictors of patient status. To note, the relevant odds ratios (ORs) were outstanding.

Indicators of previous stressors and stress level were significantly higher in the inpatient population.

Some markers of inflammation (IL-1β, IL-8, MCP-1, monocytes) correlated significantly with the markers of stress level.

These results should be considered primary exploratory evidence, which need to be tested by further investigation. They are, however, consistent with general findings in child and adolescent psychopathology, where a recent systematic review concluded that there is preliminary evidence for elevated markers of inflammation (Mitchell and Goldstein, 2014). A recent review also points to an activation of monocytes in at least some young psychiatric patients (Bergink et al., 2014). The possibility that cytokines may be a predictor of patient condition is an attractive perspective in current medical research (Shahzad et al., 2010; Lepore et al., 1994). The presence of higher stress levels in the psychiatric population and the correlation between stress and inflammation measures are also coherent with the recent findings from the psychoneuroimmunology (PNI) field as will be discussed below.

These five cytokines belong to the innate immune system and are monocyte-macrophage related: they are all mainly pro-inflammatory and/or chemotactic molecules that act through multiple paths, both peripherally and at a central level, and that interact with each other. Their main actions on the Immune System (IS) are summarized in Appendix D of Supplementary information (available on request from the authors). Findings from the last decades, though, suggest that besides regulating inflammation, these molecules play a key role in brain development and influence brain functioning. Some authors have posited that peripheral monocyte activity reflects microglia activation or causes it (Bergink et al., 2014): both cells belong to the same developmental lineage (the myelomonocytic cell lineage), and it is speculated whether the same abnormalities detected in the peripheral cells can also be found in the microglia. The fact that monocytes are higher and apparently more active in our patient population supports this hypothesis.

One of the first issues raised at study design was whether peripheral cytokines could actually reach the brain, and if so, whether they could be related to inflammatory changes there. It is now clear that cytokines and chemokines can access the brain from the peripheral system, by crossing the blood brain barrier (BBB), communicating to relevant brain regions through afferents from the vagal nerve; activating endothelial cells and perivascular macrophages in the cerebral vasculature, and helping in recruiting activated immune cells to the brain parenchyma (Felger and Lotrich, 2013). Furthermore, it is known that these molecules can be produced by resident cells in the brain, especially microglia and astrocytes (Hanisch, 2002).

The actions of these molecules on the CNS vary along the life span and in relation with inflammatory processes and brain insults. They have proven critical for both physiological and pathological neurodevelopment. Levels which are too high can affect and "prime" both microglia and the hypothalamus-pituitary-adrenal (HPA) axis, crucial for brain development and functioning (Chrousos and Kino, 2005), and render the individual more sensitive to subsequent hits, with a higher risk of acquiring a subsequent mental illness after post-natal insults (Ratnayake et al., 2013; Feigenson et al., 2014). This is accounted for in the "developmental programming" model and theory (Beumer et al., 2012; Gluckman et al., 2008). It can be speculated whether the elevated levels of cytokines we found in the patients had been so since earlier stages, and had already primed microglia and/or HPA axis in the patient group.

Cytokine actions on the brain continue along the whole lifespan: in adult life IL-1β, IL-6, TNF-α—as well as specific T cells, macrophages, microglia and astrocytes are vital to the diverse

Table 4
Independent predictors of patient status identified by multiple logistic regression. Model A including only cytokines and leucocytes and model B considering also clinical variables.

	Model A		Model B	
	OR [95%CI]	*P*-value	OR [95%CI]	*P*-value
FAM_INTACT		8.14 [1.76–37.54]	0.007	
IL-8	1 (1Q, Ref.)	0.002	1 (1Q, Ref.)	0.001
2Q	0.92 [0.21–3.92]		0.82 [0.17–4.10]	
3Q	12.11 [2.16–67.83]		27.07 [3.57–205.14]	
4Q	32.02 [3.05–335.95]		54.13 [4.18–700.43]	
IP-10	1 (1Q, Ref.)	0.044	1 (1Q, Ref.)	0.042
2Q	14.06 [2.24–88.27]		19.26 [2.48–149.67]	
3Q	2.53 [0.52–12.24]		2.09 [0.38–11.49]	
4Q	3.67 [0.71–18.99]		4.03 [0.70–23.19]	
MONOC_ABS	1 (Ref.)	0.030	1 (1Q, Ref.)	0.063
2Q	2.10 [0.42–10.39]		1.24 [0.22–6.84]	
3Q	9.73 [1.60–59.28]		6.03 [0.84–43.30]	
4Q	18.67 [1.90–183.48]		19.44 [1.53–246.52]	

1Q. . . 4Q: 1st quartile. . . quartile 4. Quartiles cut-off points (11.98, 27.81, 115.16) for IL8, (129.11, 175.14, 213.4) for IP10 and (0.40, 0.40, 0.50) for monocytes count. ROC AUC [95%CI] for model A was 0.90 [0.83– 0.97] and for model B 0.91 [0.86–0.97]

processes of neuroplasticity (Mills et al., 2013), exert direct effects on the HPA axis (Mills et al., 2013) and on the metabolism of multiple neurotransmitters by inducing IDO (indoleamine 2–3 dioxegenase) enzyme(Miller et al., 2013). Chemokines, such as IL-8 and MCP-1, have been shown to have a neurotransmitter and neuromodulatory role, as well as both direct and indirect effects on regulation of neurogenesis (Stuart and Baune, 2014). If these actions were also confirmed in C&A brains, further research should investigate whether higher cytokines as found here contribute causally to the disorder itself, or are part of a recovery or reactive process activated by the acute psychopathology (Miller and Cole 2012; Jones and Thomsen 2013). Adolescence can be a time of special vulnerability: changes in gonadal hormones can interact with cytokines and play a role in brain development (O'Connor et al., 2014; Mills et al., 2013). Inflammation-related brain damage may be heightened during adolescence when myelination processes within the central corticolimbic circuitry of the brain occur (Benes, 1989)

Another interesting observation is the fact that the inflammatory phenotype seems related to a history of childhood adversities (Miller and Cole, 2012; Dennison et al., 2012). Early psychosocial stress, both prenatal and during infancy and adolescence, would "get under the skin" (O'Connor et al., 2014; Miller et al., 2011b) through epigenetic embedding (Tsankova et al., 2007), as well as mutual influences across the immune, endocrine and nervous systems (O'Connor et al., 2014; Miller et al., 2011b; Fagundes et al., 2013), and start a progression trajectory of elevated inflammation, hypersensitivity to further stressors, and higher risk for the development of psychiatric pathology, metabolic and other organic disease (Danese et al., 2008; Dennison et al., 2012; Coelho et al., 2014; Miller and Cole 2012). This inflammatory phenotype would be responsible for a subset of adult psychopathology (Miller and Chen, 2010; Miller and Cole, 2012) and be associated with a worse response to usual medical treatment (Felger and Lotrich, 2013; Nanni et al., 2012). In depression the concept of ICAD (inflammatory cytokine-associated depression) has been recently proposed (Lotrich, 2014).

Even "mundane" and common stressors, such as parental separation, could promote association between inflammation and psychopathology (Miller and Cole, 2012). Our patients might already be on this trajectory: they showed marked indicators of high stress levels in the last year before admission, but most likely also earlier in life. The majority came from families that had lost their original structure and this associated well with the stress scale scores and resulted a significant predictor of the patient's condition itself.

Cytokines could be the mediator in connecting pre- and early life stress with both predisposition to and further development of some subsets of mental illness (Ratnayake et al., 2013; Felger and Lotrich 2013). Even though most studies have been carried out in depression, research is also emerging for other diagnoses (Dennison et al., 2012), and a recent transdiagnostic meta-analysis has found that IL-1β and IL-6 levels associate to trauma exposure in clinical population, without differences between the specific psychiatric diagnosis (Tursich et al., 2014). This is also coherent with our results that show IL-1β, IL-8 and MCP-1 correlating with stress measures and being elevated across the diagnostic spectrum.

Also of note are the elevated ORs associating IL-8, IP-10 and monocyte count with the patient condition. The search for biomarkers is as active in psychiatry as in other medical conditions, and these same parameters have also been pointed out for various other pathologies (Shahzad et al., 2010; Prahalad et al., 2008). In C&A psychiatric population they could be more specific of a psychiatric condition than in adults, given the frequent lack of other medical comorbidities. A challenge in their use is the lack of reference values for both healthy and psychiatric population: our cut-off points should be replicated by other studies and validated by prospective investigations.

In order to further investigate and model these causal hypotheses, an exploratory post-hoc Path Analysis was conducted, assessing whether the association between past stress and psychiatric diagnosis can be mediated by higher monocytes and thus higher cytokine levels. Despite all the limitations of applying such a model to our data, this analysis confirms a possible causal effect of stress over patient condition, and of stress over monocytes, of monocytes over cytokines, and of cytokines over patient condition. The results are illustrated and discussed in Appendix E of Supplementary information.

Various limitations of this study must be considered, the major being that it is a cross-sectional study and does not therefore clarify temporal dynamic association between markers and symptoms. Prospective studies including C&A population will be needed to better understand the causal mechanisms and temporal sequence. Still, we consider ours an exploratory work: our results suggest that it would make sense to investigate a broad panel of cytokines across diagnostic categories.

One of the difficulties we faced at study design was to establish the adequate sample size in advance, since there were no previous studies with similar design and objectives. We therefore referred to similar studies in adults and collected all consecutive patients in a defined time period. While this might be a limitation for a

confirmatory project, it is a common and acceptable practice in the context of an exploratory work. Also, the recruitment of 77C&A inpatients makes our sample one of the largest reported to date in this area of C&A literature.

Another limitation is the relatively small number of control subjects, determined by time constraints: this may have limited reaching statistical significance in some parameters.

The sizes of the patients' subgroups are also small. The main purpose of the study was to compare patients vs controls, in the search for common markers across psychiatric psychopathology. The analysis on subgroups was mainly exploratory and targeted at double-contrasting the primary hypothesis, i.e., at detecting possible markers which were actually shared across the different groups, or on the contrary which were more specific to some single cluster. With regard to the high number of statistical contrasts, since no multiplicity adjustments have been applied justified on the basis of the exploratory nature of this study, the results should be taken with caution.

Some of the analyzed cytokines were undetectable, despite the use of ultrasensitive test: this has been described before (Lepore et al., 1994; Prahalad et al., 2008), and could depend on the sensitivity of available tests, and could have limited the number of different cytokines found between the two samples.

Regarding stress measures, the first limitation were the relevant missing data in the SLES among the patient population. This was mainly due to difficulties related with the psychopathological status, language or cultural barriers of the parents'. Missing data were handled without any imputation, and affected sample sizes for analyses of stress and correlation measure. We consider it relevant that, despite these reduced sample sizes, some significant association has been found between stress and inflammatory markers. The missing data also impeded the use of SLE-s scores in the multiple logistic regression, as the valid sample size was reduced too much.

The reliability of the stress scales themselves can also be questioned, being subjective measures. Other objective/biological measures should be added in future studies, for example linked to long-term cortisol release (Wosu et al., 2013).

What is more, we consider that our stress measures account mainly for chronic stress. The recent hospitalization may itself be an acute stressor, and its possible effect on inflammatory markers like IL-8 – as suggested by some recent works (Dutheil et al., 2013) – should also be investigated and ruled out. This issue could be approached using a cohort of patients that has not yet been hospitalized as an additional clinical group.

The results on psychosocial stress also indicate that it could be relevant for future studies to account for it in a standardized and longitudinal manner, and to correlate stress measures with inflammatory markers.

Further investigations should focus on the underlying pathways and the complex interactions between cytokines to understand the ethiopathogenetics of the model.

A better break-down of the underlying pathways and the complex interactions between cytokines will be important. Also, if the neuroinflammation hypothesis for stress and psychopathology is confirmed, this could be extremely relevant with respect to treatment options. A relevant treatment investigation line already targets inflammation and immunity. Trials with minocycline, an antibiotic with likely anti-inflammatory and neuroprotective actions, have given positive results both in early and in treatment resistant schizophrenia (Qurashi et al., 2014). Studies on use of cytokine-antagonists such as anti- TNF-α in depression, suggest that they may improve depressive symptoms, and possibly only in patients with high baseline inflammation (Raison et al., 2013). Adjunctive therapy with non-steroidal anti-inflammatory drugs seems to reduce symptomatology both in depression (Müller et al., 2006) and in schizophrenia (Andrade 2014). Physical exercise could also improve psychopathology via its anti-inflammatory effects (Mills et al., 2013; Eyre and Baune, 2012). Omega-3 are another potential candidate treatment (Lin et al., 2007), due to their anti-inflammatory effects, and the first studies and reviews suggest they would have a possible antidepressant effect both in adults (Lin et al., 2007) and in children (Nemets et al., 2006). Promotion of healthy psychosocial experiences for children and adolescents, as well as family interventions, could have a much greater effect than attempting to modify health-related behaviours or improve access to health care in adulthood (Shonkoff et al., 2009).

6. Conclusions

This investigation shows that C&A acute psychopathology is associated with an elevation of various pro-inflammatory agents across the psychiatric diagnostic spectrum, and that IL-8, IP-10 and monocyte count could be promising biomarkers. Stress may be a causal factor, and cytokines the mediating agents, along an inflammatory trajectory, such as hypothesized by psychoneuroimmunology developmental models. If this is confirmed by longitudinal research, intervention in C&A population could have a strong impact in terms of treatment and prevention strategies.

Conflict of interest

All authors declare that they have no conflict of interest.

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Authors' contributions

Maria Gariup: data collection and analysis, literature review, paper editing.

Azucena González: immunology consultant, laboratory tests, paper review.

Luisa Lázaro: consultant in study design, paper review.

Ferrán Torres: statistical analysis, paper review.

Carles Serra: immunology consultant, laboratory tests, paper review.

Astrid Morer: study design and coordination, paper co-editing and reviewing.

All authors have approved the final article.

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Appendix A. Overview of most studied cytokine alterations in psychiatric disorders

	PSYCHOSIS SPECTRUM					BD SPECTRUM				MDD	OCD	PTSD	ASD
	AR	FEP	SO	TR	SCZ nes	BD Trait	MAN	EUTH	BPDEP				
References:	1	1	1	1	1	2	2	2	2	5–7	3	8–10	4
IL-1α	-	-	-	-	-	-	-	-	-	-	-	-	n.s.
IL-1β		>HC			> HC (trend)					n.s./ in EU >HC	<HC	>HC	>HC
IL-1RA	>HC				n.s.		>HC	>HC		-	-	-	n.s.
IL-2		n.s.			n.s.					n.s.	-	-	-
sIL-2R		>HC		>HC	>HC		>HC. >EUTH	>HC		>HC	-	-	-
IL-4	-	-	-	-	>HC		>HC	>HC	>HC	n.s.	-	-	n.s.
IL-6	>HC	>HC		n.s.	n.s.		>HC; > BPDEP	n.s.	n.s.	>HC	n.s.. >HC in med.free pts.	>HC	>HC
sIL-6R	-	-	-	-	>HC					-	-	-	-
IL-8	>HC				>HC				>HC	n.s.	-	-	>HC
IL-10	<HC				>HC		trend >HC		>HC	n.s.	-	-	n.s.
IL-12		>HC			-	-	-	-	-	-	-	-	-
IL-12p40	-	-	-	-	-	-	-	-	-	-	-	-	n.s.
IL-17	-	-	-	-	-	-	-	-	-	-	-	-	n.s.
IL-23	-	-	-	-	-	-	-	-	-	-	-	-	n.s.
IFN-Y	>HC	>HC			n.s.		n.s.	n.s.	n.s.	n.s.	-	-	>HC
TGF-β	>HC	>HC			-	-	-	-	-	-	-	-	-
TGF-β1	-	-	-	-	-	-	-	-	-	-	-	-	<HC
TNF-α	>HC	>HC			>HC					>HC	n.s.	>HC	n.s.
sTNF-R1	-	-	-	-	>HC		>HC	>HC		-		-	-
G-CSF	-	-	-	-	-	-	-	-	-	-		-	n.s.
Eotaxin/CCL11	-	-	-	-	-	-	-	-	-	-		-	>HC
MCP-1=CCL2	-	-	-	-	n.s.			n.s.		-		-	>HC
RANTES	-	-	-	-	-	-	-	-	-	-		-	n.s.
MIP-1α	-	-	-	-	-	-	-	-	-	-		-	n.s.
MIP-1β	-	-	-	-	-	-	-	-	-	-		-	n.s.
CRP													

AR= acute relapse; FEP=1st episode psychosis; SO=; TR= ; SCZ nes= schizophrenia patients; BD= Bipolar disorder; MAN= Mania; EUTH= euthymia; BPDEP= Bipolar depression; MDD= Major Depression; ASD=Autism Spectrum Disorder

Appendix B. Comparison between controls and all patients - Medians (IQR)

	Unity	CONTROL (n=34)	PATIENT (n=77)	TOTAL (n=111)	p-value (all)
CRP	mg/dL	0.03 (0.02 . 0.04)	0.03 (0.01 . 0.06)	0.03 (0.02 . 0.04)	0.897
BMI	Kg/sqmt	20.82 (19.70 . 22.23)	20.21 (18.42 . 23.80)	20.51 (19.22 . 22.67)	0.419
NR_INGR		(.)	1.00 (1.00 . 1.00)	1.00 (1.00 . 1.00)	NA
GAF		85.00 (85.00 . 90.00)	31.00 (15.00 . 45.00)	41.00 (21.00 . 81.00)	<.0001
GMCSF	pg/mL	0.00 (0.00 . 3.08)	1.82 (0.00 . 3.80)	1.43 (0.00 . 3.47)	0.142
IFN-γ	pg/mL	0.00 (0.00 . 0.00)	0.00 (0.00 . 0.55)	0.00 (0.00 . 0.49)	0.307
IL1b	pg/mL	**0.00 (0.00 . 0.00)**	**0.35 (0.00 . 1.61)**	**0.00 (0.00 . 1.08)**	**<.0001**
IL2	pg/mL	0.00 (0.00 . 0.00)	0.00 (0.00 . 1.17)	0.00 (0.00 . 0.98)	0.284
IL4	pg/mL	0.00 (0.00 . 0.00)	0.00 (0.00 . 2.44)	0.00 (0.00 . 2.44)	0.485
IL5	pg/mL	0.00 (0.00 . 0.00)	0.00 (0.00 . 0.00)	0.00 (0.00 . 0.00)	0.632
IL6	pg/mL	**0.00 (0.00 . 0.38)**	**0.51 (0.00 . 1.17)**	**0.38 (0.00 . 0.99)**	**0.004**
IL8	pg/mL	**12.43 (9.77 . 16.49)**	**59.21 (19.81 . 176.85)**	**27.81 (11.98 . 115.16)**	**<.0001**
IL10	pg/mL	0.00 (0.00 . 0.00)	0.00 (0.00 . 0.00)	0.00 (0.00 . 0.00)	0.550
TNFα	pg/mL	0.00 (0.00 . 0.00)	0.00 (0.00 . 1.74)	0.00 (0.00 . 1.09)	0.111
IP10	pg/mL	**125.83 (82.35 . 199.06)**	**179.70 (145.75 . 227.48)**	**175.14 (129.11 . 213.40)**	**0.005**
MCP_I	pg/mL	**182.30 (135.97 . 229.05)**	**228.08 (147.91 . 281.07)**	**204.48 (142.46 . 280.13)**	**0.047**
LEUKOCYT_TOT	10^9/L	7.25 (6.45 , 8.74)	7.53 (6.10 , 8.49)	7.30 (6.10 , 8.50)	0.851
NEUTROPH_PERC	%	52.80 (48.50 , 61.30)	50.90 (45.10 , 57.90)	51.90 (45.80 , 59.90)	0.169
LYMPHOC_PERC	%	34.75 (29.40 , 38.80)	34.40 (30.20 , 41.60)	34.40 (29.60 , 40.00)	0.568
MONOC_PERC	%	**4.90 (4.40 , 6.00)**	**6.20 (5.30 , 7.30)**	**5.90 (4.90 , 7.10)**	**<0.001**
EOSINOPH_PERC	%	2.40 (1.70 , 4.80)	3.00 (2.00 , 4.30)	2.90 (2.00 , 4.60)	0.367
BASOPH_PERC	%	0.60 (0.50 , 0.80)	0.50 (0.40 , 0.80)	0.50 (0.40 , 0.80)	0.322
LUC_PERC	%	2.10 (1.90 , 2.60)	2.00 (1.80 , 2.60)	2.10 (1.80 , 2.60)	0.668
NEUTROPH_ABS	10^9/L	3.75 (3.00 , 5.00)	3.60 (2.90 , 4.70)	3.70 (3.00 , 4.70)	0.695
LYMPHOC_ABS	10^9/L	2.40 (1.90 , 2.90)	2.50 (1.90 , 3.00)	2.50 (1.90 , 2.90)	0.487
MONOC_ABS	10^9/L	**0.40 (0.30 , 0.50)**	**0.50 (0.40 , 0.50)**	**0.40 (0.40 , 0.50)**	**0.001**
EOSINOPH_ABS	10^9/L	0.20 (0.10 , 0.30)	0.20 (0.20 , 0.30)	0.20 (0.10 , 0.30)	0.374
BASOPH_ABS	10^9/L	0.00 (0.00 , 0.00)	0.00 (0.00 , 0.10)	0.00 (0.00 , 0.00)	0.346
LUC_ABS	10^9/L	0.20 (0.10 , 0.20)	0.20 (0.10 , 0.20)	0.20 (0.10 , 0.20)	0.534
SLES_Child		**14.00 (6.00 . 27.00)**	**39.00 (24.00 . 61.00)**	**31.00 (14.00 . 48.00)**	**<.0001**
SLES_Parents		**11.00 (6.00 . 19.00)**	**35.50 (20.50 . 47.00)**	**23.00 (11.00 . 42.00)**	**<.0001**

APPENDIX C - INTER-SUBGROUPS COMPARISON

	CONTROL* (n=34)	ADJUSTMENT* (n=5)	ANXIETY* (n=9)	OCD & TICs* (n=8)	DEPRESSION* (n=19)	BAD MANIA OR MIX * (n=14)	PSYCHOSIS & SAD * (n=22)	TOTAL * (n=111)	p-value (all)	p-value (C,ADJ)	p-value (C, ANX)	p-value (C, OCD)	p-value (C,DEPRE)	p-value (C,BAD)	p-value (C,PSYCH)	p-value (ADJ,ANX)	p-value (ADJ.OCD)	p-value (ADJ.DEPRE)	p-value (ADJ.BAD)	p-value (ADJ.PSYCH)	p-value (ANX,OCD)	p-value (ANX,DEPREE)	p-value (ANX,BAD)	p-value (ANX,PSYCH)	p-value (OCD,DEPREE)	p-value (OCD,BAD)	p-value (OCD,PSYCH)	p-value (DEPRE,BAD)	p-value (DEPRE,PSYCH)	p-value (BAD,PSYCH)
GMCSF	0.00 (0.00 , 3.08)	1.42 (0.00 , 1.44)	0.00 (0.00 , 2.01)	8.90 (2.18 , 12.67)	2.17 (0.00 , 6.02)	2.01 (0.00 , 4.08)	0.00 (0.00 , 2.67)	1.43 (0.00 , 3.47)	0.043	0.945	0.934	**0.017**	0.054	0.232	0.963	1.000	0.991	0.998	0.186	0.865	**0.046**	0.130	0.276	1.000	0.251	0.100	**0.014**	0.634	0.079	0.208
IFNg	0.00 (0.00 , 0.00)	0.00 (0.00 , 0.60)	0.00 (0.00 , 0.00)	0.23 (0.00 , 1.13)	0.00 (0.00 , 0.68)	0.00 (0.00 , 0.00)	0.00 (0.00 , 0.40)	0.00 (0.00 , 0.49)	0.681	0.399	0.802	0.138	0.242	0.924	0.744	0.683	0.815	1.000	0.558	0.469	0.411	0.681	1.000	0.978	0.576	0.245	0.181	0.439	0.348	0.849
IL1b	0.00 (0.00 , 0.00)	0.90 (0.00 , 0.94)	0.00 (0.00 , 0.17)	0.34 (0.00 , 2.13)	1.08 (0.00 , 2.47)	0.46 (0.00 , 1.84)	0.00 (0.00 , 1.51)	0.00 (0.00 , 1.08)	**0.001**	**0.005**	**0.020**	**0.007**	**<.0001**	**0.001**	**0.006**	0.489	1.000	0.476	0.885	0.565	0.448	0.116	0.386	0.810	0.536	0.746	0.556	0.590	0.074	0.292
IL2	0.00 (0.00 , 0.00)	0.00 (0.00 , 0.00)	0.00 (0.00 , 0.00)	1.33 (0.00 , 2.33)	0.00 (0.00 , 1.54)	0.00 (0.00 , 2.43)	0.00 (0.00 , 1.17)	0.00 (0.00 , 0.98)	0.309	0.883	0.868	0.039	0.408	0.251	0.744	1.000	0.117	0.486	0.475	0.603	0.658	0.412	0.216	0.557	0.301	0.422	0.071	0.731	0.173	0.420
IL4	0.00 (0.00 , 0.00)	0.00 (0.00 , 0.00)	0.00 (0.00 , 0.00)	1.01 (0.00 , 4.57)	0.00 (0.00 , 3.78)	0.00 (0.00 , 4.92)	0.00 (0.00 , 1.33)	0.00 (0.00 , 2.44)	0.701	0.799	0.857	0.259	0.411	0.366	0.974	1.000	0.377	0.559	0.475	0.841	0.301	0.447	0.448	0.889	0.658	0.791	0.239	0.850	0.406	0.420
IL5	0.00 (0.00 , 0.00)	0.00 (0.00 , 0.00)	0.00 (0.00 , 0.00)	0.00 (0.00 , 0.00)	0.00 (0.00 , 0.00)	0.00 (0.00 , 0.00)	0.00 (0.00 , 0.00)	0.00 (0.00 , 0.00)	0.312	0.146	0.650	0.304	0.482	0.554	0.359	0.254	0.733	0.078	0.138	0.464	0.360	1.000	1.000	0.392	0.156	0.233	0.894	1.000	0.203	0.277
IL6	0.00 (0.00 , 0.38)	0.00 (0.00 , 0.51)	0.49 (0.00 , 0.63)	0.82 (0.00 , 1.37)	0.70 (0.49 , 2.74)	0.00 (0.00 , 5.95)	0.53 (0.00 , 0.89)	0.38 (0.00 , 0.99)	0.022	0.834	0.130	0.069	**0.001**	0.102	0.062	0.317	0.302	0.064	0.511	0.172	0.501	0.094	0.869	0.690	0.579	0.857	0.534	0.472	0.141	0.896
IL8	12.43 (9.77 , 16.49)	42.05 (32.66 , 252.16)	28.55 (13.38 , 82.32)	64.43 (24.94 , 198.81)	85.15 (20.92 , 511.66)	53.17 (31.15 , 302.08)	28.14 (11.54 , 136.88)	27.81 (11.88 , 115.16)	**<.0001**	**0.014**	**0.026**	**0.001**	**<.0001**	**0.006**	**0.028**	0.438	1.000	0.375	0.820	0.442	0.282	0.059	0.310	1.000	0.864	0.973	0.280	0.428	**0.049**	0.453
IL10	0.00 (0.00 , 0.00)	0.00 (0.00 , 0.00)	0.00 (0.00 , 0.00)	0.92 (0.00 , 2.59)	0.00 (0.00 , 1.52)	0.00 (0.00 , 0.00)	0.00 (0.00 , 0.00)	0.00 (0.00 , 0.00)	0.190	0.391	0.245	0.065	0.353	0.652	0.845	1.000	0.115	0.242	0.321	0.348	0.038	0.117	0.176	0.201	0.367	0.165	0.121	0.683	0.442	0.907
TNFa	0.00 (0.00 , 0.00)	0.00 (0.00 , 0.00)	0.00 (0.00 , 0.00)	0.55 (0.00 , 3.58)	0.00 (0.00 , 2.78)	0.00 (0.00 , 4.03)	0.00 (0.00 , 2.26)	0.00 (0.00 , 1.09)	0.241	0.263	0.967	0.093	0.064	0.168	0.264	0.343	0.115	0.112	0.169	0.180	0.254	0.250	0.404	0.555	1.000	0.850	0.438	0.902	0.402	0.592
IP/Ibre	125.83 (82.35 , 199.06)	193.92 (165.96 , 203.19)	175.50 (151.70 , 210.72)	206.11 (187.12 , 227.68)	182.55 (160.69 , 233.44)	188.98 (146.36 , 235.50)	159.47 (120.11 , 181.84)	175.14 (129.11 , 213.40)	**0.010**	0.129	0.112	**0.024**	**0.021**	0.078	0.222	0.896	0.339	0.877	0.891	0.207	0.134	0.670	0.828	0.334	0.165	0.279	**0.029**	0.859	0.132	0.291
MCP 1	182.30 (135.97 , .	187.84 (182.06 , 481.90)	241.57 (232.57 , 286.50)	203.92 (155.33 , 260.15)	231.46 (146.08 , 273.09)	241.66 (195.99 , 281.07)	198.48 (152.26 , 291.84)	204.48 (142.46 , 280.13)	**0.040**	0.291	**0.014**	0.536	0.267	0.098	0.373	0.696	0.721	0.529	1.000	0.643	0.247	0.384	0.598	0.240	0.833	0.403	0.871	0.601	0.928	0.413
* median (IQR)																															
p-values are for two-by-two comparisons between the different subgroups of subjects. C = Controls, ADJ = Adjustment Disorders; ANX = Anxiety; OCD = Obsessive- Compulsive Disorders; DEPRE = Depression; BAD = Bipolar Dis.; PSYCH = Perchotic Disorders																															

Appendix D. Summary of main functions of the five cytokines

Interleukin-1β (IL-1β) is a pro-inflammatory cytokine produced mainly by activated macrophages that exerts numerous biological effects, including activation of several inflammatory processes (through activation of T cells among others) and induction of expression of acute-phase proteins. It has also an important function in neuro-immune responses and direct effects on the brain itself, where it influences neurodegenerative and neuroprotective processes and is involved in modulation of synaptic plasticity (Allan, Tyrrell, and Rothwell 2005). There is now extensive evidence to support the direct involvement of interleukin-1 in the neuronal injury that occurs in both acute and chronic neurodegenerative disorders (Allan, Tyrrell, and Rothwell 2005). IL-1β has been repeatedly associated with various psychiatric disorders, and recent meta-analysis confirm it is higher in FEP, schizophrenia (trend), in European population with MDD, and in ASD (Miller et al. 2011; Modabbernia et al. 2013; Gray and Bloch 2013; Masi et al. 2014).
Due to these finding it was suggested that IL-1β gene (IL1B) might be involved in the development of these disorders. The first study on the matter, though. does not provide supportive evidence for the contribution of IL1B to schizophrenia susceptibility(Shibuya et al. 2014).

Interleukin-6 (IL-6) is peripherally produced by macrophages as an acute phase response, as well as by T cells, having an important role in the differentiation of lymphocytes. Moreover it may be the most important cytokine involved in microglial activity and inflammatory responses (Na, Jung, and Kim 2014). Depending on the microenvironment of the CNS, IL-6 can exert a neurotoxic or a neuroprotective effect (Krady et al. 2008). Overexpressed IL-6 inhibits hippocampal neurogenesis, possibly by acting on the IL-6 receptor or a common signal transducer, glycoprotein 130 (gp130), in the dentate gyrus and by stimulating the hypothalamus-pituitary-adrenal (HPA) axis. IL-6 also

inhibits long-term potentiation (LTP) in animal models, and the neutralization of IL-6 with an anti-IL-6 antibody prolongs LTP and improves long-term memory (reviewed in (Krady et al. 2008)). Serum IL-6 levels in humans correlate with poor cognitive performance and predict risk of dementia (Weaver et al. 2002). Even though it was classically associated with depression, recent meta-analysis in adult population (Miller et al. 2011; Modabbernia et al. 2013; Gray and Bloch 2013; Masi et al. 2014) indicate that besides in MDD, IL-6 is higher in acute relapse and first episode psychosis, mania and ASD.

In-utero exposure to both IL-1β and IL-6 in rats - mimicking a maternal infection/inflammation during pregnancy - significantly reduced dendrite development and complexity of developing cortical neurons(Gilmore et al. 2004; Liu et al. 2013), consistent with the neuropathology of schizophrenia. In animal models IL-6 has been described to shape neuron morphology, and to be produced by neurons as well. IL-8 might also play a role in brain neurodevelopment: a prospective study showed that the mothers to schizophrenia patients had had nearly doubled serum levels of IL-8 during the 2nd trimester of their pregnancy, in comparison to the mothers of controls(Brown et al. 2004).

Microglial activation and increased density are in fact a consistent finding in post-mortem brain of both schizophrenic and autistic patients (Ratnayake et al. 2013; Bayer et al. 1999; Morgan et al. 2010).

Interleukin-8 (IL-8 or CXCL8) is a chemokine produced mainly by macrophages and is an important mediator of the innate immune response with pleiotropic effects on the peripheral immune system. It is a potent chemoattractant for neutrophiles, and has chemotactic effects of

variable potency also on B and T lymphocytes, natural killer and dendritic cells (Murphy et al.. 2000). Additionally it may have pro-inflammatory cytokine-like effects in supporting activation and degranulation of neutrophils, basophils and monocyte/macrophages. The effects of CXCL8 on the CNS and the CNS immune milieu are less well studied (see (Stuart and Baune 2014) for a review). The receptors for IL-8 are constitutively expressed on multiple brain cells: neurons, astrocytes, microglia, oligodendrocytes, BBB endothelial cells, of neural stem/progenitor cells (NSC/NPCs). Its ligand is believed to be primarily expressed by CNS resident and infiltrating immune cells, however BBB endothelial cells may express particularly high levels of this protein in response to other pro-inflammatory cytokines such as tumour necrosis factor (TNF-α). It is likely that in conditions of gross BBB compromise IL8 may regulate the activity of infiltrating peripheral immune cells, however the role of this factor in chronic low-grade CNS inflammation remains unclear. In-vitro studies have also suggested that IL-8 might play a neuromodulatory role, and might contribute in regulating the migration of neural stem/progenitor cells in adult neuro/gliogenesis or in early neurodevelopmental periods. The in-vivo relevance of this factor to NSC/NPC migration remains to be studied. No genetic studies have been found analysing this chemokine(Stuart and Baune 2014).

In adult psychiatric population recent meta-analyses indicate that IL-8 is higher in acute psychotic relapse, schizophrenia, bipolar depression and autism spectrum disorder. Studies in other populations have been less consistent(Miller et al. 2011; Modabbernia et al. 2013; Gray and Bloch 2013; Masi et al. 2014) . The only prospective study followed up an elderly population (70-90 y/o) during two years (Baune et al. 2012): serum IL-8 was positively associated with depressive symptoms both at baseline and at two years follow-up, with an increase in depressive symptoms from baseline to two years. These results though cannot be generalised to younger populations.

Monocyte chemoattractant protein-1 (MCP-1 or CCL2) is primarily secreted by monocytes, macrophages and dendritic cells and best recognised for its chemotactic and activating actions on monocyte/macrophages, T lymphocytes and dendritic cells. Besides, recent evidence suggests it can have a neurotransmitter/ neuromodulatory role on brain functions similar to several neuropeptides with both pro and anti-inflammatory actions (reviewed in (Mélik-Parsadaniantz and Rostène 2008)). Additionally, similar to IL-8, in vitro studies have suggested that CCL2 may also direct the migration and differentiation of NPC/NSCs. Specifically the effect of BBB endothelial cells in directing NPC/NSC proliferation and differentiation is mediated by CCL2. The pleiotropic actions of this chemokine on the CNS are likely to be relevant, not only to the pathophysiology of psychiatric disorders in adulthood but potentially also to the developmental pathogenesis of these disorders– as suggested by its extensive and dynamic expression during in utero neurodevelopment (see (Stuart and Baune 2014) for a review).

In adult psychiatric population, meta-analyses give conclusive results only in the case of ASD, where MCP-1 has been found higher than in controls. Recent reviews suggest that MCP-1 might be elevated in depression and schizophrenia patients (Stuart and Baune 2014), and that it might play a role in mood disorders (Padmos et al. 2008). There are also reports of higher expression of MCP-1 in Tourette syndrome post-mortem brains (Morer et al. 2010).

IFN-γ-inducible protein 10 (IP-10 or CXCL10) is secreted by monocytes / macrophages, endothelial cells and T cells in response to IFN-α, β and γ, TNF-α (via NF-kB pathway), LPS. It is a pro-inflammatory cytokine, a chemoattractant for T and NK cells and has been involved in pathogenesis of infection and shock. It has rarely been analysed in psychiatric disorders and a few studies have described it higher in depression, bipolar disorder, suicidal behaviour (reviewed in (Stuart and Baune 2014)).

Appendix E

Supplementary analysis: Path Analysis exploring the relationship between psychiatric diagnosis, stress and cytokines

In this study it is proposed that cytokines and the immune system may be the mediator linking stress with psychopathology. In order to further investigate and model these causal hypotheses, an exploratory post-hoc Path Analysis was conducted, assessing whether the association between past stress and psychiatric diagnosis can be mediated by higher monocytes and thus higher cytokine levels.

The parameters included were a stress levels quantitative scale (SLE scale parents), a quantitative measure that could be associated with psychiatric condition (GAF – Global Assessment of Functioning - scale), monocyte absolute counts and the five cytokines which had been found significantly different between the patient and the control condition (IL-1β, IL-6, IL-8, IP-10, MCP-1). The analysis was conducted using the Proc CALIS of SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

Despite all the limitations of applying such model to our data (please see below), this analysis confirms a possible causal relation between stress levels and patient condition, as well as between stress, monocytes, cytokines and patient condition respectively, supporting the idea that the influence of stress over psychopathology might be mediated by cytokines.

Figure E. Results of the Path Analysis – coefficients and p-values.

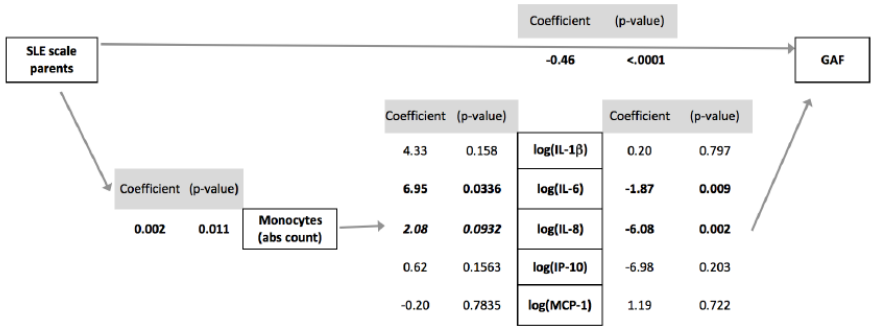

Figure E.1 footnote: SLE = Stressful Life Events Scale; abs count = absolute counts; log = logarithm; GAF = Global Assessment of Functioning Scale.

It has to be acknowledged that this modelling has several limitations. Originally, path analysis required quantitative variables, and for this reason GAF and SLE scales were adopted. However, the distinction between patients and controls is not fully represented by the GAF scale, e.g. some patients can function moderately well even with a high degree of psychological suffering. For stress level variables (SLE scale parents) there were a number of missing values among the patients, which might have limited the reached significance (in the logistic regression model analysis the dichotomous variable "family intact" was used instead as a stress indicator). Regarding the cytokines related variables, due to a lack of normal distribution we have used log-transformed data but its suitability is still doubtful (we had used quartiles in the logistic regression models, which is not appropriate for the SEM approach).

4.2 STUDY 2

Title

Autoantibodies, elevated cytokines and neurocognitive abnormalities in offspring of women with systemic lupus erythematosus: comparison with healthy controls

AIM

To investigate immune, inflammatory and neuropsychological asset of a sample of 21 offspring of women with Lupus (age 8-17), in comparison with healthy controls and the general population.
To search for possible associations between offspring health and perceived stress, and between these and maternal conditions.
In particular, we will analyze:

- An extensive panel of cytokines IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL_10, GM-CSF, IFN-γ, TNF-α, White cells, CRP
- Various antibodies, among which those described as neurotoxic in SLE patients
- Neurocognition
- Rates of psychopathology
- Stressors: measure of family structure, and parent and child-reported measures of stress in the past 12 months
- Maternal psychophysical health

RESÚMEN EN CASTELLANO:

Introducción
Investigaciones recientes describen una mayor incidencia de trastornos del neurodesarrollo y del aprendizaje en los hijos de mujeres diagnosticadas con Lupus Eritematoso Sistémico. Los factores implicados son las adversidades del embarazo y el parto y la exposición a anticuerpos y citocinas maternos. Se sabe poco sobre la condición inmunológica de los hijos o la relación entre la salud psicofísica materna y la filial.

Objetivos
Este estudio se realizó con el objetivo de analizar la configuración inmunológica, la psicopatología y las características neuropsicológicas de niños y adolescentes hijos de mujeres con Lupus, comparándoles con controles sanos y relacionando su estado con la condición psicofísica materna.

Métodos
Se reclutaron 21 hijos (edades 8 -17 años) de 17 mujeres con Lupus y 34 controles sanos. Se compararon las condiciones del embarazo, los factores de estrés y las características inmunológicas, psicopatológicas y neuropsicológicas. Las pruebas inmunológicas incluyeron batería estándar de Lupus, autoanticuerpos relacionados con el Lupus, anticuerpos contra la subunidad GluN2 del receptor de N-metil-D-aspartato (NMDAR) (anti-DWEYS-GluN2 Ab) y niveles de diez citocinas (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, GMCSF, IFN-γ, TNF-α).

Resultados
Los hijos tenían un recuento de leucocitos más bajo ($p = 0,001$) y niveles más altos de anticuerpos anti-dsDNA ($p = 0,022$), anti-DWEYS-GluN2 Ab ($p <0,001$) y ocho citocinas (IL-1β, IL-2, IL- 4, IL-5, IL-6, IL-10, TNF-α - todos $p <0,001$ - e IFN-γ, $p = 0,026$) que los controles. Sus niveles de citocinas no diferían de los de sus madres; El 23,9% de los hijos cumplía criterios para un diagnóstico clínico psiquiátrico. No se encontraron diferencias en las medidas de inteligencia. Varias puntuaciones neuropsicológicas se correlacionaron inversamente con la salud psicofísica materna.

Conclusiones
El perfil de los hijos de mujeres con Lupus sugiere activación proinflamatoria y autoinmune. Su tasa de diagnóstico psiquiátrico aparece más elevada que en la población general y su desempeño cognitivo resulta relacionado con la salud psicofísica materna. Estudios longitudinales podrían aclarar en cual medida e intervalos temporales, las condiciones inmunológicas y psicosociales influyen en la psicopatología y la neurocognición.

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ORIGINAL ARTICLE

Autoantibodies, elevated cytokines, and neurocognitive abnormalities in offspring of women with systemic lupus erythematosus: comparison with healthy controls

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Abstract

Introduction Research describes higher incidence of neurodevelopmental disorders and learning disabilities in offspring of women affected by lupus. Factors implied are pregnancy and delivery adversities and exposure to maternal antibodies and cytokines. Little is known about the offspring immunological condition or the relation between offspring and maternal condition.

Objectives This study was conducted in order to analyze immunological configuration, psychopathology, and neuropsychological performance of young offspring of women with lupus, in comparison with healthy controls and in relation to maternal psychophysical condition.

Methods Twenty-one offspring aged 8–17 of 17 women with lupus and 34 controls were recruited. Pregnancy conditions, stress factors, and immunological, psychopathological, and neuropsychological characteristics were compared. Immunological tests included standard lupus screening, lupus-related autoantibodies, antibodies against GluN2 subunit of the *N*-methyl-D-aspartate receptor (NMDAR) (anti-DWEYS Ab), and levels of ten cytokines (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, GMCSF, IFN-γ, TNF-α).

Results Offspring had lower leukocyte count ($p = 0.001$) and higher levels of anti-dsDNA Ab ($p = 0.022$), anti-DWEYS-GluN2 Ab ($p < 0.001$), and eight cytokines (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, TNF-α—all $p < 0.001$—and IFN-γ, $p = 0.026$) than

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controls. Their cytokine levels did not differ from their mothers'; 23.9% of offspring met the criteria for a clinical psychiatric diagnosis. No differences were found in intelligence measures. Various neuropsychological scores correlated inversely with maternal psychophysical health.

Conclusions Offspring's profile suggests proinflammatory and autoimmune activation. Their rate of psychiatric diagnosis appears higher than in the general population, and their cognitive performance is related to maternal psychophysical health. Longitudinal research might investigate whether immunological and psychosocial conditions influence psychopathology and cognition.

Keywords Anti-DWEYS · Anti-NMDA/glutamate receptor antibodies · Cognitive development · Cytokines · Parental depression · Systemic lupus erythematosus

Introduction

Increasing evidence suggests that the immune system can influence psychopathology and neurodevelopment and be affected by psychosocial stress. Children of mothers affected by systemic lupus erythematosus (SLE) represent an interesting and complex model in this respect. Studies suggest an increased risk of neurodevelopmental disorders such as autism spectrum disorders (ASD) and attention deficit and hyperactivity disorder (ADHD) in these offspring, as well as higher frequency of learning disabilities (LD) (reviewed in [1]). In addition to unspecific risk factors such as prematurity, low birth weight, and medication exposure, maternal IgG antibodies and cytokines would cross the placenta through an immature blood–brain barrier (BBB) and reach the fetal brain, altering neurodevelopment [1].

Research has, e.g., identified a subset of the anti-dsDNA antibodies, the anti-DWEYS-GluN2 Ab: in murine models, they cross the placenta and induce neuronal apoptosis in fetal brain by binding the *N*-methyl-D-aspartate receptor (NMDAR), causing cognitive impairment in offspring [2]. They react against the GluN2A/B subunit of the NMDAR and can be identified as binding the DWEYS peptide sequence in the receptor [3]. Another discussed mediator is IL-6. It is known for its primordial role in brain development [4] and can be elevated in SLE patients, where it is involved in autoantibody production. During SLE pregnancies, IL-6 could directly alter the development of the fetal brain [4] or indirectly enhance the production of maternal antibodies (reviewed in [1]).

These mediators act also on the SLE patients' brains [5], and they are considered responsible for the cognitive dysfunction, mood and anxiety disorders, psychosis, acute confusion state, and headache [6] seen in neuropsychiatric lupus (NPSLE).

Some works suggest that SLE offspring (SLE-O) have an increased risk for allergic and nonrheumatic autoimmune disorders [7, 8]. It is then arguable whether the immune mediators implied in NPSLE and in fetal damage are also produced independently in SLE-O during their growing up, and thus may trigger similar damage [9].

It is likewise arguable whether having a chronically ill parent throughout growing up can have an impact on SLE-O's psychophysical condition. Despite some sparse results [10–12], extensive studies on the immunity and inflammatory profile of SLE offspring have not been carried out yet.

Aims of the study

This study was conducted in order to investigate the immunological profile in a sample of young SLE-O, to compare them to a control sample of healthy subjects born to mothers without autoimmune disease, and to analyze SLE-O's neurocognitive function, comparing it to that of the controls.

A secondary objective was to explore possible associations between immunological/neurocognitive markers in SLE-O and maternal psychophysical condition.

Method

Subjects

All mothers followed up at the Outpatient Unit of the Department of Autoimmune Diseases, Hospital Clinic, Barcelona, with children aged 8–17, were invited to participate in the study together with their children, in the period June 2010–February 2012. Controls were community healthy children (HC) within the same age range as SLE-O, who did not meet any criterion for a psychiatric diagnosis and whose mothers whose mothers did not have a systemic rheumatic disorder. These criteria were chosen to confine possible effects of personal/familiar autoimmunity and of psychopathology within the offspring group. HC were recruited from local pediatric and family medicine practices within the Hospital Clínic's referral area and through local advertisement. Exclusion criteria for

HC included an acute or chronic medical condition, as well as regular medication intake, counting anti-inflammatory drugs. This cross-sectional study was approved by the Ethics Committee of Hospital Clínic, parents or legal guardians gave written informed consent before the study began, and subjects over 14 years old gave their assent. For each young subject, at least one parent was always also interviewed.

Measurement

Young subjects

Conditions of child pregnancy and delivery measured by the OCS (obstetrical complication scale [13]); birth weight and birth week; personal and family history of immune/allergic conditions (as in [14]); demographic measures such as age, gender, body mass index (BMI), and socioeconomic status (SES scale, as in [15]); data on family structure (intact vs reorganized family structure since child's conception, as in [15]); and family history of psychiatric diagnosis, were collected for the HC and SLE-O at the time of recruitment by interviewing the parents.

Immunological screening included the standard blood battery used at our hospital for the follow-up of SLE: leukocyte count and formula, C-reactive protein (CRP), complement (C3, C4, CH50), and anti-double strand DNA [anti-dsDNA] and anti-nuclear [ANA], anti-Ro, anti-La, and anti-ribosomal antibodies.

Antibodies and cytokines associated in the literature with psychopathology and/or cognitive dysfunctions were also assessed: anti-thyroidal and anti-streptolysin-O (ASLO) antibodies, described in mood and obsessive–compulsive disorder (OCD)/tic/Tourette disorders, respectively [16, 17], and anti-DWEYS-GluN2 Ab determined by ELISA following the procedure described in [3], kindly provided by Dr. Diamond's Laboratory. Serum levels of IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, GM-CSF, IFN-γ, and TNF-α were assessed by a Luminex ultra-sensitive kit, Invitrogen LHC6004, sensibility < 1 pg/mL, as described in [15]. All samples were assayed in duplicate and compared to a standard curve. Values below the detection threshold were set to zero, and extrapolated values were accepted as valid. Blood samples were collected with fasting, early morning extraction. Analyses were performed at the Core Facility and Immunology Department Laboratories of Hospital Clínic and used standard techniques unless elsewise indicated. Serum for specific tests was obtained by centrifugation at 2000 rpm for 10 min and then kept frozen at − 80°°C until the time of the assay (between 12 and 30 months after extraction).

Psychopathological screening was performed through the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version (K-SADS-PL [18]), administered to young subjects and caregivers by a trained psychiatrist or psychologist. Psychiatric diagnosis was given according to DSM-IV criteria. Continuous measures of depression and anxiety were obtained using the Children's Depression Inventory (CDI, children under 16 years old) [19], the Beck Depression Inventory (BDI, children over 16 years old) [20], and the Screen for Child Anxiety Related Emotional Disorders (SCARED) [21]. Recent stress levels in subjects were assessed through the Stressful Life Events Schedule (SLES), child (SLES-C) and parent (SLES-P) versions [22].

The cognitive included the following: (1) *Wechsler intelligence scales* for children 4th edition (WISC-IV) and *Wechsler adult intelligence scale 3rd edition* (WAIS-III) for participants aged 7–16 and 17, respectively [23]; (2) *Rey–Osterrieth complex figure* test (ROCF) for perceptive abilities to organize a complex visual stimulus, visual–motor skills to copy it, and immediate visual memory [24]; (3) *Test of memory and learning* (TOMAL) for verbal and nonverbal attention processes and memory [25]; (4) *Tower of London* for planning abilities and executive functions [26]; (5) *Conners' Continuous Performance Test-Second Edition* (CPT-II) for attentional function [27]; and (6) *Reading (PROLEC) and Writing (PROESC) Process Assessment* for reading and writing learning abilities [28]. Results are presented in typical scores, with a mean of 50 and standard deviation of 10. Scoring 1.5 standard deviations below the mean suggests difficulties in the area.

Mothers

Disease activity in SLE mothers was assessed through the SLEDAI (SLE Disease Activity Index), measured both at recruitment point and retrospectively during pregnancy. Pregnancy value was calculated considering all the problems which occurred and remembered during that period; therefore, it can be considered an estimation of the highest SLEDAI reached during the whole pregnancy. Maternal physical condition and cumulative damage of disease were measured by the SLICC/ACR (Systemic Lupus International Collaborative Clinics/American College of Rheumatology) Damage Index (SLICC-DI) [29].

Mothers underwent the same immunological tests as young subjects.

Their psychopathological condition was assessed through the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) and quantitatively by HADS (Hospitalary Anxiety and Depression) Scales [30]). Scores for HADS anxiety and depression subscales range from 0 to 21: not clinical 0–7, mild 8–10, moderate 11–14, and severe symptoms 15–21.

Statistical analysis

Continuous variables were described as median and interquartile range and compared by Mann–Whitney test. Categorical

variables were described as frequencies and percentages and compared between SLE-O and HC using Fisher exact test. Correlations between chosen continuous variables were assessed using Spearman's correlation. Univariate logistic regression was conducted on a set of variables, selected between those significantly different between SLE-O and HC at a $p < 0.05$ using clinical criteria. A multivariate logistic regression analysis was performed to search for markers characterizing the SLE-O condition, considering variables with a p value < 0.1 in the univariate testing.

Analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA) or Statistical Package for Social Sciences version 20.0 (SPSS, Chicago, IL), and a level of significance was established at the two-sided 5% level.

Results

Sample description

Young subjects

Twenty-one offspring (SLE-O, $n = 21$, mean age 14.9, %female 40%) of 17 mothers and 34 healthy controls (HC, $n = 34$, mean age 15.1, %female 48%) were recruited. No significant difference was found in age, sex, BMI, and socioeconomic status, nor in maternal age at birth, between the two groups. SLE-O had significantly higher proportion of intact family structure (meaning biological parents still together) than HC (90.5 vs 66.7%, $p = 0.046$). No significant differences were found in the rates of psychiatric diagnosis in family members among the two groups (a maternal lifetime psychiatric diagnosis was present in 34% of HC and in 57.1% of SLE-O, $p = 0.102$). All HC and SLE-O had been conceived by natural fecundation. No significant difference was found in the rate of twin–triplet pregnancies or rate of siblings in the study. Offspring were more frequently only children (57.1 vs 9.9%, $p < 0.001$) and first children (76.2 vs 48.5%, $p = 0.043$).

SLE-O had more complications during pregnancy/delivery (OCS, median (IQR) for HC—.5 (1–3), and for SLE-O—4 (2–7), $p = 0.006$), and shorter pregnancy length than HC (week of delivery: HC—40 (39–40); SLE-O—38 (34–40), $p = 0.004$).

No significant difference was found in birth weight among the two groups ($p = 0.294$).

SLE mothers: physical health and psychopathological measures

Median for the disease activity scale SLEDAI in SLE mothers was 2 (IQR 0–6) during pregnancy and 3 at test point (0–10). At pregnancy, most patients (40%) had elevated anti-dsDNA Ab. Proteinuria, pericarditis, fever, arthritis, cytopenia, or mouth ulcers were described in single cases. At test point, the most frequent complaints were anti-dsDNA Ab (45%), reduction of complement and mouth ulcers (both 30%), and arthritis and pericarditis (15%), followed by cytopenia, proteinuria, and alopecia.

The median for the SLICC index at test point was 2 (1–5), mainly consisting of cognitive impairment and muscular weakness (38%). Myocardial infarction, malignancy, scarring alopecia, and erosive arthritis were present in single cases.

Disease scales correlated positively between each other (SLEDAI-current vs SLEDAI-pregnancy: $R = 0.708$, $p < 0.0005$; SLEDAI-current vs SLICC: $R = 0.543$, $p = 0.003$; SLEDAI-pregnancy vs SLICC: $R = 0.617$, $p = 0.001$). A lifetime psychiatric diagnosis was found in 53% of SLE women ($n = 9/17$): depression in 24% and anxiety, adjustment disorders, and affective disorder secondary to medical illness in 12% each. At test point, 30% of women met the criteria for a clinical psychiatric diagnosis (depression $n = 2$, anxiety $n = 2$, and affective disorder secondary to medical illness $n = 1$), and 35% more for a subclinical affective diagnosis. Median for the HADS-anxiety scale was 8 (7–11) and for the HADS-depression scale 6 (3–7). The two scales did not correlate significantly with each other. The HADS-depression scale—but not the anxiety scale—correlated with disease scales: SLEDAI-pregnancy (Spearman's $R = 0.756$, $p = 0.002$), SLEDAI-current ($R = 0.650$, $p = 0.009$), and SLICC ($R = 0.695$, $p = 0.004$).

Immunological results: comparisons of SLE-O versus HC

SLE-O had significantly higher proportions than HC of history of nonallergic autoimmune conditions (19 vs 0%, $p = 0.009$, one each: autoimmune glomerulonephritis, thyroid dysfunction, vitiligo, and cryoglobulinemia). There was no difference among overall allergic conditions between the two groups (32 vs 16%, $p = 0.20$); however, asthma was more frequent in SLE-O than in HC (24 vs 3%, $p = 0.018$). SLE-O had lower leukocyte, monocyte, and lymphocyte count than HC, albeit generally within normal range. Anti-dsDNA antibodies were quantitatively higher in SLE-O ($p = 0.022$), even though all subjects fell within the normal range. Anti-DWEYS-GluN2 Ab and eight cytokines (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, IFN-γ, and TNF-α) were higher in SLE-O than in HC. Anti-Ro/SSA and anti-La/SSB Ab were negative in all young subjects. No other immunological differences were found between the two groups. See Table 1 for the results of continuous variables.

CRP showed a positive correlation with age in the SLE-O group but not in the controls ($R = 0.615$, $p = 0.025$ in SLE-O), and lymphocyte count had a negative correlation with age in the SLE-O ($R = -0.709$, $p = 0.001$) and not in the HC ($R = -$

0.330, $p = 0.057$). No association with age of subjects was found for the cytokines or autoantibodies in either group.

Neurocognitive testing: comparison between SLE-O and HC

No differences were found in IQ measures between the two groups, and almost all scores fell within the normal range (5% of SLE-O scored below 1.5 standard deviation below the intellectual cognitive index mean). SLE-O scored significantly differently from the HC in the three neuropsychological measures: time of copy in visual–spatial organization of Rey figure—SLE-O slower than HC (typical score = T.S. median [IQR] 45 (36–58) vs 59 (51–61), $p = 0.001$**); Tower of London, transgression of rules—SLE-O better performance, i.e., less transgressions, than HC (T.S. = 52 (52–53.5) vs 52 (35–52), $p = 0.002$**); and PROESC quality of writing—worse performance of SLE-O (T.S. = 47 (43–55) vs. 55 (45–65), $p = 0.039$*). Even though there were no significant differences between groups in the other learning assessments, a range of 10–20% of young subjects of the whole sample showed deficits in mechanical reading, 20–25% in reading comprehension, and 15–20% in words writing.

The working memory index of Wechsler scales, as well as the scores in verbal memory task and visual–spatial skills, showed a negative correlation with age in SLE-O, indicating that older children in SLE-O performed worse than younger

Table 1 Immunological data and comparisons between lupus offspring, healthy controls, and lupus mothers

	SLE-O $n = 21$	HC $n = 34$	SLE-M $n = 17$
*Leukocytes (RI 4–10*10^9/L)*[1]	*5.64 (4.84–6.51)*	*7.25 (6.45–8.74)*	5.57 (3.9–8.34)
*Neutrophiles (RI 2.5–7 *10^9/L)*[1]	*2.9 (2.4–3.5)*	*3.75 (3–5)*	3.35 (2.45–6.2)
*Lymphocytes (RI 0.9–4.5*10^9/L)*[2] *[M-O1; M-C1]*	*1.9 (1.6–2.5)*	*2.4 (1.9–2.9)*	1.35 (1.05–1.75)
PCRnum (RI < 1.00) [M-O4, M-C3]	*0.02 (0.02–0.04)*	*0.03 (0.02–0.04)*	0.07 (0.03–0.48)
C3 (RI 0.82–1.87 g/L) [M-O1, M-C1]	1.16 (1–1.23)	1.06 (0.96–1.14)	0.92 (0.87–1.03)
C4 (RI 0.11–0.45 g/L)	0.23 (0.2–0.29)	0.26 (0.2–0.29)	0.19 (0.13–0.27)
CH50 (RI 34–71 U/mL)	44 (28–53)	45 (38–50)	46 (31.5–50.5)
Anti-dsDNA (RI < 10 UI/mL)[4] *[M-O3, M-C3]*	*1.3 (0.65–3.25)*	*0.7 (0.3–1.1)*	18 (2.2–45)
ANA (RI <= 3 +) [M-O4, M-C3]	3 (2–4)	3 (2–4)	6 (5–8)
Anti-ribosomal Ab (RI < 12 UI/mL)	1.6 (1–3)	1 (1–13)	2 (1–2.9)
Anti-DWEYS-GluN2 Ab (UI/ml) [3] *[M-O2, M-C3]*	*0.15 (0.12–0.2)*	*0.07 (0.05–0.1)*	0.1 (0.07–0.14)
ASLO Ab (RI < 200 UI/mL) [M-O1, M-C1]	232 (122–346)	300.5 (155–523)	104 (28–159)
Anti-TPO Ab (RI < 35 UI/mL)	40 (37–48)	48.5 (39–57)	41 (34–50)
Anti-TG-Ab (RI < 60 UI/mL)	27 (23–30)	31 (25–36)	28 (21–36)
IL-1β (pg/ml) [3] *[M-C3]*	*0.71 (0.39–0.94)*	*0 (0–0)*	0.72 (0.55–0.86)
IL-2 (pg/ml) [3] *[M-C3]*	*0.39 (0.13–3.24)*	*0 (0–0)*	0.42 (0–10.65)
IL-4 (pg/ml) [3] *[M-C3]*	*2.52 (1.51–6.65)*	*0 (0–0)*	4.01 (0–24.87)
IL-5 (pg/ml) [3] *[M-C3]*	*0 (0–0.31)*	*0 (0–0)*	0 (0–0.71)
IL-6 (pg/ml) [3] *[M-C3]*	*0.82 (0.46–1.81)*	*0 (0–0.38)*	1.82 (1.01–4.47)
IL-8 (pg/ml)	16.66 (9.99–24.82)	12.43 (9.77–16.49)	13.26 (11.58–16.95)
IL-10 (pg/ml) [3] *[M-C3]*	*0.56 (0.12–1.02)*	*0 (0–0)*	0.38 (0.24–1.56)
IFN-γ (pg/ml) [4]	*0.2 (0–1.07)*	*0 (0–0)*	0 (0–1.07)
TNF-α (pg/ml) [3] *[M-C3]*	*0.58 (0.23–1.73)*	*0 (0–0)*	0.41 (0.23–7.7)
GMCSF (pg/ml)	0 (0–0)	0 (0–3.08)	0 (0–0)

In italics, the parameters significantly different between offspring and controls. Descriptive statistics are median [interquartile range]

SLE-O = offspring of women with lupus; *HC* = healthy controls; *SLE-M* = women with lupus; *Anti-dsDNA Ab* = antibodies against double-stranded DNA; *ANA* = anti-nuclear antibodies; *ASLO Ab* = anti-streptolysin-O Ab; *Anti-TPO Ab* = anti-thyroid peroxidase Ab; *Anti-TG Ab* = anti-thyroglobulin Ab; *Anti-DWEYS-GluN2 Ab* = Ab against the DWEYS peptide of the GluN2 subunit of the NMDAR identified in SLE patients [2] and determined by ELISA; RI = laboratory reference interval; *M-O1* = SLE-M<SLE-O, $p < 0.01$**; *M-O2* = SLE-M<SLE-O, $p < 0.05$*; *M-O3* = SLE-M>SLE-O, $p < 0.01$**; *M-O4* = SLE-M>SLE-O, $p < 0.05$; *M-C1* = SLE-M<HC, $p < 0.01$**; *M-C3* = SLE-M>HC, $p < 0.01$**

[1] SLE-O<HC, $p < 0.01$**

[2] SLE-O<HC, $p < 0.05$*

[3] SLE-O>HC, $p < 0.01$**

[4] SLE-O>HC, $p < 0.05$*

ones in selective attention and immediate memory and in drawing. No relations between other neuropsychological scores and age were found in the HC group (Table 2).

Psychopathological testing in SLE-O

A fraction of SLE-O (23.9%) was found to meet the criteria for a clinical psychiatric diagnosis, corresponding to a confidence interval (CI) for the estimated prevalence of clinical psychiatric diagnosis in the SLE-O population of [10.6–45.1%]. Diagnoses were ADHD ($N = 2$, frequency = 10%), anxiety, Tourette syndrome, and OCD (all $n = 1$, 5%). Another half of SLE-O ($n = 9$, 52%) had a subclinical diagnosis of the following: anxiety (9; 43%), ADHD (4; 19%), and OCD (1; 5%).

Controls were psychopathologically healthy by recruitment criteria, thus not comparable. In the young population from the same geographical area (GYP) as our subjects, the estimated prevalence for any axis I diagnosis is between 9.5 and 13% [31]. The resulting likelihood that the prevalence of clinical psychiatric diagnosis in SLE-O is not different from that in the general youth population ranged between 2–14 and 2%.

SCARED median score was 13 (IQR = 9–19) in HC and 19 (13–24) in SLE-O, BDI depression scale was 2 (0–5) in HC and 5 (1–8) in SLE-O, and SLE score was 14 (6–17) in HC and 20 (10–42) in SLE-O. No significant correlation was found between age and psychopathological or stress scales in either group.

Multiple regression analysis within SLE-O and HC

To look for parameters defining the SLE-O condition, in comparison with that of HC, multiple logistic regression analysis was performed with a forward stepwise adjustment. Independent variables were chosen to represent the different data sets (personal history of autoimmune disease, pregnancy conditions, white cells, cytokines, antibodies, neurocognitive performance) among those significantly different between the two groups at $p < 0.05$. The regression analysis selected anti-DWEYS-GluN2 Ab as the most significant variable ($p = 0.012$, OR [95% CI] 38.38 [2.25–654.44]), together with leukocyte count ($p = 0.059$, OR = 0.28 [0.08–1.05] and text writing abilities ($p = 0.051$; OR = 0.77 [0.59–1.00]) (Table 3).

Secondary results: comparison with mothers' immune profile and correlations between offspring and mothers' parameters

Both SLE-O and HC had higher lymphocyte and eosinophil counts than the SLE mothers and lower CRP, higher C3 fraction of complement, lower anti-dsDNA and anti-nuclear Ab, and higher ASLO antibodies than the SLE mother group. Anti-DWEYS-GluN2 Ab in mothers were higher than in HC and lower than in SLE-O. Mothers' cytokine levels were not different from SLE-O, and their IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, and TNF-α levels higher than in HC (Table 1 and Fig. 1).

Correlations between maternal conditions and neurocognitive, anxiety, and depression scores in their children showed that maternal disease and depression (but not anxiety) scales correlated positively with children's depression (but not anxiety) and stress scales and negatively with various neuropsychological performance indexes. The correlations were higher and more frequent with maternal disease activity scale measured at test point, than during pregnancy (Table 4).

Discussion

This is an exploratory study on offspring of SLE mothers. Offspring show an immune profile that is different from that of relevant HC, with lower leukocyte counts and higher levels of mainly proinflammatory cytokines and of anti-dsDNA Ab. An antibody that has been described as possibly neurotoxic and related to psychiatric symptoms in SLE patients, the anti-DWEYS-GluN2 Ab, is significantly higher in SLE-O, and its

Table 2 Relation between neuropsychological tests and age between lupus offspring and healthy controls

Neuropsychological parameters	SLE-O Spearman's rho (p value)	HC
Wechsler—Working Memory Index	− 0.640** (0.002)	0.002 (0.992)
TOMAL Test—Verbal memory–curve	− 0.495* (0.023)	0.14 (0.429)
ROCF—quality of copy	− 0.555** (0.009)	0.087 (0.631)

Wechsler—Working Memory Index = Working Memory Index from Wechsler intelligence scales; *TOMAL Test—verbal memory–curve* = test of memory and learning, subtest of verbal memory, learning curve; *ROCF—quality of copy* = Rey–Osterrieth complex figure test, measure for visual memory and drawing skills; *SLE-O* = offspring of women with Lupus; *HC* = healthy controls

Table 3 Uni- and multivariate logistic regression analysis, for lupus offspring condition

	Univariate model	Multivariate model		
	p value	OR [95% CI]	*p* value	OR [95% CI]
History of autoimmune or allergic disease	0.029	4.20 [1.16–15.19]		
OCS	0.004	1.54 [1.15–2.06]		
Leukocytes total count	0.004	0.49 [0.31–0.79]	0.059	0.28 [0.08–1.05]
IL-6	0.047	1.83 [1.01–3.34]		
Anti-DWEYS-GluN2 Ab	0.000	7.56 [2.51–22.79]	0.012	38.38 [2.25–654.44]
PROESC—quality of writing	0.066	0.95 [0.91–1.00]	0.051	0.77 [0.59–1.00]

Multivariate model was constructed using a forward stepwise with above indicated variables (all had a $p < 0.1$ on the univariate testing). ROC AUC, 0.947 [0.882–1.00]

SLE-O = offspring of women with lupus; *OCS* = Obstetrical Complication Scale; *IL-6* = interleukin-6; *Anti-DWEYS-GluN2 Ab* = antibodies against the GluN2A/B subunit of the *N*-methyl-D-aspartate receptor; *PROESC* = learning abilities text-writing

levels can define this group with high odds ratio, making it a possible biomarker for the offspring condition.

Neuropsychological tests show no differences in intelligence parameters in comparison with healthy controls. However, the significantly different performance of SLE-O in some subtests reflects more difficulties in written production, greater slowness in visual–motor abilities, and better impulsivity control in comparison with healthy controls. Furthermore, older SLE-O perform worse than those younger in attention and immediate memory, suggesting a possible worsening over time.

SLE-O show also a rate of psychiatric diagnosis seemingly higher than that of the general population, especially at the expense of attention deficit and anxiety disorders, consistent with previous studies [1].

Parallelly, current maternal psychophysical condition seems linked to both offspring's mood and neurocognitive performance, also in line with other studies.

The immunological findings might just be the indication of a familiar subclinical autoimmunity: little is known about cytokine profiles in SLE relatives, but higher anti-DWEYS-GluN2 Ab [10] and anti-nuclear Ab [32] have been reported in first-degree relatives of SLE patients, and a familial aspecific dysfunction of the B lymphocyte has been posited. Whether these are responsible factors in the higher prevalence of autoimmune and allergic disease found in SLE offspring [7, 8], or just casual findings, is not known yet.

Speculatively, cytokines and anti-DWEYS-GluN2 Ab might represent an inflammatory milieu, that for a long time could progressively affect these subjects both systemically and centrally, as described in the course of SLE disease.

Cytokines in SLE are involved in cardiopulmonary, cutaneous, and renal affection, by acting both on immune cells and on local cells, as the endothelial cells [33]. Increased circulating IL-6 seems characteristic of an inflammatory neurological condition, and CSF levels of IL-6, IL-8, and IL-10 have shown to correlate with NPLSE disease activity (reviewed in [34]). In particular, IL-10, predominantly an anti-inflammatory cytokine, may acquire proinflammatory activity during immune responses and a pathogenic role in SLE [35, 36].

Parallel research from child and adolescent psychiatry has associated systemic proinflammatory condition and elevated cytokines, with inflammatory and immunological processes in the brain, resulting in insults to brain parenchyma and progressive development of psychopathology along the lifespan [37–40].

Anti-DWEYS-GluN2A Ab have been associated with damage of non-nervous tissue, such as bone, pancreas, and skin [41], but also blood cells, relating with reduced counts of leukocytes [42]. In murine models, they can cause cognitive impairment (especially hippocampus-dependent memory impairment) [43]. Human studies have often found an association between intrathecal anti-DWEYS-GluN2 Ab levels and NPSLE manifestations (reviewed in [44]) and sometimes between serum anti-DWEYS-GluN2 Ab and cognitive dysfunction or decline in cognitive performance over time [45] in both adult and pediatric SLE patients, as well as depressive mood in adult patients. Inconsistencies in results might be related to the need of a breach in the BBB for the antibodies to reach the CNS, both in animal and human studies (reviewed in [6, 44]).

The same processes might occur also in SLE offspring, where it would be only with repetitive passages through the BBB that these mediators could affect development and cause some of the same alterations described in SLE women.

The findings that older SLE-O had lower leukocyte count and higher CRP and performed worse in attention and immediate memory than younger ones are compatible with this hypothesis of a progressive action.

Anti-DWEYS-GluN2 Ab in SLE-O were also higher than in SLE mothers. This is an interesting datum. Longitudinal explorations might clarify whether there is a trend along the lifespan in this parameter, where the titers tend to go down with age in SLE patients and relatives. If so, the antibodies may be the expression of nonspecific autoimmunity, possibly

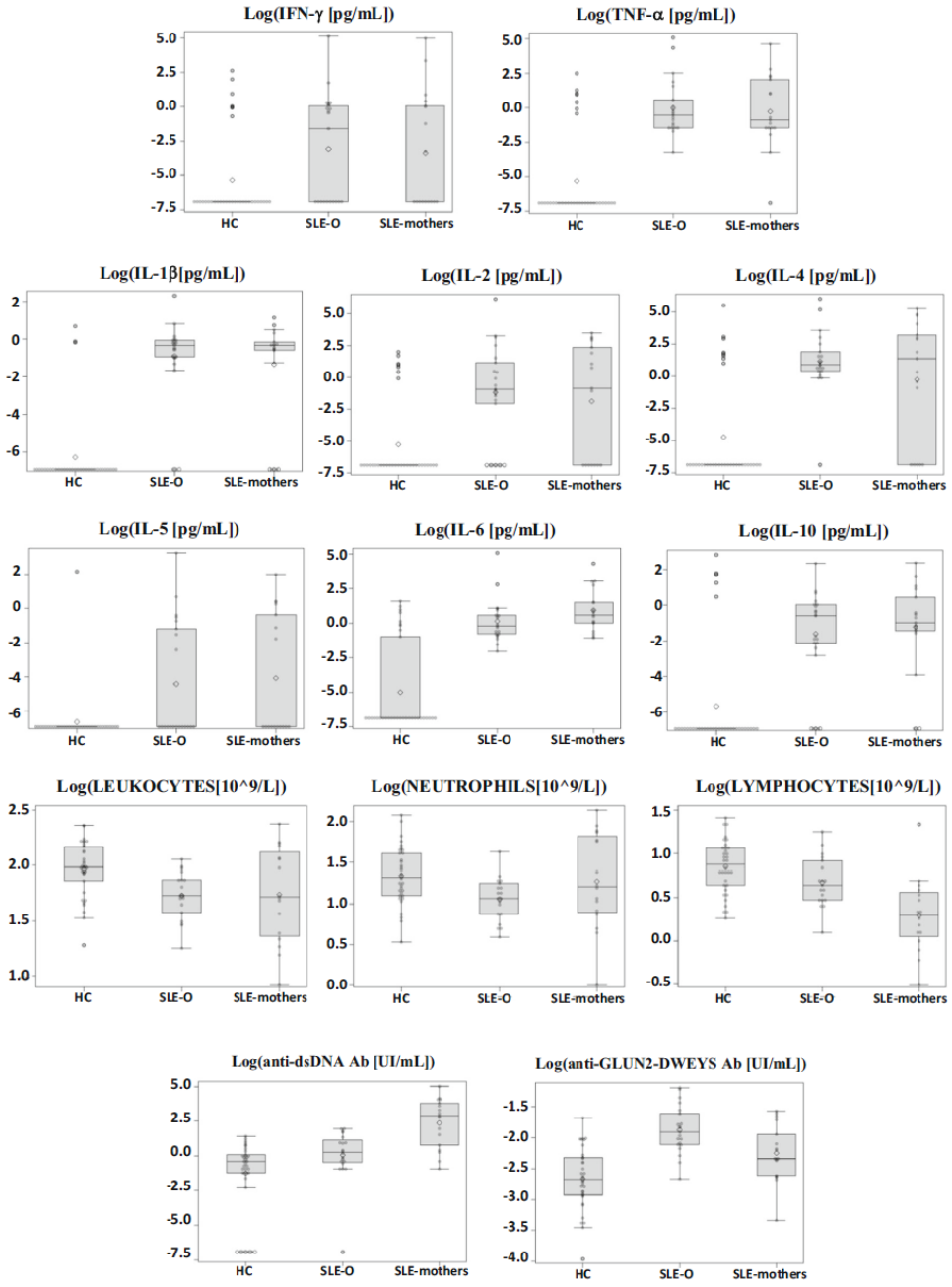

Fig. 1 Immunological results: differences between lupus offspring and healthy controls and comparison with lupus mothers. Graphical comparison of values for cytokines (IFN-g, TNF-a, IL-1b, IL-2, IL-4, IL-5, IL-6, IL-10), anti-GluN2-DWEYS and anti-dsDNA antibodies, and leukocyte, lymphocyte and neutrophil count for healthy controls, and SLE offspring and SLE mothers, respectively. In the box-plot figures, values are transformed into their logarithms, and zero values are imputed to a very small value of 0.001 before the log transformation. The bottom and top edges of the box indicate the intra-quartile range (IQR). The whiskers extending from each box indicate the range of values that fall within a distance from the box less than or equal to 1.5*IQR. Median value is the line within the box, and mean is the rhombus dot. HC = healthy controls; SLE-O = offspring of women with lupus; SLE-mothers = mothers with lupus

Table 4 Significant correlations between depression and stress scales in lupus offspring, and physical and psychopathological ratings in lupus mothers

SLE-O scales	Mothers' scales			
	SLEDAI-pregnancy	SLEDAI-current	SLICC-DI	HADS-depression
Depression (CDI-BDI)	0.594* (0.015)	0.798** (<0.001)	0.499* (0.049)	0.606* (0.017)
Stressful Life Events—SLES		0.760** (<0.001)		0.606* (0.017)
Verbal Capacity Index		− 0.709** (0.002)	− 0.585* (0.022)	− 0.632* (0.015)
Working Memory Index			− 0.580* (0.023)	− 0.538* (0.047)
ROCF-Copy Exactness		− 0.633** (0.006)	− 0.557* (0.025)	
CPT-II time of reaction			− 0.516* (0.041)	− 0.521* (0.046)
Text comprehension	− 0.549* (0.028)	− 0.608** (0.010)		

Statistically significant Spearman's rho coefficients (p value) at the 0.05* or at the 0.01** levels

SLE-O = offspring of women with lupus; *CDI* = Child Depression Inventory; *BDI* = Beck Depression Inventory, *SLES* = Stressful Life Events Schedule in children; *ROCF-Copy Exactness* = Rey–Osterrieth complex figure test, measure for exactness of copy; CPT-II time of reaction = Conners' Continuous Performance Test—second edition, time-of-reaction subscale; *SLEDAI-pregnancy* and *SLEDAI-current* = SLE Disease Activity Index reconstructed at pregnancy and current score; *SLICC-DI* = Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index; *HADS-depression* = Hospital Anxiety and Depression Scale—depression subscale

more active during development than in adult life, where titers may increase again during episodes of acute NPSLE decompensations. It is important to note that these SLE patients were in relatively good health, with limited disease activity and accumulated damage, and without signs for acute serious NPSLE.

The high correlations found between offspring measures for depression scale and neurocognitive parameters, with maternal psychophysical condition at test time, are worth commenting on. Several large studies have shown how parental depressive symptoms increase in offspring the overall risk for onset of depressive and externalizing disorders (reviewed in [46]) and how cognitive performance and in particular verbal capacities appear lower in children of mothers with persistent depressive symptoms [47–49]. Potential mechanisms include reduced overall warmth and sensitivity and qualitative and quantitative differences in a variety of specific maternal behaviors that shape cognitive and language development [47]. Even though in our population such effect could partly be counteracted by a stable and supportive familiar structure, and by the mothers' investment and expectations, our results indicate a tight connection between maternal and filial well-being.

The model is summarized in the figure found in the graphical abstract.

Limitations/future developments

The study has various limitations. The sample size of the SLE-O is relatively low, and the study is cross-sectional, which impedes assessing causality of events. Assessment of pregnancy and delivery conditions was run retrospectively from mothers' recollections, and laboratory data about mothers' immune/inflammatory profile and medical treatment during pregnancy were missing. Measure of anti-phospholipid antibodies, repeatedly associated with later development of learning disabilities (reviewed in [1]), was not included in the protocol.

This work was though intended as exploratory and focusing on the offspring immunological and neuropsychological characteristics.

HC were psychopathologically healthy subjects and offspring of mothers without any systemic rheumatic disorders, though not an exactly general population sample. This had though the advantage of comparing SLE-O with "pure" subjects, i.e., subjects free from immune alterations linked to possible comorbid psychopathology and from exposure to maternal immunity and maternal hereditary risk for autoimmune diseases [39].

Conclusions

These results endorse a multifactorial etiology for the development of these offspring, where prenatal maternal factors would combine with intrinsic immune condition and with environmental exposure to maternal psychophysical state and together contribute to the psychoneurological trajectory of this population. The clinical impact on cognition and mental health of the subclinical autoimmunity found in the SLE-O should be investigated in longitudinal studies.

If results are confirmed, approaches targeting the proinflammatory condition as well as intervention aiming to support both mothers and offspring might protect these children toward a sound psychophysical development.

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Compliance with ethical standards

Disclosure None.

List of abbreviations *Ab* , autoantibodies; *ADHD*, attention deficit and hyperactivity disorder; *ANA Ab*, anti-nuclear antibodies; *Anti-DWEYS-GluN2 Ab*, antibodies against the GluN2 subunit of the NMDAR; *anti-RP* Ab, anti-ribosomal P protein antibodies; *aPL* Ab, antiphospholipid antibodies; *ASD*, autism spectrum disorders; *ASLO* Ab, anti-streptolysin-O (ASLO) antibodies; *BBB*, blood brain barrier; *BDI*, Beck Depression Inventory; *BMI*, body mass index; *CBA*, cell based assays; *CDRS-R*, Children's Depression Rating Scale—revised; *HADS*, Hospital Anxiety and Depression; *HC*, healthy controls; *IHC*, immunochemistry; *LD*, learning disabilities; *NMDAR*, *N*-methyl-D-aspartate receptor; *NPSLE*, neuropsychiatric lupus; *OCD*, obsessive-compulsive disorder; *OCS scale*, obstetrical complication scale; *SCARED*, Screen for Child Anxiety Related Emotional Disorders; *SES* scale, socioeconomic status scale; *SLE*, systemic lupus erythematosus; *SLEDAI scale*, SLE Disease Activity Index scale; *SLE-O*, offspring of women with SLE; *SLES-C*, Stressful Life Events Schedule, child version; *SLES-P*, Stressful Life Events Schedule—parent version; *SLICC-DI*, Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index scale; *WAIS-III*, Wechsler adult intelligence scale 3rd edition; *WISC- IV*, the Wechsler intelligence scale for children 4th edition

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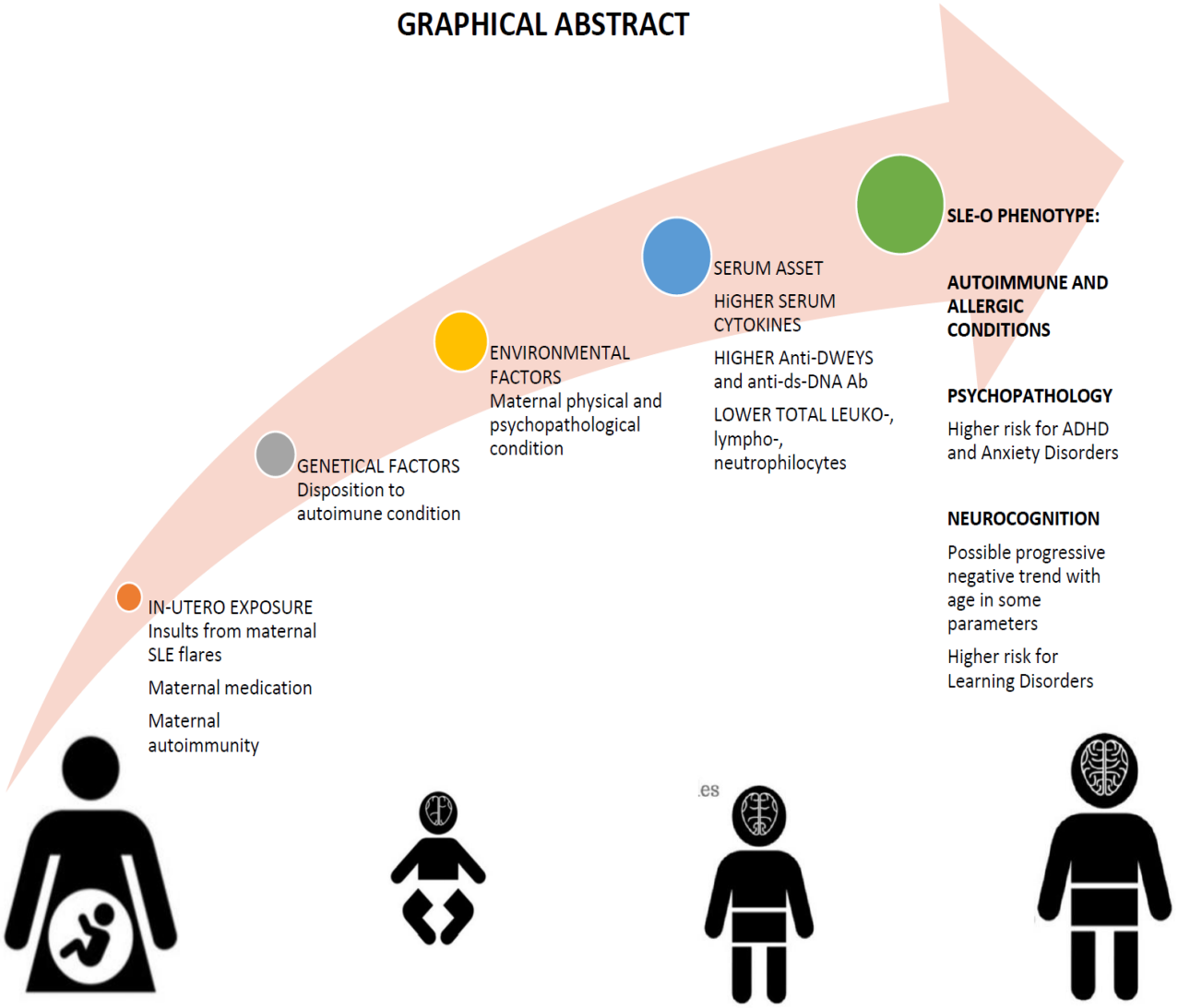
GRAPHICAL ABSTRACT



4.3 UNPUBLISHED RESULTS

Unpublished results complete the characterization of the samples and have already been presented at international conferences.

Title 1:

Three-group comparison of inflammatory and autoimmune asset in child and adolescent population: acute psychiatric in-patients, offspring of women with lupus and healthy controls

AIM:

To extend the comparison of inflammatory and immune markers analyzed in the two published studies, across the three groups of subjects (77 child and adolescent psychiatric inpatients, 34 healthy controls, and 21 offspring of women with Lupus), and investigate the presence in the two clinical groups of antibodies with reactivity against live rat hippocampal neurons.

The parameters compared are:

- 10 cytokines: 12 cytokines IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL_10, GM-CSF, IFN-γ, TNF-α, white cells count, CRP
- Anti-DWEYS-GluN2 antibodies
- History of allergic and autoimmune conditions
- In the two clinical groups serum antibodies with reactivity against brain antigens and in particular against NMDA-receptor.

Title 2:

Monocyte/lymphocyte Ratio (MLR) as a proxy for inflammation in a sample of Child and Adolescent Psychiatric Inpatients

AIM:

To study the applicability in our sample of emerging inexpensive proxies for assessing systemic inflammation in psychiatric patients:

- the monocyte to lymphocyte ratio(MLR), neutrophil/lymphocyte ratio (NLR), and platelet/lymphocyte ratio (PLR).

These are compared across the groups of 77 inpatients and 34 healthy controls.

THREE-GROUP COMPARISON OF INFLAMMATORY AND AUTOIMMUNE ASSET IN CHILD AND ADOLESCENT POPULATION: ACUTE PSYCHIATRIC IN-PATIENTS, OFFSPRING OF WOMEN WITH LUPUS AND HEALTHY CONTROLS

Abstract

Our group has previously presented the data for a group of 81 young psychiatric inpatients, showing that they had higher levels of 5 cytokines than healthy controls (HC), and for a group of 21 offspring with women with SLE, showing that they had higher levels of anti-DWEYS-GluN2 antibody and of eight cytokines, in comparison with the same group of HC. Here we expand the analyses on these samples, by comparing across the three conditions the immune markers found different in inpatients or Lupus offspring with respect to HC. We compare also the rates of allergic and autoimmune conditions among the three groups and in the two clinical groups look for serum antibodies with reactivity against brain antigens, in particular antibodies against the NMDA receptor.

We found that inpatients had the highest IL-8 values of all groups, and similar IL-1β values than SLE-O. Levels of IL-6, TNFα, IL-2, IL-4 and IL-5 for inpatients were intermediate between HC and SLE-offspring. Inpatients had the highest level of monocyte count, and offspring the lowest levels of total leukocyte, neutrophile, lymphocyte and monocyte count of the three groups.

Lupus offspring had higher rates of autoimmune conditions than both other groups, and of asthma than controls. Anti-DWEYS-GluN2 antibodies were significantly increasing between controls, inpatients and offspring, and their titers showed correlated with depression and anxiety clinical scales.

Of all subjects, two patients had sera with reaction against live rat hippocampal neurons, suggesting the presence of neuronal surface antibodies, the antigen could not be identified.

Results confirm links between alterations in psychopathology and immune system already from young ages. Findings about antibodies suggest different interpretations, which are discussed.

1. Introduction:

A growing body of literature is investigating the association between psychiatric pathology and autoimmune and inflammatory processes, both in adult and in young population. [1–3]

Our group has previously presented the data for a group of 81 young psychiatric inpatients, showing that they had higher levels of 5 cytokines than healthy controls (HC)[4], and for a group of 21 offspring with women with SLE, showing that they had higher levels of anti-DWEYS-GluN2 antibody and of eight cytokines (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, TNF-α and IFN-γ), in comparison with the same group of HC [5].

This work expands the analyses on these samples, and compares data between them.

Across the three conditions, we compare the immune markers that were found different in inpatients or Lupus offspring with respect to healthy controls.

In the two clinical groups – inpatients and offspring - we compare also the rates of allergic and autoimmune conditions, and look for serum antibodies with reactivity against brain antigens, and in particular for antibodies against the NMDA receptor.

1.1. Antibodies involved in psychiatric disorders

In the past decades there has been increasing interest in a putative role of antibodies with reactivity against brain antigens in causing neuropsychiatric symptoms and alterations in neurodevelopment.

Of special interest are the antibodies directed against neuronal surface, and in particular against the NMDA receptor, subunits 1 and 2 (anti-GluN1 and anti-GluN2 antibodies). Autoantibodies of the IgG class against N-methyl-D-aspartate-receptor subunit GluN1 (NMDAR1) were first described in anti-NMDAR encephalitis and identified as causal mechanisms. It is now questioned, whether there may exist partial presentations of the disorder, manifesting primarily with psychiatric symptoms. If that is the case, there would be subsets of psychiatric patients, where symptoms are actually related to the action of these antibodies [6]- Recent works on over 4000 individuals, suggest that antibodies against the NMDA receptor subunit GluN1 can be present also in healthy carriers, and that irrespective of epitope and immunoglobulin class, they all have pathogenic potential in situations of increased blood–brain–barrier permeability [7].

Parallelly, research carried out in a classic autoimmune process, Systemic Lupus Erythematosus (SLE), has identified a subset of the anti-dsDNA autoantibodies as possible causal agents for the psychiatric symptoms present in SLE. It is antibodies that cross-react against the NR2 subunit of the NMDA receptor (NMDAR), causing neuronal damage and apoptosis. The target sequence in the NMDAR would be a pentapeptide consensus sequence (D/E W E/D Y S/G) present in the NR2A and NR2B subunits of the

NMDAR, identified as DWEYS. Mice immunized with the DWEYS peptide develop anti-DWEYS-GluN2 Abs that have also anti-dsDNA and anti-NMDAR activity, and that can cause neuronal damage when allowed into brain tissue by a breach in the blood-brain-barrier (BBB)[8,9]. In animal models anti-GluN2-Ab can cause cognitive impairment (esp. hippocampus-dependent memory impairment), and studies that analyze intrathecal anti-GluN2-Ab have often found an association between antibody levels in central spinal fluid (CSF) and NPSLE manifestations(reviewed in [10]). The association between serum anti-DWEYS-GluN2-Ab and neuropsychiatric symptoms is less consistent, and some – but not all – human studies have showed association between serum anti-DWEYS-GluN2-Ab and cognitive dysfunction in both adult and pediatric SLE patients, as well as depressive mood in adult patients. Inconsistencies in results might be related to the need of a breach in the BBB for the antibodies to reach the CNS, showed both by animal and human studies (reviewed in [10,11]).

Psychiatric investigations have furthermore suggested an association between anti-thyroidal Ab and mood disorders [12], and anti-streptolysin-O (ASLO) Ab and OCD/tic/Tourette disorders respectively [13].

2. Materials and Methods

2.1.Subjects

All patients between 8 and 17 years of age admitted to the Child and Adolescent Psychiatry Acute Inpatient Unit of Hospital Clínic of Barcelona between June 2010 and February 2012 with a diagnosis of Affective, Anxiety, Adjustment, Psychotic, Obsessive–Compulsive, Tic or Tourette Disorders, according to DSM-IV TR Criteria, were invited to participate in the study.

Offspring of women with Lupus were recruited through their mothers, attending the Outpatient Unit of the Department of Autoimmune Diseases at Hospital Clinic, in the period June 2010–February 2012.

Controls were healthy community subjects within the same age range.

2.2 Clinical assessment

For detailed description of sample characteristics and data gathering we refer to previous works [4,5]. Relevant to this study, depression and anxiety symptoms were measured using the Children's Depression Rating Scale–Revised (CDRS-R, children under 12 y.o.) [14], the Beck Depression Inventory (BDI, children over 12 y.o.) [15], and the Screen for Child Anxiety Related Emotional Disorders (SCARED) [16].

Recent stress levels in subjects were assessed through the Stressful Life Events Schedule (SLES), child (SLES-C) and parent (SLES-P) versions (as used in [4]).

Personal history of infectious, autoimmune and allergic disease was collected for all participants.

Details on full clinical and psychosocial screening are reported in [4].

Immunological Assessment:

Blood samples were collected with fasting, early morning extraction, and stored as described in [4,5].

Determination of antibodies included:

1. The most common antibodies associated to autoimmune diseases and Lupus in particular: *antinuclear ANA; anti-DNA-ds, anti-Ro, anti-La, anti-ribosomal antibodies.* Antibodies associated with altered thyroid function: *anti-thyroid peroxidase (TPOAb), anti-thyroglobulin (TGAb).* Antibodies associated with Streptococcal infections: *Anti-streptolysin-O (ASLO).* All these determined by standardized techniques, as described in [5].
2. *Anti-DWEYS-GluN2 Ab* in patients, determined by ELISA following the procedure described in [17] and kindly provided by Dr. Diamond's Laboratory.
3. *Antibodies against the NMDAR and other known neuronal surface antigens* in patients and offspring, searched according the procedure described in [18,19].

Screening in serum (diluted from 1:40) was carried out in all cases using immunohistochemistry with rat brain optimized for membrane-bound antibodies. Brains from adult female Wistar rats were fixed by immersion in 4% paraformaldehyde at 4°C for 2 h, cryoprotected with 40% sucrose for 24 h, and snap frozen in cold isopentane. 7 µm thick frozen tissue sections were incubated with 0.3% hydrogen peroxide for 15 min, with 10% goat serum in PBS for 1 h, and with patients sera (1:200). After using the appropriate secondary antibody (1:2000 diluted in PBS with 5% goat serum), the reactivity was developed with the avidin–biotin–peroxidase method. Results were photographed under a fluorescence microscope to confirm the presence of neuronal surface antibodies.

All samples showing any staining were tested by immunocytochemistry (serum diluted from 1:200) using live hippocampal neurons and HEK cells recombinantly expressing GluN1/N2B to test for NMDA receptor antibodies (cell-based assay, CBA). Serum samples with immunocytochemistry labeling but negative for NMDA receptor antibodies were screened with immunoblot (Euroimmun, Lübeck, Germany) or cell based assays (CBA) using HEK293 cells transfected with the appropriate plasmids for all other known CNS antigens, including AMPA receptor, GABAA receptor, GABAB receptor, LGI1, Caspr2, DPPX, mGluR5, D2 receptor, and glycine receptor.

Sera with antibodies to NMDAR and from a healthy individual were used as controls.

2.3 Statistical Analysis

Statistical analysis was performed with SPSS program, version 20.

3. Results:

Eighty-one patients (mean age 15,7, % female 59%) and 34 controls (mean age 15,1, %female 48%) were recruited. No significant sociodemographic difference was found between the two groups. Inpatients had significantly higher scores in clinical scales for anxiety, depression and stressful life events in the past year, than both controls and offspring (Table 1), without differences between the six diagnostic subgroups previously identified [4] (results not shown).

3.1 Comparison of immune markers between the three groups

Cytokines and white cells

We found that inpatients had the highest IL-8 values of all groups, similar IL-1β values than SLE-O, and IL-6 values intermediate between controls and SLE-offspring. Of the other cytokines found higher in SLE-offspring than in HC, TNFα, IL-2, IL-4 and IL-5 resulted also higher in SLE-offspring than in inpatients. Inpatients had highest level of monocyte count, and offspring the lowest levels of total leukocyte, neutrophile, lymphocyte and monocyte count. Yet, the differential count of monocytes was in both study-groups higher that in controls (Table 1). The was no significant difference in monocyte count between the six diagnostic subgroups. .

Table 1. Comparison of immune markers across the three groups

	HC		PATIENTS median (IQ range)		SLE-OFFSPRING		HC
TNFα	0,00(0,00; 0,00)		0,00(0,00; 1,74)	<	**0,58(0,23; 1,73)**	>	0,00(0,00; 0,00)
IFNγ	0,00(0,00; 0,00)		0,00(0,00; 0,55)		0,20(0,00; 1,07)		0,00(0,00; 0,00)
GMCSF	0,00(0,00; 3,08)		1,82(0,00; 3,80)		0,00(0,00; 0,00)		0,00(0,00; 3,08)
IL1β	0,00(0,00; 0,00)	<	**0,35(0,00; 1,61)**		**0,71(0,39; 0,94)**	>	0,00(0,00; 0,00)
IL2	0,00(0,00; 0,00)		0,00(0,00; 1,17)	<	**0,39(0,13; 3,24)**	>	0,00(0,00; 0,00)
IL4	0,00(0,00; 0,00)		0,00(0,00; 2,44)	<	**2,52(1,51; 6,65)**	>	0,00(0,00; 0,00)
IL5	0,00(0,00; 0,00)		0,00(0,00; 0,00)	<	**0,00(0,00; 0,31)**	>	0,00(0,00; 0,00)
IL6	0,00(0,00; 0,38)	<	**0,51(0,00; 1,17)**	<	**0,82(0,46; 1,81)**	>	0,00(0,00; 0,38)
IL8	12,43(9,77; 16,49)	<	**59,21(19,81; 176,85)**	>	16,66(9,99; 24,82)		12,43(9,77; 16,49)
LEUKOCYT_TOT	7,25(6,45; 8,74)		7,53(6,10; 8,49)	>	**5,64(4,84; 6,51)**	<	7,25(6,45; 8,74)
NEUTROPH_ABS	3,75(3,00; 5,00)		3,60(2,90; 4,70)	>	**2,90(2,40; 3,50)**	<	3,75(3,00; 5,00)
LYMPHOC_ABS	2,40(1,90; 2,90)		2,50(1,90; 3,00)	>	**1,90(1,60; 2,50)**	<	2,40(1,90; 2,90)
MONOC_ABS	0,40(0,30; 0,50)	<	**0,50(0,40; 0,50)**	>	**0,40(0,30; 0,40)**	<	0,40(0,30; 0,50)
NEUTROPHILES %	52,80(48,50; 61,30)		50,90(45,10; 57,90)		50,30(43,20; 56,70)		52,80(48,50; 61,30)
LYMPHOCITES %	34,75(29,40; 38,80)		34,40(30,20; 41,60)		34,50(31,20; 42,80)		34,75(29,40; 38,80)
MONOCITES %	4,90(4,40; 6,00)	<	**6,20(5,30; 7,30)**		**5,90(5,10; 7,30)**	>	4,90(4,40; 6,00)
Anti-DWEYS-GluN2	0,07(0,05; 0,10)	<	**0,11(0,08; 0,14)**	<	**0,15(0,12; 0,20)**	>	0,07(0,05; 0,10)
antiDNAds	0,70(0,30; 1,10)		0,50(0,30; 1,00)	<	**1,30(0,65; 3,25)**	>	0,70(0,30; 1,10)
ANXIETY - SCARED	13(9; 19)	<	**30,5(19; 46)**	>	16,5(12,5; 24)		13(9; 19)
DEPRESSION - CDI	6(5; 7)	<	**19(12; 23)**	>	6(3; 11)		6(5; 7)
DEPRESSION - BDI	2(0; 5)	<	**22(14; 26)**	>	5(1; 8)		2(0; 5)
STRESS -SLES_subject	14(6; 27)	<	**39(24; 61)**	>	20(10; 42)		14(6; 27)
STRESS -SLES_parent	11(6; 19)	<	**36(21; 47)**	>	11(4; 21,5)		11(6; 19)

Legenda: Three-group comparisons of inflammatory/autoimmune markers and psychopathological scores. Signs "<" and ">" indicate directions of significant differences at .05 significancy level. In red color the highest, in orange the intermediate, and in blue the lowest values among the groups.

Medical history

The only significant difference we found, were higher rates of autoimmune conditions in offspring than in both other groups, and of asthma in offspring than in controls.

Inpatients showed a trend to significance for higher rate of tonsillectomy and allergies than controls.

The autoimmune disorders found in inpatients (n=4) were psoriasis in three cases and fibromyalgia in one case, in offspring (n=4) there were one case of autoimmune glomerulonephritis, thyroid dysfunction, vitiligo, and cryoglobulinemia respectively.

Table 2. Main differences found in personal and family history of infectious and autoimmune disease

Medical history	HC		PATIENTS		SLE-OFFSPRING		HC
REPEATED INFECTIONS IN INFANCY	36.7%		46.9%		36.8%		36.7%
TONSILLECTOMY	3.3%	<? p= 0.063	16.9%	>? P=0.200	5.3%		3.3%
ALLERGIES	16.1%	<? p=0.109	31.4%		31.6%	>? P=0.201	16.1%
ASTHMA	3.0%	<? p=0.197	10.4%	<? p=0.108	23.8%	> P=.018	3.0%
AUTOIMMUNE CONDITIONS	0%	<? p=0.18	5%	< p=0.010	**19.0%**	> p=.004	0%

Legenda: Three-group comparisons of clinical history for infections, allergic and autoimmune conditions. Signs "<" and ">" indicate directions of significant differences at .05 significancy level, "<?" and ">?" tendencies to significance with relevant p values.

Autoantibodies

Common autoantibodies

Lupus offspring had significantly higher levels of anti-DNAds than both other groups.

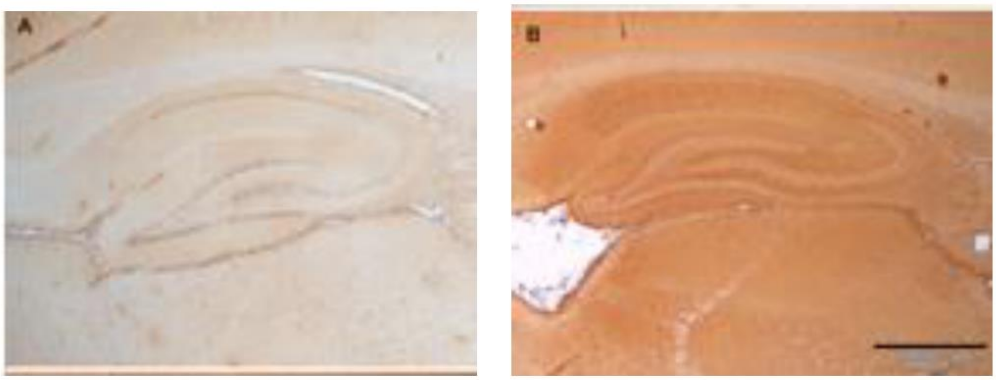
We did not find any other significant differences of all the other antibodies between the three groups.

Antibodies against neuronal surface

Using the combination of IHC, CBA and live-cells staining, we identified two (2.4%) patients with clear extracellular immunocytochemistry labeling of live hippocampal neurons, suggesting the presence of neuronal surface antibodies. None of the two patients showed reactivity against known neuronal surface antigens by CBA. Inpatients were both male, 17.7 y.o., one had a diagnosis of psychotic disorder, the other

of depression without psychotic symptoms. In Figure 2 the immunohistochemistry staining of one of the patients, the first screening step of the procedure.

Figure 1. Demonstration of serum antibodies reacting with the neuropil of rat hippocampus



Panel A Panel B

Panel A shows a section of rat brain immunolabeled with serum from a healthy individual. Panel B shows a similar section of rat brain immunolabeled with serum from one of the patients. Note the intense reactivity of patient's serum antibodies with the neuropil of hippocampus

Tests were repeated two years later on the first patient, who had showed the highest positivity. He had meanwhile received a schizophrenia diagnosis, was attending a day center, receiving antipsychotic treatment, and his estimated GAF was about 50, where negative symptoms were predominant. No immunoreactivity was found then.

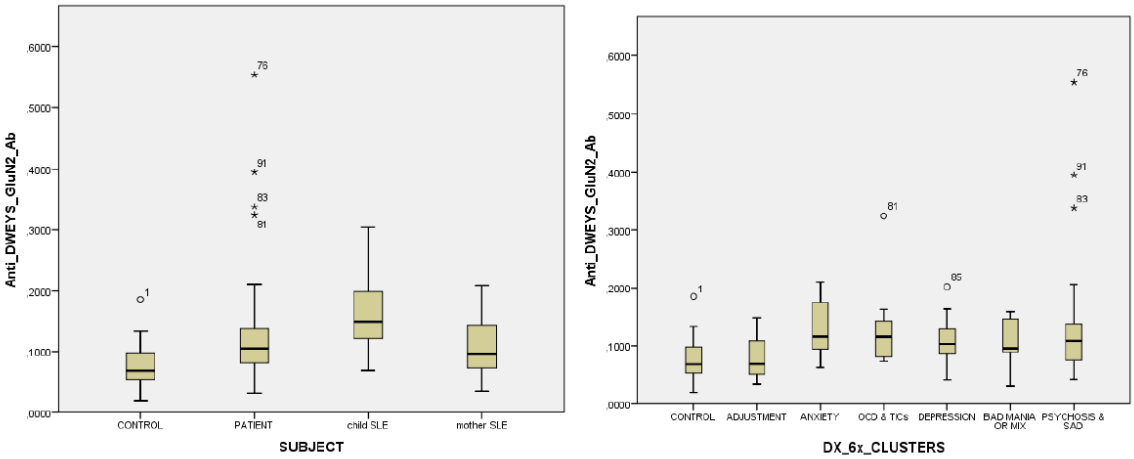
No subject in the offspring group was positive for antibodies against the neuronal surface with this procedure.

Anti-DWEYS-GluN2 Ab

Anti-DWEYS-GluN2 antibodies were significantly increasing between controls, inpatients and offspring, respectively. Levels in Lupus mothers were intermediate between those of offspring and those of controls, and not different from inpatients ($p = .96$). Among inpatients, no significant difference was found in Anti-DWEYS-GluN2 levels between subjects with and without psychotic symptoms, or between the different diagnostic clusters. Table 1 and Figure 2.

Within inpatients, there was no difference of the anti-DWEYS_GluN2 titers between the six diagnostic clusters previously identified [4]. Figure 2.

Figure 2. Serum values of Anti-DWEYS-GluN2 antibodies in the three groups and in Lupus mothers, and in the diagnostic subgroup of inpatients:

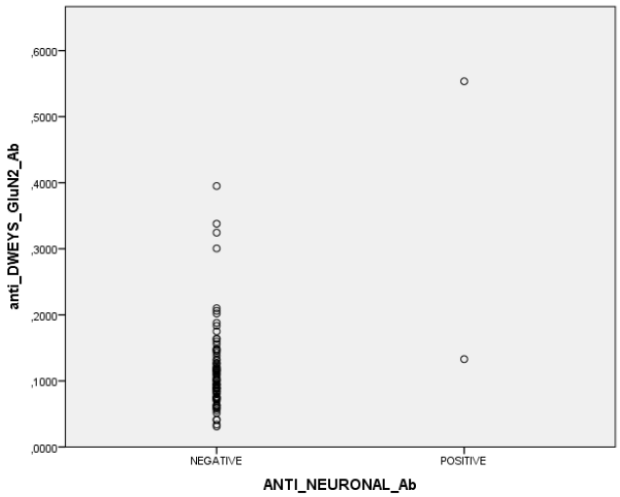


Secondary results

Correlation between anti-DWEYS-GluN2 and anti-neuronal surface antibodies

One question that arose was whether the presence of anti-DWEYS-GluN2 translated in reactivity against life neurons. We analyzed then whether there was a correspondence between titers of anti-DWEYS-GluN2 and neuronal reactivity. The one patient with highest immunoreactivity against anti-neuronal surface antibodies, was also the one with highest levels of anti-DWEYS-GluN2 antibodies. The other patient had concentrations of anti-DWEYS-GluN2 antibodies within the range for inpatients. Figure 3.

Figure 3. Distribution of anti-DWEYS-GluN2 antibodies within patients, grouped after positivity and negativity to anti-neuronal surface antibodies.



Correlation of anti-DWEYS-GluN2 antibodies with clinical scales in inpatients

We analyzed whether anti-DWEYS-GluN2 antibodies were linked to measures of psychopathology. In the subgroup controls + inpatients, the anti-DWEYS-GluN2 antibodies correlated positively and significantly with anxiety, depression and stressful life events scales. Table 3.

Table 3. Correlations between DWEYS-AB and Anxiety, Depression and Stressful Life Events Scales (SLES) in inpatients and controls.

		SCARED SPA	SCARED GA	SCARED SA	SCARED SocPh	SCARED SchoolPh	SCARED Total	CDI < 16 y.o.	BDI >= 16 y.o.	SLES self	SLES parents
anti_DWEYS_GluN2 Antibodies	*Correlation Coefficient*	**.444****	**.365****	0.267	**.416****	0.06	**.391****	**.387***	**.485****	**.347****	0.226
	Sig. (2-tailed)	0.001	0.008	0.058	0.002	0.674	0.004	0.038	0.009	0.001	0.051

*/**correlation is significant at 0.05/0.01 level (2-tail); SCARED = Screen for Child Anxiety Related Emotional Disorders, SPA = somato-psychic anxiety; GA = generalized anxiety; SA = separation anxiety; SocPh = social phobia; Total = total score; CDI = Child Depression Inventory (<16 y.o.); BDI = Beck Depression Inventory (>=16y.o.)

When considering all subjects together. including offspring. only some correlations remained valid. Table 4.

Table 4. Correlations between DWEYS-AB and Anxiety, Depression and Stressful Life Events Scales (SLES) in the whole sample.

		SCARED SPA	SCARED GA	SCARED SA	SCARED SocPh	SCARED SchoolPh	SCARED Total	CDI < 16 y.o.	BDI >= 16 y.o.	SLES self	SLES parents
anti_DWEYS_GluN2 Antibodies	*Correlation Coefficient*	.215	**.239***	.091	**.352****	.078	.232	.032	**.359***	.181	.050
	Sig. (2-tailed)	.073	.045	.448	.003	.519	.050	.847	.025	.065	.628

LEGENDA SEE TABLE 3

4. DISCUSSION

This work expands knowledge of immune asset in two population of young subjects: acute psychiatric inpatients and offspring of women with Lupus.

Both groups show elevation of some inflammatory cytokines. IL-8 appears here again highest in the inpatient condition, suggesting a putative role for this cytokine as a marker of psychopathological distress. In our previous work IL-8 was an independent predictor of the inpatient versus the control condition [4].

The results on the other cytokines, suggest that the level of inflammatory cytokines in young psychiatric inpatients are often comparable, and sometimes lower, than the levels in lupus offspring, a population with possible autoimmune diathesis.

The trend to higher rate of tonsillectomy – a proxy for throat infections – in the inpatient group, supports a possible coexistence of psychiatric and infectious disorders, as reported by vast literature (e.g. [20,21]). Inpatients show lower rates of autoimmune disorders than offspring. Works in adult show bilateral longitudinal association between autoimmune and psychiatric disorders, and it may be that comorbidities will get higher as age increases.

Both study groups had a higher differential count of monocytes than healthy controls, compatible with an activation of monocytes in conditions associated with chronic, low grade inflammation [22].

About 2% of acutely ill psychiatric young patients showed serum antibodies reacting with unknown surface antigens in the neuropil of brain, when serum reactivity was tested against neuronal surface. The most positive of the two patients, re-tested outside the acute phase, had negativized for such reactivity, and was still functionally impaired, even though no longer productively hallucinating. It is difficult to draw causal conclusions from these results, but the findings of such reactivity, support the meaning of continuing researching the presence and role of autoantibodies in acutely ill psychiatric patients.

The finding of titers of the anti-DWEYS-GluN2 antibodies increasing between controls, inpatients and Lupus offspring, suggests different possibilities of the role of these antibodies. The main question that emerges is: do these antibodies have a psychopathogenic role, are they just markers of increased immune activation, or is their increase just a casual finding? In the first hypothesis, potential treatments directed against the antibody might ensure a better clinical outcome for psychiatric patients, justifying more spread screening for antibody presence. Even if this question can't be answered by our cross-sectional data, some considerations can be drawn. Some works have shown that this antibody can be neurotoxic and be related to psychiatric symptoms in Lupus patients [23], and that a breach in the blood-brain barrier is necessary for the antibody to exert its effects [23]. Our inpatients had experienced increased stress levels [4], and possibly higher rates of previous infections: both factors might have contributed to damage the BBB, allowing the antibody to access the brain and facilitating its central action. Titers of the antibody correlated positively with anxiety, depression and stress measures in the group of inpatients + controls, supporting a possible link between presence of antibody and clinical symptoms.

Correlations appeared less strong when offspring also were included, despite the increase in sample size. This may suggest that anti-DWEYS-GluN2 are more specifically related to psychopathology in population without familiar/genetic risk for immune dysregulations, and/or in population more exposed to insults

damaging the BBB, as stress and infections. In case of familiar risk for autoimmune disease, these antibodies may represent a background finding.

Another question that appears from this work, is: why isn't there a clear correspondence between anti-DWEYS-GluN2 antibody levels and positivity for neuronal surface, if anti-DWEYS-GluN2 are also antibodies against the neuronal surface, as claimed by the researchers that described them [17]? One explanation could be, that cell-based assays and immunohistochemistry used for finding antibodies against neuronal surface, capture conformational epitopes, while ELISA, used in determining anti-DWEYS-GluN2 antibodies, measures low affinity/avidity antibodies, that bind the receptor only in in-vivo conditions, and can't be captured in invitro tests and at high dilutions as those used. It may also be that the antibody is an epiphenomenon, suggestive of a general tendency to elevated autoimmunity and inflammation, but without pathogenicity, as some other researchers defend [24,25]. Future work analyzing anti-DWEYS-GluN2 titers in CSF and relating them to psychopathology would help clarify these points.

Limitations

One general limitation of this work has been not to have tested the CSF, where sensitivity is higher both for anti-neuronal antibodies (100% vs 85% in serum) and for anti-DWEYS-GluN2 antibodies [26].
The study is cross sectional, and except for one follow-up, no data are available on antibody levels at follow up. The study is though intended as exploratory, and the anti-DWEYS-GluN2 antibodies are measured for the first time in a psychiatric population.
Sample size for the offspring group is small.

5. CONCLUSIONS

Results confirm association of psychopathology with immune alterations, in line with evidence suggesting coexistence of such disturbances (e.g. [27,28]). The presence of antibodies with neuronal activity in two cases, and of elevated titers of anti-DWEYS-GluN2 with correlation with clinical scales, support broader and longitudinal studies, to confirm findings, and clarify possible causal versus epiphenomenal associations [24,25,29].

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Work 2

Title: Monocyte/lymphocyte Ratio (MLR) as a proxy for inflammation in a sample of Child and Adolescent Psychiatric Inpatients

Background: Research shows increased inflammatory state in subgroups of psychiatric patients through the diagnostic spectrum. Most data regard CRP and certain proinflammatory cytokines (CK), as interleukin-6 (IL-6), IL-1beta, TNF-alfa and the chemokine MCP-1 (Monocyte chemoattractant protein-1). Cytokines have shown complex properties both in the peripheral system and in the central nervous system (CNS). Their measurement though is not part of the standard laboratory tests.

In search of more inexpensive and reproducible inflammation markers, recent psychiatry research has focused on monocyte/lymphocyte ratio (MLR), neutrophil/lymphocyte ratio (NLR), and platelet/lymphocyte ratio (PLR), predictors of poor prognosis or elevated inflammation in cardiovascular, autoimmune and other systemic diseases (Afari & Bhat, 2016; Chandrashekara et al., 2020; Li et al., 2017; Yang et al., 2017).

In psychiatric disorders, they have been suggested proxies of inflammation (Neutrophil-to-Lymphocyte, Platelet-to-Lymphocyte and Monocyte-to-Lymphocyte Ratio in Bipolar Disorder, 2021). Recent evidence have found them elevated among adult patients with psychotic and mood disorders versus healthy controls (HC), especially in acute phases of diseases (Inanli et al., 2019; M.G. Mazza et al., 2019; Mario Gennaro Mazza et al., 2018; Mario Gennaro Mazza, Capellazzi, et al., 2019; Mario Gennaro Mazza, Tringali, et al., 2019; Özdin et al., 2017; Özdin & Böke, 2019; Yüksel et al., 2018).

Preliminary studies in children and adolescents (C&A) populations, have also shown higher MLR and/or NLR in adolescents with depression, psychosis or ADHD (Avcil, 2018; Bustan et al., 2018; Cevher Binici et al., 2018; Moody & Miller, 2018; Özyurt & Binici, 2018).

We have described higher cytokines (IL-1beta, IL-6, IL-8, MCP-1 and IP-10) and monocyte count in a transdiagnostic group of C&A acute inpatients, vs. a control group in the same age range (8-17). Here we compare MLR, NLR and PLR between the two groups and analyze their correlation with cytokines and clinical scales.

Methods: 77 consecutive Child and Adolescent inpatients and 34 Healthy Controls (HC) were recruited. Mean age (SD) were 15.1 (2.4) and 15.7 (2.7), male ratio 52% and 41% respectively (p>0.05 for both). MLR, NLR and PLR were compared between the two groups, and between HC and 5 diagnostic clusters of inpatients (U- Mann Whitney). Spearman correlations between MLR, NLR and PLR with cytokines, CRP, age, BMI, and stressful-life events (SLE), anxiety (SCARED), global assessment of functioning (GAF), Autism Spectrum Screening Questionnaire (ASSQ) and Conners Parent Rating Scales Revised (CPRS) were assessed for the whole sample.

Results: MLR was higher in the whole patient group (p=0.049) and in the subgroup of anxiety and OCD disorders (p=0.015) vs HC. We found no significant differences in NLR and PLR distribution between patient group/subgroups and HC. Table 1.

MLR, NLR and PLR correlated significantly with each other and with CRP. Moreover, MLR correlated with IL-1beta, IL-2, IL-8, IP-10, and ASSQ, with a trend for IL-6, IFN-gamma and GAF; NLR with IL-2, IL-6, with a trend for BMI and IL-4; PLR with IP-10. Table 2.

Table 1: mean and SD for MLR in controls, patients, and diagnostic subgroups:

	CONTROLS (n=34)	PATIENTS (n=77)	ADJUSTMENT (n=5)	ANXIETY & OCD (n=17)	DEPRESSION (n=19)	BAD MANIA or MIXED (n=14)	PSYCHOSIS & SAD (n=22)
MLR mean (SD)	0.17 (0.07)	0.20 (0.08)	0.20 (0.07)	0.21 (0.05)	0.19 (0.09)	0.18 (0.06)	0.21 (0.12)
P		0.049*	0.223	0.015*	0.584	0.370	0.140

Tab- 2: Spearman's Rho correlations between MLR, NLR and PLR and metabolic and inflammatory markers

	MLR	NLR	PLR	CRP	BMI	IFNg	IL1b	IL2	IL4	IL6	IL8	IP10	ASSQ	EEAG
MLR		.584**	.585**	.389**		0.159	.221*	.199*		0.164	.193*	.196*	.343*	-0.163
		p<.001	<.001	0.001		0.096	0.02	0.036		0.086	0.042	0.047	0.01	0.088
NLR	.584**		.606**	.510**	0.174			.256**	0.181	.190*				
	<.001		<.001	<.001	0.093			0.007	0.057	0.045				
PLR	.585**	.606**		.326**								.237*		
	<.001	<.001		.008								.016		

Discussion: Results show higher MLR in a cohort of acute C&A psychiatric inpatients with described higher inflammatory cytokines vs HC. Of the three parameters, MLR showed the most correlations with cytokines.

Despite mutual correlations between the three markers, and with CRP, no difference was found for NLR and PLR between patients and controls, in contrast with adult literature and with some previous studies on C&A population with mood or psychotic disorders. This may be due to sample size, young age and/or heterogeneity of diagnosis.

Results support a possible role of MLR as an inexpensive biomarker of the inflammatory profile in C&A psychiatric population.

To our knowledge this is the first work in psychiatric population relating MLR, NLR and PLR to cytokine levels.

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5 DISCUSSION

5.1 Main findings

This work contributes to expanding the current knowledge about relation between inflammation, autoimmunity, psychosocial stress and psychiatric conditions, in adolescent population. It studies two groups of subjects: acute psychiatric inpatients and offspring of women with Lupus, comparing them with the same group of healthy controls.

In Study 1, we find that young psychiatric inpatients across the diagnostic spectrum have higher monocyte count and higher levels of five proinflammatory cytokines, IL-1β, IL-6, IL-8, IP-10 and MCP-1, than controls, also after adjustment for other potential causes for inflammation as BMI, age, gender and drugs intake at admission (except for MCP-1). Inpatients come more often from families where the original biological structure is not conserved (parental separation, divorce, adoptions, custody under public institutions), and they have experienced higher levels of recent stress, as captured by the Stressful Life Events Schedule for Children and Adolescents (SLES) (Williamson et al., 2003). Monocytes and various cytokines correlate with measures of recent stressors, which are higher in patients from disrupted families. Disruption of biological family is an independent predictor of the patient condition, together with monocyte count, IL-8 and IP-10.

In Study 2, we find that offspring of women with Lupus have a different immune asset than controls, with higher levels of 8 cytokines (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, IFN-γ and TNF-a), lower white cell count, higher levels of anti-dsDNA and of anti-DWEYS-GluN2 antibodies. The latter is an antibody described in women with SLE, with neurotoxic effects in animal studies, and a plausible candidate for neuronal damage and symptoms of Neurolupus when present in the CSF. Offspring have also higher rate of autoimmune and asthma than controls. Offspring showed more difficulties in written production and greater slowness in visual–motor abilities, and better impulsivity control in comparison with healthy subjects. CRP increases with age in offspring and not in control group, and leucocyte count, attention and immediate memory scores decrease. About one fourth (23.9%) of offspring met criteria for a psychiatric diagnosis, and a half of them had subclinical symptoms. The diagnoses found were anxiety, ADHD, OCD, and TS, and their prevalence was significantly higher than that estimated in the general population. Offspring scores in SLES and depression scales correlate positively, and various neuropsychological performance indexes correlate negatively with mother scales for depression and disease activity at test point.

We have also described some unpublished results, showing that psychiatric inpatients had higher allergy rates, higher monocyte to lymphocyte ratio (MLR) and higher anti-DWEYS-GluN2 antibodies than controls. Values of anti-DWEYS-GluN2 antibodies increase progressively between controls, inpatients and Lupus offspring. When looking for antibodies with reactivity against neuronal antigens though, no inpatient presented activity against cells expressing known neuronal antigens, including NMDA-R, and two patients presented reactivity against an unknown antigen expressed by live rat hippocampal neurons.

The discussion relates these results with the work studying the role of stress and inflammation on lifelong health, described in the introduction. It will also link the results with recent research, describing the importance of parental and social support for lifelong health, and their capacity to buffering other adversities. Attachment measures and attachment-focused interventions will be also analyzed, as emerging tools to respectively assess how some forms of early psychosocial stress can “get under the skin”, and how it is possible to prevent long-lasting consequences of early stress on health.

The Future Directions section presents implications of the results for clinical activity and future research: lines for assessment of inflammation and stress, and lines for intervention to reduce inflammation, stress and their consequences, in adolescent population.

The Limitations sections summarizes the main limits of this work.

5.2 Interpretation of the findings in the frame of the theoretical models

The introduction reviewed evidence about presence and putative causal role of inflammation in psychiatric conditions; links between mental and physical health; the role of stress as common trigger and of inflammation as common soil in chronic diseases; the importance of exposure to insults in special sensitive windows, as prenatal period, early life and adolescence; the theoretical models and biological mechanisms implied in embedding of stress and insults, and in production of inflammation.

Results on the inpatient group support the presence of both peripheral inflammation and monocyte activation in young psychiatric inpatients: the panel of cytokines found elevated - IL-1β, IL-6, IL-8, IP-10, and MCP-1 - are all produced by activated monocytes, and monocyte counts were also higher in the patient group. This is in accordance with the reviewed literature, that finds elevated cytokines and CRP, changes in white cell profiles, with monocytes with a proinflammatory phenotype, and upregulation of inflammation-related genes across both adult and child and adolescent psychopathology (e.g. (Bergink et al., 2014; Chiang et al., 2019; Colasanto et al., 2020; Mitchell & Goldstein, 2014; Yuan et al., 2019). Even if these are measures of peripheral inflammation, and cytokines are big molecules that in normal conditions do not to cross the blood-brain barrier (Liebner et al., 2011), peripheral inflammation has been shown to be able to reach the brain and influence psychopathology in various ways. For example, IL-1β, IL-6 and MCP-1 have transport molecules through the BBB (Banks, 2015), and once in the brain, IL-1β and IL.6 can e.g. bind receptors on neurons and directly impact synapse strength (Wohleb & Delpech, 2017). IL-1β has also been involved in neurodegenerative and neuroprotective processes, including possible neuronal injury (Allan et al., 2005) and IL-6 can activate microglia (W.-Y. Wang et al., 2015). MCP-1 and IL-8 may have neurotransmitter/neuromodulatory roles and chemotactic properties, and attract activated monocytes to the brain (Stuart & Baune, 2014)(Baune et al., 2012; Mélik-Parsadaniantz & Rostène, 2008; Stuart & Baune, 2014). As per peripheral monocyte activation, besides marking activation of innate immunity, it may reflect or trigger microglia activation according to some authors (Bergink et al., 2014).

It is interesting that our study found elevation across a broad number of cytokines and diagnosis: in particular, IL-1β and IL-8 remained higher than in controls in all diagnostic subgroups, despite the reduction in group sizes. Previous literature often focuses on specific markers (e.g. IL-

6, or CRP) in specific diagnoses, and our findings suggest that more general results can be reached, if adopting a broad-spectrum panel and a trans-diagnostic approach.

Even more relevant than the effects of the single cytokines, may be the indication for elevated systemic inflammation and changes in immunity system in inpatients. This is also supported by the yet unpublished data on inpatients, that have increased monocyte/lymphocyte ratio, a proxy for systemic inflammation and a proposed marker for inflammatory activities in psychiatric disorders (Fusar-Poli et al., 2021), a trend for higher rates of allergic conditions, and higher titres of an antibody described in autoimmune disorders, with respect to healthy subjects. These results altogether support the presence of a diathesis towards general inflammation and immune dysregulation in psychiatric population, already from young ages, before chronic somatic conditions manifest.

It is not possible to know from our data, whether some of these inpatients will go on developing clinical somatic and autoimmune conditions. Yet, the presence of elevated inflammation and immune dysregulation at early ages supports this possibility. Inflammation is not only a possible causal mechanism for psychiatric disorders, as reviewed, but also a risk factor for several somatic ones: metabolic syndrome (Hotamisligil, 2017; Jin et al., 2013), atherosclerosis (Liuzzo et al., 2019; Nandkeolyar et al., 2019), endothelial dysfunction (Aboonabi et al., 2020), cardiovascular disease (Ellulu, 2017), development and progression of cancers (Singh et al., 2019; Taniguchi & Karin, 2018), chronic kidney disease (Ferrucci & Fabbri, 2018), and also neurodegenerative (Heneka et al., 2014) and autoimmune disease (Furman et al., 2019). Also, the presence of one type of antibodies described in Lupus patients, suggests a possible increased risk for development of autoimmune disorders. The presence of autoantibodies precedes the debut of various autoimmune disorders, even if the presence alone is not sufficient to predict development of disease (Yusof et al., 2017): antibodies against citrullinated proteins ACPA or rheumatoid factors increase risk of rheumatoid arthritis (Mankia et al., 2021; Petrovská et al., 2021), and various antinuclear antibodies increase risk of Lupus and other connective tissue diseases (Selmi et al., 2016). We have reviewed in § 1.5 evidence suggesting that psychopathology may be associated with higher rates of somatic conditions, and results from our studies confirm the presence of possible causal mechanisms: increased inflammation and altered autoimmunity.

Results in the offspring group show that children of women with SLE show immune changes as higher inflammatory markers, higher rates of asthma and autoimmune conditions, higher rates of psychiatric diagnosis than would be expected, and some changes in neurocognitive profile, with respect to healthy controls. Here again, there is coexistence of neuropsychiatric and immunological changes, that without permitting conclusions on causality, supports comorbidity between psychiatric and somatic conditions, and inflammation being a common soil for them, as reviewed in §1.5 and §1.7.

The potential relevance of inflammation and immune changes on mental and clinical conditions, emerges also from another observation. In both studies, immune/inflammatory markers were predictive of the study condition: in inpatients, IL8, IP10 and monocytes absolute count predicted the inpatient versus control condition, and in offspring, anti-DWEYS-GluN2 antibody, followed by leukocyte count, predicted the offspring versus control condition. This suggests that these changes are central in differentiating inpatients/offspring from healthy controls.

The specific findings on the anti-DWEYS-GluN2 antibodies suggests further considerations. The antibody titres were highest in SLE-offspring, intermediate in inpatients and Lupus women, and lowest in controls (details in unpublished results). As reviewed, this antibody is suggested to bind the NMDAR and to modulate its function (Chan et al., 2020; Faust et al., 2010), to have a potential role in Neurolupus symptoms (B. Diamond et al., 2009; Faust et al., 2010), and to possibly affect the development of offspring of women with SLE in case of foetal exposure, contributing to some of the neuropsychiatric alterations described in this group (É Vinet et al., 2014; Yousef Yengej et al., 2017).

The main question that emerges from our results is: do these antibodies have a psychopathogenic role, are they simply markers of increased immune activation, or is their increase in inpatients and offspring only a casual finding? In the first hypothesis, potential treatments directed against the antibody might ensure a better clinical outcome for psychiatric patients, justifying more spread screening for antibody presence. Even if this question can't be answered by our cross-sectional data, some considerations can be drawn. Some works have shown that in order for this antibody to be neurotoxic and related to psychiatric symptoms, a breach in the blood-brain barrier is necessary (Kowal et al., 2004). Our inpatients had experienced

increased stress levels(Gariup et al., 2015), and possibly higher rates of previous infections than either other groups: both factors might have contributed to damage the BBB, allowing the antibody to access the brain and facilitating its central action. The fact that titers of the antibody correlated positively with anxiety, depression and stress measures in the group of inpatients + controls, support a possible link between presence of antibody and clinical symptoms. Correlations appeared less strong when Lupus offspring also were included, despite the increase in sample size. This may suggest that anti-DWEYS-GluN2 are more specifically related to psychopathology in population without primary (i.e. familiar, genetic) risk for immune dysregulations, and/or in population more exposed to insults damaging the BBB, as stress and infections. In case of familiar risk for autoimmune disease, these antibodies may represent a background finding.

Another possible mechanism for these antibody to have a health impact, could be by contributing indirectly to inflammation and immune alterations, by the peripheral action they can have on blood cells (Gono et al., 2011) and on non-nervous tissue, as bone, pancreas, and skin (Skerry & Genever, 2001). The differences in white cell counts seen in the offspring group, may have a relation with antibody presence. Studies with bigger sample sizes and longitudinal design may help clarify this point.

Another question that arises from these results is: why isn't there a clear correspondence between anti-DWEYS-GluN2 antibody levels and positivity for neuronal surface, if anti-DWEYS-GluN2 are also antibodies against the neuronal surface, as claimed by the researchers that described them (DeGiorgio et al., 2001)? One explanation could be, that cell-based assays and immunohistochemistry used for finding antibodies against neuronal surface capture conformational epitopes, while ELISA, used in determining anti-DWEYS-GluN2 antibodies, measures low affinity/avidity antibodies, that bind the receptor only in in-vivo conditions, and can't be captured in invitro tests and at high dilutions as those used. It may also be that the antibody is an epiphenomenon, suggestive of a general tendency to elevated autoimmunity and inflammation, but without pathogenicity, as some other researchers defend (S. H. Tay et al., 2017; Varley et al., 2020). Future work analyzing anti-DWEYS-GluN2 titers in CSF and relating them to psychopathology would help clarify these points.

A third relevant question is: had the maternal antibodies exerted an effect on offspring during gestation and neurodevelopment? Again, our cross-sectional work can't give an answer.

Our results support the association of the antibodies with the SLE condition, and suggest that mothers likely had the antibodies in their serum also during gestation, making it plausible that the antibody reached the foetal brain. Here again, longitudinal work monitoring level of maternal and offspring antibodies from gestation age, and along development, and relating it to clinical outcomes, could help clarify this question.

The presence of serum antibodies with reactivity against unknown rat neuronal antigens, found in two patients and described in the unpublished results, leaves other questions open*:* did the antibodies have a role in causing the clinical manifestations? And which were the neuronal antigens? One of the two patients negativized at follow up two years later, but presented with chronic negative symptoms and was still on antipsychotic treatment, and the other, who had had a depression diagnosis, was in remission and functioning well. Our result may encourage further studies on CSF in acute patients.

We have adopted a transdiagnostic approach in studying psychopathology. We found shared immunological changes across diagnoses between inpatients: cytokines as IL-8 and IL-1β were higher than controls in all diagnostic clusters, and there was no difference in monocyte count and anti-DWEYS-GluN2 titres between the different diagnostic clusters. This indicates some shared inflammatory and immune changes across psychopathology, supporting transdiagnostic research. Results are also in line with what proposed by some transdiagnostic taxonomies reviewed in the introduction: the HiTop taxonomy identifies a shared higher order dimension (P-factor) and subordinated subfactors (Kotov et al., 2017), and the taxonomies linked to neural circuits propose common cross-disorder dysfunction across large-scale networks, and then more specific circuit-symptom changes (Buckholtz & Meyer-Lindenberg, 2012; Sha et al., 2019). Whether shared immune and inflammatory changes support these shared psychopathological or neural changes is an interesting possibility, already supported by some preliminary research (Nusslock et al., 2019; Swartz et al., 2021), as reviewed in §1.2.

One question raised by investigators, is whether inflammation affects only a subset of patients, or psychiatric patients in general. Some authors have suggested the existence of subtypes or clusters of psychopathology, where early stress, inflammation and treatment resistance concatenate along lifetime (Danese et al., 2009; G. E. Miller & Cole, 2012) possibly in relation with microglia activation (Valeria Mondelli et al., 2017). A recent meta-analysis of

inflammatory markers in depression has found that some markers as CRP and IL-12 have reduced variability in depressed patients, supporting greater homogeneity in terms of an inflammatory phenotype in the disorder than thought (Osimo et al., 2020). Looking at the similar finding described in the introduction about inflammation across the psychopathological spectrum, findings from this meta-analysis may apply also in case of other diagnoses. This inference is only speculative and requires further investigation. The fact that in our work, inflammation and immune markers were clearly elevated in most subgroups of patients, even when numbers were reduced, is in line with this thought, where inflammation may be a hallmark of psychiatric conditions.

In the introduction we have reported on research studying the role of lifelong stress and insults of various nature on health and inflammation. A summarizing overview of this evidence is provided in the box. Various researchers propose that many mental and somatic disorders may have a developmental nature (Shonkoff et al., 2009), associated with increasing inflammation, as allostatic load accumulates.

In the offspring group, various inflammatory and neurocognitive parameters showed a correlation with age: CRP was higher, leukocyte count was lower, and working and verbal memory scores were lower in older offspring vs younger, while controls showed no age-related trends. These findings are supportive of a developmental trajectory for this group, where exposure to allostatic load combined with a genetic predisposition, gives rise to increasing immune and neuropsychiatric changes along development, as proposed in Study 2 Graphical Abstract and reported by literature (Couture et al., 2017; Nacinovich et al., 2008; Neri et al., 2004; Tincani et al., 2006).

In both study groups, results support the association of psychosocial stress with inflammation and psychophysical health that various work suggest (Wolf & Schnurr, 2016).

In inpatients, measures of recent stressful events correlated with IL-1β, IL-8, MCP-1 and monocyte counts; disruption of family structure, a proxy for accumulated familiar stressors (G. E. Miller & Cole, 2012), was a predictor for the inpatient condition; and the inflammatory cytokines IL-1β and IL-6 tended to be higher in subjects with non-conserved family structure. In offspring, maternal mental and physical distress - putative proxies of family stress - correlated with higher depression scores and lower neuropsychological performance in offspring. These findings underscore the importance of family climate and parental well-being for children health.

SUMMARY OF THE REVIEWED EVIDENCE ABOUT INFLUENCES OF STRESS ON HEALTH

This box provides a short overview of the evidence regarding the role of stress along lifetime, from before conception to adulthood, on mental and physical health and inflammation (as reviewed in §1.8-§1.10 of the Introduction).

Prenatal stress associates with asthma, allergic and atopic disorders (meta-analyses: (N. W. Andersson et al., 2016; Flanigan et al., 2018; Van De Loo et al., 2016)) and affects neurocognitive development and psychiatric disorders in offspring (Manzari et al., 2019; Van den Bergh et al., 2017). Maternal inflammation is one implied mediating factor (Hantsoo et al., 2019).
Also early life stress associates with impaired physical health, both in childhood (Oh et al., 2018), and later on, with increased risk of negative health outcomes (Wegman & Stetler, 2009), among which cardiometabolic (Jakubowski et al., 2018) and autoimmune diseases (Dube et al., 2009; C. H. Feldman et al., 2019). Early adversities increase also risk for later mental disorders, as psychosis, anxiety, depression and suicidality (Angelakis et al., 2019; M. Li et al., 2016; Varese et al., 2012). Findings suggest a dose-response effect (Hughes et al., 2017), and the importance of even "trivial" or "silent" stressors, as parental divorce or psychological abuse (Afifi et al., 2009; Infurna et al., 2016).
Evidence indicates that early stress leads also to increased inflammation, manifesting already in childhood (higher CRP and IL-6, (Kate R. Kuhlman et al., 2019)) and more so in adulthood (higher CRP, fibrinogen, various cytokines as IL-1β, IL-6, and TNF-α (Baumeister et al., 2016; Coelho et al., 2014; Deighton et al., 2018; Lanius, 2014)).
Psychosocial stress have similar effects when occurring later in life: associates to poorer health (Braveman et al., 2010; Holt-Lunstad et al., 2010; Kivimaki & Steptoe, 2018; Pejtersen et al., 2015; Pollitt et al., 2005) and to increased inflammation, both when occurring in adolescence (Chiang et al., 2012; Fuligni et al., 2009; Marin et al., 2009; M. L. M. Murphy et al., 2013), and in general (Hänsel et al., 2010; Kiecolt-Glaser, Gouin, et al., 2010; Seiler et al., 2020).

These findings altogether have made various authors posit that that stress can trigger a trajectory towards poor health, and that systemic low-grade inflammation may be a pathway linking adversity with morbidity and mortality (Baumeister et al., 2016; Lanius, 2014). Many adult diseases may thus be viewed as developmental disorders that begin early in life (Shonkoff et al., 2011).

The mechanisms implied and reviewed in §1.9 are changes in the HPA axis, the Sympathetic Nervous System, the Immune System, microglia and other brain cells, epigenetic programming, telomere length and the microbiome. All the mechanisms appear to influence, and be influenced by, systemic inflammation. Regarding effects of timing and quantity of stress exposure, three hypothesis are suggested (§1.9.7). *The early-life sensitization model* implies that stress in early life has special impacts because of the heightened plasticity of homeostatic and neurological systems during prenatal time and infancy. Early stress would thus calibrate the physiological systems and render them more sensitive to further insults. The *stress accumulation model* posits that all stress exposures have an impact, and what determines the end outcome is the total amount of stress experienced (G. W. Evans et al., 2013; G. W. Evans & Kim, 2010). The *stress generation model* proposes that early stress generates adult stress, by environmental continuity (e.g. low SES in childhood predicts low SES in adulthood, and that is linked to poor health, (B. Galobardes et al., 2008)), or by influencing one's cognitive styles (Shackman et al., 2007) (Edith Chen et al., 2009), coping strategies (Fagundes et al., 2011) and self-regulation skills (Blair & Raver, 2012), and by increasing risk for re-exposure to traumatic situations (Widom et al., 2008). All this would increase risk to continuous exposure to high stress levels.
The *Fetal Origins Hypothesis* (Barker, 1998) and the subsequent *Developmental Origins of Health and Disease* (DOHaD) hypothesis (P. D. Gluckman et al., 2008; Wadhwa et al., 2009), embrace the stress sensitization model. Within neurosciences, we cited three models. The *Neuroimmune Network Hypothesis*(Hostinar et al., 2018; Nusslock & Miller, 2016) proposes that multiple bidirectional pathways exist between the immune system and brain circuits, and that early stress amplifies this crosstalk, leading to processes that self-sustain chronic inflammation and its consequences. The *Social Signal Transduction Theory of Depression* (Slavich & Irwin, 2014) posits that interpersonal life stressors activate inflammatory processes that in turn increase sensitivity to social stressors, perpetuating a circle that sustains increased inflammation and depressive symptoms. The *Theory about microglia activation in a subset of psychopathology* (Valeria Mondelli et al., 2017) posits that early stress leads to inflammation and microglia activation in subgroups of the various disorders, and that this activation associates with severity, treatment resistance, and suicide risk. All three models give special importance to stress sensitization but incorporate also effects of later exposures.

Influence of maternal psychophysical wellbeing on offspring depression and neurocognition is supported by a vast literature. Parental depression and psychological distress are linked to offspring psychopathology (Goodman & Gotlib, 1999; Ramchandani et al., 2008), offspring altered electrocortical measures of emotional information processing (Nelson et al., 2015), and offspring cognitive development, with longitudinal work showing that maternal depression associates with lower child IQ whenever it occurs, with an accumulative effect of depression over time (J. Evans et al., 2011). Maternal depression has also been associated with childhood immune health and inflammation. Caregiver depression mediates the relation between socioeconomic status/family stress and children asthma outcomes (Wood et al., 2018), and caregiver's depression in offspring's infancy is a robust predictor for elevated CRP in early adolescence, after accounting for other covariates (T. G. O'Connor et al., 2019). Authors suggest that caregiver depressive symptoms may be the most reliable long-term predictor among those studied, because it represents more reliably the family and caregiving actual environment than, for example, poverty (T. G. O'Connor et al., 2019). Influences extend also to somatic health: children exposed to lifetime maternal depression and anxiety had 2-5 fold increased risk for allergic conditions in a recent survey (Wan et al., 2021). In our work, we did not find direct associations between maternal conditions and children inflammation or health. Reasons for not detecting them, could have been various: the sample size was small, most women were only subclinically depressed, their pregnancies were all desired, and women with SLE usually make big investments in being pregnant and in subsequent children care (Tincani et al., 2006).

Family disruption and maternal depression are also indirect measures of psychosocial stress linked to trivial, daily stressors, related to family atmosphere and parent-child interaction. Disruption of family structure is linked to quality of parent-child relation and attachment quality ((Tan et al., 2018) for a meta-analysis), and parental depression has been linked to impaired caregiving quality (T. G. O'Connor et al., 2019). Our findings suggests that also trivial, daily stressors, reflecting family atmosphere and parent-child interaction, may have a major influence on individual's health and development, besides major adversities as maltreatment, traumas, and abuse, which are the stressors mostly reviewed in the stress literature.

In fact, mounting evidence is linking family environment and parent-child interaction with offspring health, and ascribing a primary role to parent-child relationship, with respect to all other

stress sources: when optimal, parent-child relationship would also be able to neutralize, “buffer”, the harmful effects of other stress sources. This evidence carries important implications, particularly meaningful to our study group, child and adolescent population. It is thus described in a separate paragraph.

5.3 The role of parental and social bonds on health: the buffering function

Parent-child and social bonds have proved determinant in which consequences stressful experiences can have, in children and adolescents.

5.3.1 Family strain and parent-child conflict: impacts on health

Familiar and parental relations that are dysfunctional can be an important stressor, and impact physical and mental health of offspring.

Family emotional strain has been found to mediate for children allergies (Wan et al., 2021), interparental conflict has been linked to exaggerated HPA-axis responses to acute stress in youth (Kate Ryan Kuhlman et al., 2018), and harsh family climate early in life associated with a proinflammatory phenotype in adolescence (G. E. Miller & Chen, 2010), and with atypical responses of amygdala and prefrontal cortex to emotional stimuli (SE et al., 2006).

Parent-child relation has also shown important impacts on psychophysical health. Lower parental responsivity to the child at age 4 predicted diminished or blunted cortisol reactivity to a social stressor at age 15-19 (Hackman et al., 2013), and inconsistency in quality of parent–child relationship related to greater production of stimulated proinflammatory cytokine in youth (Manczak et al., 2017). Parent-child conflict at age 9 was the strongest mediator between child adversity at age 9 and persistent externalizing and internalizing problems at age 13 (Dhondt et al., 2019), and a significant mediator between psychopathology at age 13 and psychotic experiences at age 17 ((Healy et al., 2020), N = 7,500), and high perceived parental criticism robustly predicted worse outcome of youth depression over 18-months ((Rapp et al., 2021), N = 418).

The mechanisms implied in these outcome are close to those seen in other stress models: genetic vulnerabilities; developed disruptions in psychosocial functioning - as emotion processing and social competence - and in stress-responsive biological regulatory systems, including sympathetic-adrenomedullary and HPA functioning: and poor health behaviors, especially substance abuse (Goodman & Gotlib, 1999; Repetti et al., 2002, 2011).

5.3.2 Parental sensitivity and support: impacts on health

Just as parent-child conflict and family strain can be highly distressing experiences for children, a rich literature is showing how parental warmth and sensitivity can protect children from consequences of other major stressors, as e.g. poverty and childhood abuse.

Adult individuals who had experienced high levels of maternal warmth and nurturance during childhood, resulted protected from some health consequences of low childhood SES, as pro-inflammatory signaling profiles (E. Chen et al., 2011) and metabolic syndrome (G. E. Miller, Lachman, et al., 2011). The same results have been found for childhood abuse: reports of childhood abuse associated with higher measures of multisystem risk in adulthood, yet subjects with higher parental warmth showed no association, whereas those with limited parental warmth had the strongest positive association (Carroll et al., 2013). Effects may also show on telomere length: while high-risk children referred to Child Welfare System showed shorter telomere lengths, the subgroup with more responsive parents had same telomere length as control children (Asok et al., 2013). Longitudinal studies reach similar conclusions. Greater cumulative stressors (poverty, crowding) associated with greater allostatic load among adolescents who experienced low maternal responsiveness, but not among those who experienced high maternal responsiveness (G. W. Evans et al., 2007). In the Minnesota Longitudinal Study of Risk and Adaptation, stress in early life, in adolescence, and at age 32 predicted worse health at age 32 with synergistic pattern, but higher maternal sensitivity in childhood could fully buffer these effects: individuals who had received higher maternal sensitivity during childhood had equally good health outcomes, independently on they had experienced higher or lower early stress (Farrell et al., 2017). Higher early maternal sensitivity predicted lower cardiometabolic risk at midlife in the same cohort (Farrell et al., 2019). Being able to depend on parents in times of need predicted lower CRP at age 32 in a group of African American (J. D. Jones et al., 2016b). High quality parental care and low level of current stressors in early adolescence, would also be able to revert a blunted HPA axis to normal in early institutionalized children (Wade et al., 2020), and stronger bonds and positive parenting in adolescents would shape cortisol patterns six years later, so as to facilitate encoding of socially-salient signals (Shirtcliff et al., 2017).

Parental support and good family climate would also protect over effects of early adversities on development of psychopathology, showing more beneficious effects in more

adverse conditions. In the Environmental Risk Longitudinal Twin Study (E-Risk, N= 2232, twins), more positive atmosphere at home was protecting poly-victimized children against development of psychotic symptoms at age 12 (Crush, Arseneault, Jaffee, et al., 2018), and together with maternal and sibling warmth, was particularly important in bullied children in promoting emotional and behavioural adjustment, compared to non-bullied children (Bowes et al., 2010). In the same cohort, poly-victimization in adolescence related with higher risk for psychotic symptoms at age 18 in a dosis-response way (40-60% of victimized subjects had psychotic experiences, vs ca 25% of non-victimized subjects), and greater social support - both practical and emotional - from family and friends were the only protective variables (Crush, Arseneault, Moffitt, et al., 2018). Parental support and supervision showed also a mediating, protective effect between adversities and psychotic experiences in community sample of Irish adolescents (N=973, (McMahon et al., 2021)). Among early adolescents reporting psychotic experiences, experiencing multiple adversities was associated with the poorest outcomes 9 year later , but the presence of secure attachment relationships was protective, even among individuals who had experienced adversity (Coughlan et al., 2019). Strong parental bonds mitigated also the effects of exposure to childhood adversity on development of internalizing symptoms, in a 21-year follow-up of over 1,200 children seen since birth (Fergusson & Horwood, 2003).

Cognitive development shows similar patterns. A recent meta-analysis found significant associations between both sensitive-responsive parenting and parental warmth with child language, with stronger effects for responsive parenting and more disadvantaged groups (Madigan et al., 2019). Similarly, high maternal responsivity protects children exposed to high degree of childhood adversities, from developing lower working memory in late adolescence (Doan & Evans, 2011). Both works evidence the protective effect of high-quality parent-child interactions especially in the context of adversity (Madigan et al., 2019). Maternal sensitivity during the first 3 years of life, predicted also social skills and academic achievement through midadolescence (Raby et al., 2015).

Parental support would maintain a buffering function at least in early adolescence, e.g. against effects of peer victimization on mental health problems (Stadler et al., 2010), or against effects of daily stressors on negative affect and physical health (Lippold et al., 2016). Along development, other social support begin also to contribute to this buffering function, as peers (S.

Cohen & Wills, 1985; Stadler et al., 2010). From childhood on, peers start functioning as stress buffers in certain circumstances, i.e. when other peers are the source of stress: children with at least one supportive friend are less negatively impacted by being bullied than children without any friends ("the friendship protection hypothesis", (Kendrick et al., 2012)). Such HPA-axis buffering effects of close friends are described from age 9-10 (Peters et al., 2011) and throughout youthhood (Calhoun et al., 2014), just as prolonged stress responses are reported in case of less supportive friends (e.g. who encouraged youth to ruminate on negative aspects of their performance, (J. G. Stewart et al., 2013).

For a unifying perspective, the group of Chen, Miller and Brody, that have long researched on relation between stress, inflammation and health (see e.g. (Nusslock & Miller, 2016)), have recently proposed a model that incorporates evidence about the buffering function of parents and close others, and adds a developmental dimension to it. It is named a "Developmental stress buffering model", and it accounts for the role that positive, close childhood family relationships play in terms of buffering the effects that childhood stressful life experiences typically have on health, and emphasizes the dynamic nature of parent-child relationships, and how the characteristics of optimal support are not static, but change along development, from childhood and adolescence, corresponding to an increasing need for autonomy (Edith Chen et al., 2017).

In conclusion: parental sensitivity, warmth and support, good family climate, and later on supportive close friends, appear as protective factors, buffering against the harmful effects of childhood and adolescent stress on physical and mental health.

5.3.3 Results and efficacy of preventive interventions

The Importance of parent-child bond and familiar environment for a healthy development is confirmed by the results of interventions directed at improving these factors. Various works have appeared in the past two decades on that.

The group of Brody, Chen and Miller has run some longitudinal RCT studies on the impact of preventive family interventions on later physical health and inflammation. They used some different adaptations of a short family centered program, the Strong African American Families (SAAF) program, or the Adults in the Making (AIM) program: six to seven weeks family-based,

skills-training group intervention, with separate and jointed training sessions for parents and youths, for a total of 12 to 14 hours (G H Brody et al., 2006; Gene H. Brody et al., 2015). In a large sample of rural African American pre-adolescents (N = 476), parental psychological dysfunction and non-supportive parenting at age 11, predicted elevated sympathetic nervous system (SNS) activity 9 years later in the control condition, while no association was present in youths whose families had been randomly assigned to the SAAF program (Gene H. Brody et al., 2014). The SAAF program at 11 y.o. was also helpful in neutralizing the effects of harsh parenting on elevated components of metabolic syndrome at age 25 (E. Chen et al., 2018), on risk of smoking at age 20 (Y.-F. F. Chen et al., 2017), and of drug use in young men and elevated BMI in young women in young adulthood (Gene H. Brody et al., 2018). African American children with low SES, randomly assigned at age 11 to a 7-week family intervention, had at age 19 lower levels of all the six inflammatory cytokines measured (IL-1β, -6, -8, and -10, TNF-α and IFN-γ) than youths assigned to the control condition (G. E. Miller et al., 2014). Exposure at age 17 to non-supportive parenting, defined as high levels of conflict and rancor with low levels of warmth and emotional support, forecasted shortened telomere length 5 years later, in another sample of rural African Americans, in the control condition, while the effect was absent in the subgroup randomly assigned to the AIM program. The effect appeared mediated by reductions in adolescents' anger (Gene H. Brody et al., 2015).

Parenting interventions have also been associated with normalization of dysregulated HPA axis and stress system function (Hostinar & Gunnar, 2018): parental interventions on small maltreated children and on foster parents of formerly institutionalized preschool children normalized cortisol levels or prevented the development of atypical diurnal patterns (Cicchetti et al., 2011; Dozier et al., 2006; Fisher et al., 2007).

Parent training in early age has also shown effectiveness for prevention of later psychopathology. A randomized parental intervention (the Incredible Years) for parents of 3- to 7-year-olds with severe antisocial behavior referred to treatment, showed effects at reassessment between ages of 10 and 17. In the intervention group there were improvements in youth antisocial behavior, antisocial character traits and reading abilities, and in parent-adolescent relationship quality, with respect to subjects assigned to the control condition (Scott et al., 2014).

Such evidence confirms causal influence of parental-child bond on later health, and the efficacy of preventive measures (Hostinar & Gunnar, 2018).

5.3.4 The role of social connections versus loneliness on mental and physical health

The reviewed impacts of close relationships on health, poses a natural question, when investigating stress and its consequences: what are the impacts of social isolation and loneliness, versus social support, on health?

Some very recent reviews have examined evidence about effects of social environment on psychophysical health. Meta-analyses have shown that social isolation, loneliness, and living alone are associated with increased likelihood of morbidity and mortality, with effects comparable to those of well-established risk factors, as e.g. physical activity, obesity, substance abuse etc (Holt-Lunstad et al., 2010, 2015; Rico-Uribe et al., 2018; Valtorta et al., 2016). A very recent umbrella-review confirms the results and extends them to psychopathology, finding that lack of social connection is associated with chronic physical symptoms, frailty, coronary heart disease, malnutrition, hospital readmission, reduced vaccine uptake, early mortality, depression, social anxiety, psychosis, cognitive impairment in later life and suicidal ideation (Morina et al., 2021).

Several works suggest that enhanced inflammation and inflammatory responsivity may be the mechanism linking loneliness and health risk (Hawkley et al., 2006; Hawkley & Cacioppo, 2010). An inflammatory diathesis changes in inflammatory gene transcription and epigenetics and increased immune reactivity to psychological stress (E. G. Brown et al., 2017; S. W. Cole et al., 2007; Hackett et al., 2012; Jaremka, Fagundes, et al., 2013) as well as to immune challenges, in lonelier healthy young adults (Balter et al., 2019). Research is relatively new and limited, but a recent meta-analysis has found associations between loneliness and IL-6, and between social isolation and CRP and fibrinogen (K. J. Smith et al., 2020). A large longitudinal study (N = 7462), the National Child Development Study in Great Britain, found that socially isolated children (age 7–11 yrs) had higher levels of C-reactive protein in mid-life (age 44), and that the association persisted after controlling for other associated outcomes, as pertaining to a less advantaged social class in adulthood, being more psychologically distressed across adulthood, and more likely to be obese and to smoke (Lacey et al., 2014).

Reviews have also shown the healthy impacts of social support. Recent meta-analyses have found that social support-social integration were significantly related to lower levels of inflammatory cytokines (Uchino et al., 2018) and to improved sleep outcomes (de Grey et al., 2018).

The group of Eisenberger, Inagaki and Muscatell has investigated the neural basis of social pain and social connection, and their links with inflammation, finding that social pain refers to the same neural regions as physical pain. This implies that experiences of social exclusion or relationship loss may be just as emotionally distressing and damaging as those of physical pain, and also that the two experiences may interact, so that negative social experiences early in life may lead to later enhanced sensitivity to physical pain, e.g. in patients with somatoform disorders (Eisenberger, 2012a, 2012b). Just as inflammation increases sensitivity to both positive and negative social stimuli (Muscatell et al., 2016), supportive attachment figures can reduce the experience of physical pain, in terms both of reduced self-reported pain and reduced neural activity of pain-related regions, and of increased activity in safety-signalling regions, as VMPFC (Eisenberger et al., 2011).

The group has also investigated mechanisms behind *giving,* vs. *receiving,* social support: giving support would changes activity of neural regions as ventral striatum, with reflection on peripheral physiology of sympathetic nervous system, HPA axis, and related inflammatory responding (Eisenberger, 2013; Inagaki, 2018; Inagaki et al., 2016; Inagaki & Eisenberger, 2016). Giving to others is in fact associated with lower mortality rates (S. L. Brown et al., 2003; Poulin et al., 2013), fewer sick days (Väänänen et al., 2005), and reduced blood pressure and heart rate (Creaven & Hughes, 2012; Nealey et al., 2002; Piferi & Lawler, 2006); acting prosocially (vs. selfishly) leads to greater happiness (Dunn et al., 2008), and volunteering has various health benefits, as e.g. reduced hypertension and increased psychological well-being (Musick et al., 1999; Sneed & Cohen, 2013).

They propose an evolutionary framework that connects inflammation and social behaviour (Eisenberger et al., 2017; Leschak & Eisenberger, 2019). Social isolation historically was linked to higher threat and risk for getting wounded: higher inflammation when isolated would both help to facilitate healing from wounds, and by increasing sensitivity to social support, would also serve the purpose of re-joining the individual to his/her own close others. Being socially

connected to others likely increased chances of survival, as being part of a group provided additional resources, protection, and safety. Thus, the experience of social pain, although distressing and hurtful in the short-term, can be seen as an evolutionary adaptation that promotes survival (Eisenberger, 2012a; Eisenberger et al., 2017)**.** On the other hand, social contact is associated with increased exposures to viruses, and the higher antiviral immunity found in relation with social connections, would protect individuals in that context (Eisenberger et al., 2017; Leschak & Eisenberger, 2019).

The innate social nature of human beings is also the core of the "Social Baseline Theory", developed by James Coan in a pioneering chapter on social neuroscience of attachment (Coan, 2008). He proposed that the human brain evolved in a highly social environment, and many of its basic functions rely on social co-regulation of emotions and physiological states. Rather than conceptualizing human beings as separate entities whose interactions with each other need to be understood, it makes more sense to consider social relatedness and its mental correlates as the normal "baseline" condition. (Coan, 2008) Using this as a starting point helps us to see why experiences of separation, isolation, rejection, abuse, and neglect are so psychologically painful, and why dysfunctional relationships are often the causes or amplifiers of mental disorders (Mikulincer & Shaver, 2012)

5.3.5 Conclusions about the concept of stress

The evidence reviewed throughout this paragraph underscores the power of parental bonding and social support in mitigating adversities. This is reflected in the definition of *toxic stress* proposed by the The National Scientific Council on the Developing Child, where toxic stress refers to *"strong, frequent, and/or prolonged activation of the body's stress-response systems in the absence of the buffering protection of adult support"* (Scientific Council, 2014). The most toxic childhood stressors would be those that occur in the absence of emotional support from a caregiver (HYVÄ Middlebrooks, J., S. & Audage, 2008).

A central message emerging is, that it may not be as much the entity of the adverse experiences, that determines their long-term consequences, but rather the lack of a support adult figure while undergoing these adverse experiences.

This would talk for assessing information on parental bond and general social support in clinical and research work, together with assessment of stressors: “incorporating assessment of factors that influence children’s interpretation of stressors, along with stressful events, has the potential to provide further insight into the mechanisms contributing to individual differences in neurodevelopmental effects of early life stress” (from (K. E. Smith & Pollak, 2020)). One possibility to assess the quality of the parental support along development, and its embedding in the offspring organism, is provided by the work on attachment.

5.4 The parallels between Early Stress Embedding and Attachment Theory and Research

The importance of parental and later social relationship for individuals' well-being, naturally connects with research around the concept of attachment (Bowlby, 1977, 1982) and its consequences for health. Attachment theory researches the relevance and influence of close relationships on the individual, from early in life to adulthood: attachment representations and styles incarnate the social experiences, in particular the ones lived with attachment figures - mainly the parents - in early life and throughout adolescence (see separate box below for an overview about a historical perspective and measure tools).

BRIEF OVERVIEW ON ATTACHMENT THEORY

Attachment theory researches the relevance and influence of close relationships on the individual, from early in life to adulthood. The theory developed initially from John Bowlby's observations of the relations between the behaviour of the mother and her infant child (Bowlby, 1977) and has since extended to analysis of social interactions along the lifetime.

Attachment is defined as a type of affectional bond, which the individual forms with a specific person, who is approached in times of distress (Bowlby, 1977, 1982)

The first attachment relationships occur in infants with their primary caregivers, who should provide a "secure base", enabling the child to engage in exploration, and a "safe haven" the child can return to for comfort, protection, and connection when needed (Mary D.S. Ainsworth et al., 1985)

Young children naturally turn to their primary caregivers for support, care, and protection when they feel threatened, vulnerable, or distressed. Caregivers, however, differ the ways in how they respond to their children's needs and distress.

Bowlby proposed that as a result of their interactions with caregivers during infancy and childhood, children develop mental representations of the self in relation to significant others, and expectations about how others behave in social relationships. Bowlby named such representations "working models": e.g. beliefs about whether oneself is worthy of attention and whether other people are reliable, or emotions associated with interpersonal experiences - such as happiness, fear and anger (Bowlby, 1977, 1982; Pietromonaco & Barrett, 2000)

Children that experience their caregivers as consistently available and sensitively responsive, are likely to see others as available and trustworthy and themselves as worthy of care, and develop a secure attachment. In contrast, children who meet with neglectful, rejecting, or variable parenting behaviour often develop working models where others are not trustable, and/or oneself is not worthy of care, and an insecure attachment (Bowlby, 1977, 1982).

Children attachment styles are traditionally classified as secure, insecure avoidant, insecure ambivalent, and disorganized, and are usually assessed by the "Strange Situation" laboratory procedure, that analyzes the infant's response to two brief separations from his or her caregiver (Mary D.Salter Ainsworth et al., 2015). An infant that can use the caregiver as a secure base for exploration, is distressed by the separation, but is easily comforted upon reunion, and is classified as secure. An infant that shows inhibited reactions to the parent's actions, e.g. actively avoids and ignores the parent, turning or moving away, and is classified as insecure avoidant: his behaviour is seen as response to a caregiver who has been insensitive to infant signals and rejective of infant attachment behavior, thus blocking the infant's attempts toward access. An infant that in the laboratory situation exhibits increased negative reactions, shows anger and resistance to the parent, a desire for proximity or contact, and an inability to be comforted, is classified as insecure ambivalent: his/her behaviour iseen as a reaction to a caregiver whose responses have been inconsistent, e.g. where the caregiver has been insensitive to signals (e.g. infant crying) but not notably rejecting, where the child learns to exaggerate negative affect in order to elicit a response. (Crowell & Treboux, 1995; Main et al., 1985).

Although the original focus of research on the secure base phenomenon revolved around young children, it is now widely accepted that adolescents and young adults continue to depend on their parents in times of need and that having a parental secure base remains important to adjustment at these later stages of development (Rosenthal & Kobak, 2010).

Attachment concept has also been extended to other times of life. In adulthood, it can be assessed by other instruments, of two main categories.

One class of instruments is linked to developmental psychology and use narrative instruments, mainly the Adult Attachment Interview (AAI, (Main et al., 1985)): the subjects is asked to provide a narrative about his/her childhood experiences, and attachment security is judged either on the *coherence* of the narrative in describing parental–child relationships (Main et al., 1985), or on the presence of a *"secure script knowledge"* (H. S. Waters & Waters, 2006; T. E. Waters & Roisman, 2019), that is of memory of past experiences where the subject could reach out for caregiver help in distress, and together with the caregiver overcome the difficulty and could return to basal occupation. Coherence of mind assesses whether the individual can be objective in describing previous relationships, and recognize the influence of these on personality, and in general tend to value attachment relationships (Main et al., 1985), while secure script knowledge assesses the extent to which individuals are able and willing to seek, and expect to receive, effective support from attachment figures during distressing and challenging situations. These measures can be predicted by parental sensitivity from infancy to early adolescence, and can predict relationship functioning and security of attachment in next generation (e.g. (T. E. Waters & Roisman, 2019)).

The other class of instruments is *Self-administered instruments,* developed within social psychology, to assess one's behaviors, emotions, and cognitions in close relationships: e.g the Relationship Scales Questionnaire (RSQ) assesses the extent to which individuals avoid closeness and worry about being unloved or abandoned in close relationships, (Griffin & Bartholomew, 1994), (see (J. A. Simpson & Rholes, 1998) for a review of the various tools)
With both diagnostic tools, attachment security can then be reated on two dimensions: attachment and avoidance, as represented in this diagram:

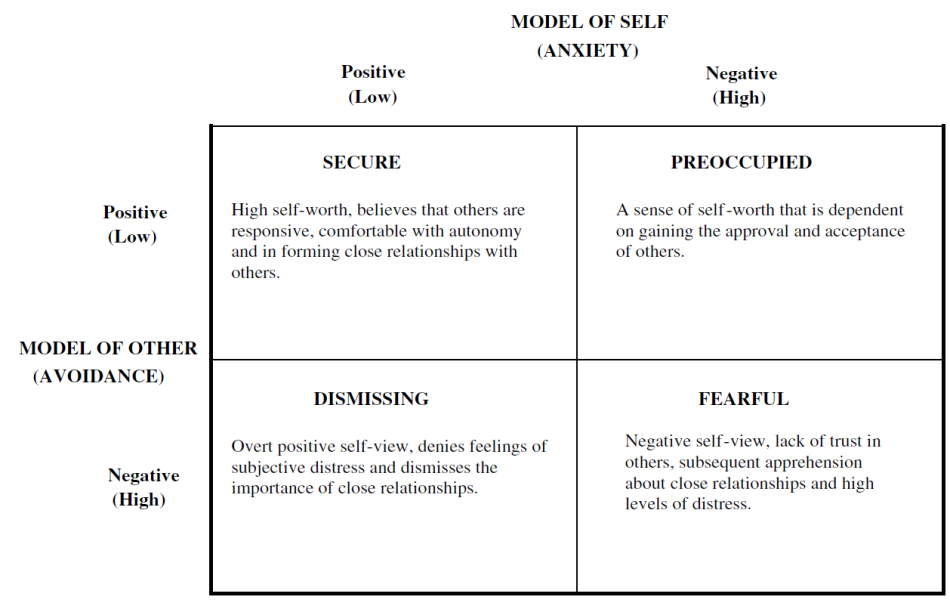

Fig. 11. Bartholomew's model (Bartholomew, 1990)

Attachment anxiety is characterized by worry about relationships. Individuals at the high end of this dimension tend to be concerned about others' perceptions of them and fear being rejected (Campbell & Marshall, 2011; Mikulincer & Shaver, 2003). They tend to rely on hyperactivating strategies – energetic attempts to achieve proximity, support, and love, combined with lack of confidence that these will be provided, and with resentment and anger when they are not provided. (Mikulincer & Shaver, 2012)
On the contrary, attachment avoidance is characterized by withdrawal from relationships. Individuals at the high end of this dimension tend to be uncomfortable with closeness and seek independence from others (Mikulincer & Shaver, 2003, 2012). They tend to rely on deactivating strategies – trying not to seek proximity, denying attachment needs, and avoiding closeness and interdependence in relationships. (R. Cassidy & Kobak, 1988).

In both cases, caregivers have likely been experienced as unreliable, most typically in times of need (Berry et al., 2014). Carried into adulthood, this fosters a sense of being unsure of others and compromises the ability to develop trust (Bentall & Fernyhough, 2008; Larose & Bernier, 2001; Mikulincer, 1995).

Existing evidence suggests that attachment in infancy may be related to inflammation, health and stress response, from infancy through adulthood. Various authors talk about attachment as the caregiving environment "getting under the skin" (Dhondt et al., 2019; Harvey et al., 2019; Shirtcliff et al., 2017) just as it was said about adversities along lifetime (e.g. (Hyman, 2009)), and there is a growing body of literature that shows how attachment measures are linked to various health outcomes, including inflammation, HPA axis changes, cardiometabolic risk, as well as risk for psychiatric disorders from infancy through adulthood (B. Ehrlich & Cassidy, 2019).

While looking at those data, we found a striking similarity with work analyzing effects of stress and adversities. We thought thus important to connect the two fields.

5.4.1 Attachment and inflammation and health

The strongest evidence to date linking attachment with inflammation and health comes probably from a prospective study, following 163 individuals from birth to age 32: individuals who were securely attached at 12 and 18 months reported the fewest physical illnesses in adulthood, while subjects classified as insecurely attached as infants were 3 to 7.5 times more likely to report inflammation-related illnesses, suggesting having a sustained history of secure attachment during infancy is a powerful antecedent of having fewer health problems in adulthood (Puig et al., 2013). Insecure attachment in infancy predicts higher CRP and higher BMI, while secure attachment predicts lower BMI in later childhood (Bernard et al., 2018, 2019). Perceiving parents as a secure base during adolescence, indicating how much the adolescent can depend on parents in times of need or distress, predicts lower CRP at age 32 even after controlling for other factors that influence CRP (J. D. Jones et al., 2016b). Attachment security has been associated with less-inflammatory phenotype and less symptoms in children with asthma (Ehrlich, Miller, et al., 2019; Stanton et al., 2017).

There is a general continuity of attachment measures through childhood and adulthood (T. E. Waters & Roisman, 2019), and also insecurity in adults has been linked to changes in inflammation and immune measure, as higher levels of IL-6 (Ehrlich, Stern, et al., 2019; Gouin et al., 2009; Kidd et al., 2014), and reduced defenses, especially anti-viral (Fagundes et al., 2014; Jaremka, Glaser, et al., 2013; Picardi et al., 2013). Recent reviews indicate that attachment insecurity is associated with dysregulated physiological responses to stress, susceptibility to

physical illness, and poorer disease outcomes, possibly more accentuated in case of anxious attachment (B. Ehrlich & Cassidy, 2019; Ehrlich, 2019; Pietromonaco & Beck, 2019). Attachment styles may also moderate effects of childhood adversities on measures of aging as telomere length (Dagan et al., 2017; Murdock et al., 2018)

5.4.2 Attachment and stress systems

Attachment insecurity in infant ((Groh & Narayan, 2019), meta-analysis), children (Ahnert et al., 2004; Megan R Gunnar et al., 1996; Nachmias et al., 1996) and adults (Brooks et al., 2011; L. M. Diamond et al., 2008; Kidd et al., 2013; Meuwly et al., 2012; Powers et al., 2006) associate with heightened physiological reactivity to interpersonal stress, as exaggerated cortisol reactivity to stressors and higher daily levels of cortisol.

Early in development, secure attachment figures would act as social buffers on the HPA axis, reducing or preventing cortisol elevations to threatening stimuli: insecurely attach children don't show this adaptation in presence of their parents, suggesting that they may rely more on their own internal physiological resources for coping with interpersonal stress (Megan R Gunnar & Hostinar, 2015; Hostinar et al., 2014). This buffering function of close others is maintained in secure adults, and impaired in individuals with avoidant attachment (Kordahji et al., 2015).

5.4.3 Attachment and mental health

Attachment theory has long argued that insecure and disorganized attachment representations are associated with vulnerability to psychopathology in general. Recent meta-analytic work in children found attachment insecurity significantly associated with externalizing (Fearon et al., 2010) and internalizing problems (Groh et al., 2012), and lower peer competence (Groh et al., 2014). In all three works, associations did not change with age of assessment perduring into early adolescence, suggesting that effect of early attachment persisted with age. Insecure lifelong attachment has also been linked to ADHD, though further research is advocated for (Storebø et al., 2013; Wylock et al., 2021).

In adults, insecure attachment has been found more frequently in clinical subjects across the spectrum (Bakermans-Kranenburg & van IJzendoorn, 2009). Recent meta-analysis and review show that paranoia – "concerns about being vulnerable to the malevolent intent of others" -

associates with attachment anxiety and avoidance (Lavin et al., 2020; R. Murphy et al., 2020). According authors, high attachment anxiety entails a negative view of the self, while high attachment avoidance entails a negative view of others: in both cases trust is compromised, and individuals are more prone to interpret interactions with others negatively, and anticipate a degree of threat in these interactions, thus creating a mechanism where paranoia is fostered and maintained (Freeman et al., 2013; R. Murphy et al., 2020; Read & Gumley, 2019). Also risk for depression appears linked to attachment insecurity in a recent meta-analysis, especially for anxious and unresolved adults (Dagan et al., 2018). Research on clinical samples suggests that individuals who recall their parents as being more overprotective, report greater paranoia, whereas individuals who recall their parents as less caring reported greater depression (Valiente et al., 2014). Depression appeared thus associated with a lack of parental care, while paranoia with parental overprotection, also previously associated with a defensive style (Yoshizumi et al., 2007).

5.4.4 Mechanisms implied

How can social experiences already from very early in life get "under the skin" and influence lifelong outcomes? The embedding of social experiences would follow three main directions: shaping brain and physiological systems under development; impacts on social functioning and on how emotional stress is handled; and health behaviors.

The first years of life are characterized by remarkable plasticity in brain and homeostatic systems. Just as seen for other stressors from early in life, disruptions in attachment bonds are thought to tax physiological systems, and calibrate how they will operate forward in time (Hertzman, 1999; G. E. Miller, Lachman, et al., 2011; G. E. Miller & Chen, 2013), with effects on HPA axis, inflammation, cardiovascular system and general health (Ehrlich, 2019; M. Gunnar & Quevedo, 2007; Pietromonaco & Beck, 2019).

Neurocognition is also tightly connected to the quality of the first exchanges: parental stimulation, encouragement, sensitivity, and support for autonomy all tend to enhance the development of subsequent working memory, flexibility and attention skills (Bernier et al., 2010, 2011; Bibok et al., 2009; Hopkins et al., 2013). The child learns how to control and inhibit impulses, direct attention and modulate emotions, and can begin to initiate voluntary and controlled actions (R. Feldman, 2007; McClelland et al., 2010; Panfile & Laible, 2012; Riva Crugnola et al., 2011; B.

Zimmerman & Schunk, 2001). Insecure children show e.g. lower level of commitment to tasks, low-level communication and attention skills, reduced exploration, receive poor quality maternal assistance, maintain poor quality relationships with teachers, which in turn associate with lower levels of cognitive abilities.(E. O'Connor & McCartney, 2007).

Insecure individuals have more difficulties in establishing satisfactory and supportive relationships (Jeffry A. Simpson et al., 2007), and would also be particularly sensitive to the consequences of their poor social life, tending to perceive social situations as more stressful, and being less effective at handling stress and reaching out for support (Shaver & Mikulincer, 2007). Insecurely attached children and adults have also a tendency to underreport their psychological distress (Borelli et al., 2013; Gouin et al., 2009; Sroufe & Waters, 1977), and suppressing emotions is in itself linked to increased mortality (B. P. Chapman et al., 2013). Insecure individuals lack also the capacity that secure individuals usually show, to tackle successfully difficult situations. The presence of a stable, positive role model during growing-up, would promote engagement in "shift-and-persist" strategies under stressful situations: the first include e.g. acceptance and reappraisal, and the latter finding meaning, having optimism and endurance towards accomplishing one's goals. Those who are able to make use of "shift-and-persist" strategies are at lower risk of negative health outcomes due to reduced stress (E Chen & Miller, 2012).

Attachment insecurity has been linked to unhealthy coping styles: children and adults with insecure attachment show poor self-regulation, and use maladaptive strategies in response to feelings of distress, which paradoxically result in unresolved or further distress (Aldao et al., 2010; Cooke et al., 2019). Insecure children can e.g. develop problematic eating behaviors: emotional eating, i.e. use of food as a way to manage negative emotions, as a substitute for a lack of support in other areas, including parental support (Haedt-Matt & Keel, 2011), decreased sensitivity to satiety, and binge eating (Braden et al., 2014; Dingemans et al., 2017; Frankel et al., 2012; Stoeckel et al., 2017). Also adulthood attachment insecurity is related to unhealthy eating behaviors and eating disorders (Faber et al., 2018; Ringer & Crittenden, 2007), with risk for metabolic syndrome and cardiometabolic disorders (C. R. Davis et al., 2014; Farrell et al., 2019). Attachment insecurity would also reduce adherence to medical treatment (Ciechanowski et al., 2002), propension to seek help when minor health symptoms develop (Farrell et al., 2019) and to maintain health-promoting behaviours (Scharfe & Eldredge, 2001), as well as promote the use of external affect

regulators as illicit substances, prescribed substances, and sexual activity (Meredith & Strong, 2019). All these strategies increase health risk.

5.4.5 Attachment as a measure of perceived stress: conclusions

Attachment patterns emerge as a regulator of stress reactivity in infancy and childhood, such that securely attached children can use the presence of a caregiver to downregulate perceptions of stress and threat responses (J. Cassidy et al., 2014).

At the same time, attachment styles mediate the effects of early positive or adverse social experience on mental and physical health (Bentall et al., 2014; Farrell et al., 2019; Sheinbaum et al., 2020). Thus, measures of attachment security could reflect the embedding of protective or toxic social experiences, providing a useful construct to work on in therapy and research with patients and their networks. Different works indicate that attachment styles are modifiable by ongoing experiences, and in particular by positive therapeutic experiences.

Adolescence and the transition to young adulthood present a number of new opportunities, with the physiological adaptation in internal homeostatic systems, and the formation of new social roles: these change create the possibility to recalibrate internal attachment working models (Allen et al., 2004; Fraley et al., 2013; J. D. Jones et al., 2016a; Steinberg, 2005; Van Ryzin et al., 2011). Changes may happen in both directions: a secure infant can turn into an insecure adolescent or young adult in high risk environments (Van Ryzin et al., 2011; Weinfield et al., 2000), as children with insecure attachment can change toward security with adequate emotional support from a caregiver, who could be a parent, but also another figure, including a therapist (Egeland et al., 1988; Levy et al., 2006; R. Saunders et al., 2011). Bowlby himself described good psychotherapy as an attachment relationship in which the client is able to use the psychotherapist as a secure base from which to explore his/her attachment models as well as current relationships with others, and as a safe haven that allows to regulate the emotional intensity, associated with the exploration needed for psychological change (Bowlby, 1988).

Implications of these findings for clinical and investigation activities, will be discussed in the next paragraph.

5.5 Implications and future directions

The results of our original investigation and the evidence reviewed in this discussion support a close link between physical and mental health, where stress without support may be a frequent trigger, and lifelong inflammation one important mediating mechanism.

Results argue for decreasing boundaries between mental and physical conditions, and within them. In this way, the transdiagnostic approach adopted in Study 1 appears adequate and defendable.

The influence of social experiences on mental and physical health is also emerging as a strong element, both as a source of potential stress and disease, and as one of healing and buffering. In case of children and adolescents, which are the studied group in this work, the influence of bonds with parents, and of well-being of family members, is suggested by our results, and supported by a consistent and exponentially increasing amount of literature. The human being is increasingly seen as a primarily social being.

The concept of attachment stands as a relevant construct, that can describe the mental and physical embedment of early and ongoing relational experiences with attachment figures, and that leverages on existing resources and potential stressful factors.

The evidence on the buffering effects of parental sensitivity, warmth and secure attachment, and of close bonds in general, on the deleterious consequences of adversities appears encouraging. As do the data on effects of short parenting interventions on lifelong wellbeing. It may be easier to work with parent-child bonds, where parents are strongly motivated in striving for their children, than on general stress factors as low SES, neighbourhood etc.

Addressing mental conditions associated with inflammation may be even more relevant, when there are indications for that they may have a more severe course, and be more resistant to classical treatments (Chamberlain et al., 2019; Ebrahim Haroon et al., 2018; Valeria Mondelli et al., 2017; Strawbridge et al., 2015).

Different possible lines of intervention and research emerge from this evidence, that recently have started being explored: research on the presence and role of inflammation in mental condition on one side, and studies of the effects of interventions aiming at reducing inflammation and stress reactivity, or at reducing psychosocial stress, on the other side.

Some of these investigations could be run on our samples and will be discussed in this light.

5.5.1 Research to characterize inflammation in mental conditions

Our results advocate for longitudinal studies, assessing relations between stress exposure, inflammatory markers, and physical and mental outcomes. Transversal research between mental and somatic conditions appears indicated and promising, as research focusing on impact and relations of peripheral inflammation at central level. It appears important to gather more information about inflammation state in childhood and adolescence, a period until now understudied. The use of simple and unexpensive markers would facilitate this task.

There is evidence for, that assessment of baseline inflammation in mental conditions may guide choice of treatment. Results come mostly from adult depression, and indicate that high inflammation at baseline, as measured by high IL-1β, IL-6 and TNF-α and CRP, is associated to resistance to SSRI and antidepressants in general (Ebrahim Haroon et al., 2018; Lanquillon et al., 2000; O'Brien et al., 2007; Yoshimura et al., 2009), but possibly to better response to other approaches as ketamine (J. Yang et al., 2015) or electroconvulsive therapy (Kruse et al., 2018).

Circulating levels of IL-1β, IL-6 and TNF-α are not yet standardized, and mostly limited to research trials (Dantzer et al., 2011). In adults, serum CRP has shown to correlate with both peripheral and central inflammation markers (Jennifer C. Felger et al., 2020), and could be used to inform treatment decisions, e.g. when choosing therapies targeting IL-6 or TNF- α. CRP is though a marker that increases with age (Wium-Andersen et al., 2013), and not all studies in children and young population find that it associates with clinical symptoms as IL-6 does (e.g. (Chu et al., 2019)). In our groups, CRP correlated modestly with two cytokines, IFN-γ and IL-6.

Other alternatives to assess inflammation emerge from this research. As described in the unpublished results, several works in the past years have begun to use NLR (neutrophil/leukocyte ratio), MLR (monocyte/leukocyte ratio) and PLR (platelet/leukocyte) ratio as proxies for inflammation in psychiatric conditions. This is an easy, effortless and unexpensive measure, worth being further investigated as a proxy of inflammation in psychiatric disorders, already from adolescence (Avcil, 2018; Bustan et al., 2018; Cevher Binici et al., 2018). To investigate whether these markers associate with treatment resistance and response may be worth exploring.

Another simple marker that is proposed by the literature, and that may be interesting to study, is the soluble urokinase plasminogen activator receptor (suPAR), whose plasma levels are thought to reflect a person's overall level of immune activity, and to be less affected than CRP by

acute conditions (Eugen-Olsen et al., 2010). Two longitudinal studies have found associations between childhood adversities and elevation of suPAR in adulthood, and the authors suggest that adding information about suPAR to traditional biomarkers of inflammation may improve the measurement of inflammatory burden associated with exposure to stress and violence (L. J. H. Rasmussen et al., 2018, 2020).

A different measure is leukocyte gene expression, still little investigated in young population: e.g. increase in expression of NF-κB, and decrease in expression of glucocorticoid receptors and interferon response factors, may appear already from adolescence and associate with depression and inflammation (Chiang et al., 2019).

The significance for psychiatric patients of serum autoantibodies requires further study. Our preliminary results on increased anti-DWEYS-GluN2 in young population with psychiatric conditions or autoimmune risk, encourage further research on these and other antibodies, and so does the reviewed comorbidity between psychiatric and autoimmune disorders. Antibodies that may be worth investigating are those that mark risk or activity in autoimmune disorders, as the anti-DWEYS-GluN2 and the anti-phospholipids (Lupus), the antibodies against citrullinated proteins or rheumatoid factor (Rheumatoid Arthritis). Results from autoimmune encephalitis support the search for antibodies with reactivity to neuronal antigens. Measures in CSF and correlation with serum levels and with psychiatric symptoms would help understand whether antibodies are implied in psychopathogenesis, or an epiphenomenon.

Other measures interesting to investigate in relation to psychopatology and immune alterations are telomere length, reflecting levels of oxidative stress and chronic inflammation (Sahin et al., 2011), and the diversity and composition of the microbiota, as part of the gut-brain axis (Rhee et al., 2020; Z. Yang et al., 2020). Even if research in adults is increasing, data in young populations are still very limited.

5.5.2 Further analyses of our samples

Some of the tests indicated could be run also on our three samples of young patients, Lupus offspring and healthy subjects: plasma levels of suPAR, leukocyte gene expression, telomere length would be easy to determine, thus expanding sample characterization.

5.5.3 Research aiming to reduce inflammation and enhanced stress reactivity

Lifestyle and pharmacological approaches are under investigation, that can reduce inflammation or normalize stress-reactive systems, as HPA axis, Autonomous Nervous System, and reactivity in threat-related brain regions.

Physical exercise is one of the measures that appear most promising for preventing both inflammation and development of psychopathology. Large scale longitudinal studies have e.g. reported that involvement in sport, and relatively high levels of physical activity in childhood are protective against subsequent psychotic symptoms (Crush, Arseneault, Moffitt, et al., 2018; Keskinen et al., 2016). In adults, physical exercise has shown to reduce inflammation, with strongest effects in subjects with high levels of inflammation at baseline (Kasapis & Thompson, 2005; Kiecolt-Glaser et al., 2015). Yet, many of the RCTs have been conducted with patients or elderly populations, and it would be relevant to study whether these benefits can be replicated with youth, and particularly with youth who experienced early-life stress. Given that physical exercise has corollary benefits for mental health, it would be warranted to conduct studies testing efficacy of exercise in preventing or mitigating both mental and physical health problems following childhood adversity (Hostinar et al., 2018).

Meditation-based techniques as Mindfulness, tai-chi, yoga may also have an effect on psychopathology, stress and inflammation. They have focus on positive emotions, and there is good evidence for a relation between positive emotions and health ((Howell et al., 2007) for a meta-analysis), in particular reduced inflammation (Steptoe et al., 2007) and likelihood for cardiovascular disease (Boehm & Kubzansky, 2012). Some studies have indicated effects of meditation practices on reduced IL-6 levels (Kiecolt-Glaser, Christian, et al., 2010; T. W. W. Pace et al., 2009), reduced activation of SNS, HPA-axis and heart rate under stress (Motivala et al., 2006; Nedeljkovic et al., 2012), and reversal of stress-induced genome-wide transcriptional responses, such as NF-κB-associated proinflammatory genes (Antoni et al., 2012; Black et al., 2013; Creswell et al., 2012). Some recent reviews and meta-analyses conclude that evidence on overall benefits (Djernis et al., 2019; D. Zhang et al., 2021) and on inflammation specifically (Rådmark et al., 2019) is still limited. Here again, studies on adolescents and on psychiatric patients and focus on inflammatory outcomes are particularly limited: a recent meta-analysis reviewed efficacy on mindfulness interventions for anxiety in young population concludes that at least in Western

population evidence does not support effects of these approaches to address youth anxiety (Odgers et al., 2020). Given the meta-analytic evidence on efficacy of such interventions for anxiety in adults (Hofmann et al., 2010; Khoury et al., 2013), it may be questioned whether these approaches are more suitable to adult and elderly population, than to children and adolescents.

Compassion-based therapies, and Compassioned-Focused therapy (CFT, (Gilbert, 2014)) in particular, are relatively new approaches, combining meditation-based techniques with psychotherapy. A recent meta-analysis has shown they are effective on several self-reported measures: compassion, self-compassion, mindfulness, depression, anxiety, psychological distress, and well-being (Kirby et al., 2017). Some of these measures are related some to stress control and positive affect, and thus may also reduce inflammation, but direct data and applicability in youth population are still lacking and may be worth exploring.

Pharmachological intervention: a great number of compounds is currently being testing to target inflammation and relevant psychopathology, from more benign to more aggressive interventions. *Omega-3* appear potential promising candidates for treatment of psychiatric and neurodegenerative conditions (Djuricic & Calder, 2021; Giacobbe et al., 2020), as they get metabolized into anti-inflammatory and pro-resolving lipid mediators, and are also precursors for endocannabinoids, with known effects on immunomodulation, neuroinflammation, food intake and mood (Fond et al., 2014; Kalkman et al., 2021). *Curcumin* has shown antidepressant and anxiolytic effects in humans, possibly through increase in monoamines and brain-derived neurotrophic factor, and by inhibiting the production of pro-inflammatory cytokines and neuronal apoptosis in the brain (Akaberi et al., 2021; Fusar-Poli et al., 2020; Matias et al., 2021). *Melatonin* has also shown anti-inflammatory effects in a recent meta-analysis on general population (J. H. Cho et al., 2021). *N-acetylcysteine* may have central and peripheral anti-inflammatory effects, and have shown preliminary results in ASD, OCD and psychotic and affective disorders (N-Acetylcysteine Augmentation for Patients With Major Depressive Disorder and Bipolar Depression, 2021; Brierley et al., 2021; Y. Liu et al., 2022; W. Zheng et al., 2018), and so has *Pentoxifylline*, a phosphodiesterase inhibitor with potent anti-inflammatory and antioxidant effects (Farajollahi-Moghadam et al., 2021; Siegel et al., 2021; Yasrebi et al., 2021). Compounds that address the microbiota, as *pre- and probiotics* (Wieërs et al., 2020) or *gut-microbiota derived vitamins* (Rudzki et al., 2021) may have effects on the gut-brain axis and possibly reduce neuroinflammation

(Carlessi et al., 2021; Leta et al., 2021). *Minocycline*, an antibiotic with anti-inflammatory properties, has shown some effects in major psychiatric disorders (Cai et al., 2020; Çakici et al., 2019; Wei Zheng et al., 2019). *Statins*, mainly as add-on, have shown effects in depression in a meta-analysis of 5 studies, possibly through their anti-inflammatory and anti-oxidant properties (Giorgi et al., 2021; Kosowski et al., 2021; Walker et al., 2021). *Cox-2 inhibitors* as celecoxib have shown evidence for effect in depression and schizophrenia (Müller, 2019). Various meta-analyses have looked at *anti-inflammatory agents*, in various groupings: global effects of add-on anti-inflammatory agents (aspirin, celecoxib, omega-3 fatty acids, estrogens, selective estrogen receptor modulator, pregnenolone, N-acetylcysteine, minocycline, davunetide and erythropoietin) are reported in schizophrenia (M. Cho et al., 2019; Jeppesen et al., 2020) and depression (O. Köhler-Forsberg et al., 2019), yet authors suggest that more research is warranted and that effects could be different depending on the single agent. A more-restricted meta-analysis on non-steroidal anti-inflammatory drugs, omega-3 fatty acids, statins and minocyclines, found that they had significant antidepressant effects for major depressive disorder (MDD) and are reasonably safe (Bai et al., 2020). Recently, *Cannabidiol (CBD)*, a component of the cannabis plant with anti-inflammatory (Henshaw et al., 2021) and antipsychotic-like properties, and improving effects on cognition (Osborne et al., 2019), is being investigated in schizophrenia (Osborne, Solowij, & Weston-Green, 2017), in ASD (Carbone et al., 2021) but also in preclinical studies where it counteracts the effects of murine models of prenatal infections and MIA (Osborne et al., 2019; Osborne, Solowij, Babic, et al., 2017), and in animal models of Autoimmune Diseases (Rodríguez Mesa et al., 2021). Whether these results will be confirmed, and CBD will find application as anti-inflammatory or immunoregulatory agent, or as a protective agent in SLE pregnancy, is yet to be discovered. *Information and investigation on nutritional approaches*, as diets rich in flavanols from fruits and vegetables, notable antioxidant and anti-inflammatory agents, probiotics (fermented foods) known to protect good gut bacteria, foods rich in polyunsaturated fatty acids, and avoiding diets high in saturated fats and refined sugars, is also advocated for (Offor et al., 2021). Currently used *psychopharmacological treatments* appear to have anti-inflammatory effects, which may partly explain their clinical effect: *SSRI* (L. Wang et al., 2019), but also *antipsychotics* (Marcinowicz et al., 2021). New experimental lines target also several of the pathways evidenced in this dissertation. A mega-analysis of RCT of immune-modulatory drugs targeting 7 inflammatory

mechanisms (IL-6, TNF-α, IL-12/23, CD20, COX2, BLγS, p38/MAPK14) in depression, showed antidepressants effects for patients with high symptom level, and larger effects for anti-IL-6 antibodies, and an anti-IL-12/23 antibody (Wittenberg et al., 2020). The HPA-axis is also addressed: a recent meta-analysis on *treatments inhibiting glucocorticoid synthesis* in in mood disorders suggests that only patients with higher cortisol levels at baseline may benefit from such treatments (Lombardo et al., 2019). As are considered *antagonists of N-methyl-D-aspartate receptor (NMDA) receptor* (Roman & Irwin, 2020).

Data in children and youth population on treatments aiming at reducing inflammation are limited, and caution is warranted: "Evidently, for the very early stages, the "do no harm" imperative is critical" (McGorry et al., 2014).

5.5.4 Research on assessment of psychosocial stress

The important implications of life stress on health and behavior, call for more consistent study of stress construct and its consequences, and for more spread use of state-of-the-art instruments to measure stress (Slavich, 2019). Several measures to assess life stress are available (reviewed e.g. in (Slavich, 2019)). A major impact of common, familiar stressors on health of children and adolescents stands out from this research, indicating that it may be adequate to assess such stressors specifically and more routinary. One important variable to study appears the quality of parent-child relationship. Different measures are described, and attachment measures among them, as *Coherence of Mind* and *Secure Script Knowledge* (see separate Box, reviewed in (E. Waters et al., 2021)). Such measures are often time-demanding and require specific training. Their value is that they can change with interventions, thus permitting to monitor the effects of these (Raby et al., 2021). Another tool used in some works to assess the quality of parental relation, and that appears easy to use, is the *Parental Bonding Instrument (PBI)*, which evaluates retrospectively the perceived parental style until the participant reached 16 years. It has 25 items, 12 items related to care and 13 items related to overprotection (Parker et al., 1979). The 'caring' scale measures a dimension from empathy, closeness, emotional warmth and affection to neglect, indifference, and emotional coldness. 'Over-protection' ranges from intrusion, excessive contact, control, infantilization, and prevention of independent behavior to autonomy and allowance of independence. High scores on both dimensions represents 'affectionate constraint'; low scores on

both represents ‘neglectful parenting’; high protection and low care is characterized as ‘affectionless control’, whereas the opposite profile- high care and low (over)protection- is considered ‘optimal parenting’(Read & Gumley, 2019). It permits a quick evaluation of the parental history, and its rutinary use may help to expand knowledge about the state of familiar bonds in relation with psychopathology and psychical outcomes.

5.5.5 Research on psychosocial interventions

Psychosocial interventions include psychotherapeutic and other approaches directed at reducing perceived stress and at increasing support. Here the focus will mostly be on outcomes in psychiatric conditions. Evidence for effectivity of familiar interventions on physical outcomes have been documented by robust longitudinal evidence, as reviewed in §3 of the discussion, and a recent meta-analysis has confirmed that psychosocial interventions can have beneficial results on Immune System function (Shields et al., 2020).

Family interventions: in the past years, several works identify the family as a central element for clinical outcomes: “while children live within multiple contexts (e.g., family, school, neighborhood), the family system is undoubtedly the most influential in terms of development” (Weinstein & West, 2021). Authors advocate for family intervention targeting parent-child attachment (Coughlan et al., 2019, 2021; J. D. Jones et al., 2016a), parental sensitivity, parent-child conflict (Dhondt et al., 2019), family relationships (McMahon et al., 2021) for improving outcomes of young people with diverse psychiatric symptoms (Song et al., 2021). Results about efficacy of family approaches for different psychiatric conditions are starting to appear (B. Wright et al., 2017). in July 2021, a special issue of the Journal of Affective Disorders: “State of the Evidence for Psychosocial Interventions for Childhood Affective Disorders: The Role of the Family” has reviewed promising results of approaches centered on family: with adolescent depression and suicidality (G. Diamond et al., 2021; Rapp et al., 2021; Tompson et al., 2020), bipolar (Miklowitz et al., 2020), anxiety (Lewin et al., 2021; Peris et al., 2020) substance use disorder (MacPherson et al., 2021), as well as child PTSD, where work is carried out with non-offending caregivers (E. J. Brown et al., 2020). The approaches are varied: *Family-Focused Therapy for Bipolar Disorder* (Miklowitz & Chung, 2016), *Trauma-Focused Cognitive-Behavioral Therapy* (J. A. Cohen et al., 2017; Judith A Cohen et al., 2012), *Attachment-based family therapy* (ABFT, (G. Diamond et al., 2016; G. Diamond

& Siqueland, 1998). They are generally time limited, 10-15 sessions, programs, focused on skill- and communication enhancement training among family members. The ABFT, e.g., builds on 5 treatment tasks, each taking one to three sessions to accomplish: the Relational Reframe Task shifts the family's focus from “fixing” the patient to improving family relationships; the Adolescent Alliance-Building Task is developed individually with the adolescent, to build a therapist–adolescent bond, identify and explore possible core family conflicts, and prepare the adolescent to discuss these issues with the parents; the Parent Alliance-Building Task is developed with the parents, to explore their own current stressors and history of attachment failures, which fosters their empathy toward the adolescent; the Attachment Task, where the adolescent discloses previously unexpressed anger about core conflicts, and if the parents respond honestly and empathetically, tension can dissolve, and forgiveness and mutual respect can emerge in the relationship; and the Competence-Promoting Task, where the adolescent works on his/her connections and success outside the home (e.g., school, peers, work, etc.). Once attachment is on the mend, the family can serve as a secure base from which the adolescent can explore his/her emerging autonomy. Parallelly, in psychotic disorders, *Open Dialogue*, a family- and network-based approach, has been showing very promising results in preventing first psychotic episodes from becoming chronic (J. Aaltonen et al., 2011; Bergström et al., 2018; Seikkula et al., 2006, 2011).

Several treatments focused on attachment are available also for parents of small children (reviewed in (Woodhouse, 2018)), all found effective for normalizing attachment in children with disorganized attachment in a recent meta-analysis (B. Wright et al., 2017).

Group interventions: Research suggests that children and adolescents can use peers as stress buffers, particularly when stress comes from other peers or from other negative experiences at school (R. E. Adams et al., 2011; Kendrick et al., 2012; Kiecolt-Glaser, Gouin, et al., 2010; Peters et al., 2011). It seems relevant to consider group therapy with peers as an option to contemplate for further investigation and clinical use. In group therapy, all participants can experience both receiving and giving social support, which can lead to a greater sense of autonomy and self-efficacy (Gruenewald et al., 2012), and as described reduce brain activity in stress and threat-related regions and increase activity in reward-related ones (Inagaki et al., 2016). Such interventions could be concurrent to family work and work in synergy with it, fighting social

exclusion, a target advocated for by many works (e.g. see (Scheepers et al., 2018)). One model is short group analytic psychotherapy (Foulkes, 2018): while it is traditionally been difficult to measure effects of such approaches (Vlastelica, 2011), one possible direction for research may be measuring of biological markers of stress and inflammation at start and end point of the treatment.

Increasement of general social support: Evidence reviewed talks also for advantages of interventions that increase the general support the young person perceives, in neighborhood, at school, during leisure activities. Greater level of social support and of neighborhood social cohesion have shown protective effect for poly-victimized children (Crush, Arseneault, Jaffee, et al., 2018) and adolescents (Crush, Arseneault, Moffitt, et al., 2018) against development of psychotics experiences. Likewise, opportunities to contribute to society are described as a protective factor for good outcomes, in young people experiencing distress or psychotic symptoms (EE & Werner, 2004; McMahon et al., 2021; Trevarthen, 1980)

A focus on attachment style within therapy: Some of the work reviewed suggests that there is at least moderate likelihood that a patient presenting with depressive, paranoia or anxiety in mental health settings, may exhibit attachment insecurity (Bakermans-Kranenburg & van IJzendoorn, 2009; R. Murphy et al., 2020). Various authors suggest taking this into account when dealing with patients, both in adapting the approach so that individuals can feel safe in the therapeutic relationship (Taylor et al., 2014; Tyrrell et al., 1999), and in using information on attachment style during the therapy, especially if the attachment style is relevant to symptoms – e.g. in formulation and in the case of paranoia – and if the clients are receptive to this (Gumley et al., 2013; Lavin et al., 2020; R. Murphy et al., 2020). A recent meta-analysis has suggested that improvements in attachment security during therapy may coincide with better treatment outcome, and that those who experience low pre-treatment attachment security may find better treatment outcome in therapy that incorporates a focus on interpersonal interactions and close relationships (Levy et al., 2018). Given the results on link between attachment and health, it is expectable and researchable that an approach that leads to more secure attachment will also contribute to decrease in inflammation and in general health.

Resilience: One interesting line of research has put the accent on the possible strengths deriving from exposure to adversities, and on how to make best use of them (Ellis et al., 2017). Some authors note how exposure to harsh environment and stressful circumstances, can shape not only impairments and difficulties, but also enhance some abilities, that allow to tackle the adverse contexts. Research has documented a variety of potentially advantageous adaptations to early-life stress, ranging from enhanced social-emotional skills (e.g., emotion recognition, empathic accuracy) to enhanced memory in specific domains (e.g., early-life memory retention; memory for negative, emotionally laden, or stressful events; working memory in the form of rapid tracking and memory updating), enhanced learning in specific domains (e.g., learning about animal danger, procedural learning), enhanced cognitive speed and accuracy in specific domains (e.g., recognition of angry or fearful faces), increased attention-shifting ability, and enhanced reward-oriented problem solving (Jay Belsky et al., 1991; Frankenhuis & de Weerth, 2013; Giudice et al., 2011; Wenner et al., 2013). For example, children who have experienced severe neglect or abuse tend to exhibit improved detection, learning, and memory on tasks involving stimuli that are relevant to them (Frankenhuis & de Weerth, 2013), such as enhanced memory for a doctor who performed an invasive examination (Eisen et al., 2007), or enhanced recall of distracting aggressive stimuli (e.g., guns, (Rieder & Cicchetti, 1989), or faster orientation to angry faces and voices (S D Pollak et al., 2009; Seth D Pollak, 2008), all cognitive skills that may promote survival in hostile environments (Ellis et al., 2017). Researcher have talked about “hidden talents in harsh environments” (Ellis et al., 2020), which can take two meanings: one with focus on enhanced abilities, that exceed the abilities of individuals growing up under more safe, stable conditions, and another one, focusing on equalization. In the latter, the hidden talents that individuals have developed as an adaptation to stress, enable them to perform as well as individuals from low-risk environments. These observations are also compatible with those from Chen & colleagues, where they described development of “shift-and-persist” strategies under stressful situations and in case of secure attachment: these abilities would render individuals more flexible and in stand to handle difficult situations later on (E Chen & Miller, 2012). The critical point for research is, how to leverage these strength, and at least ensure that these subjects can “do well in life”. Investigators propose an “adaptation-based approach to resilience”, where e.g. the education system takes into account the fact that children and youth adapted to stress, have grown up to function in harsh and

unpredictable environment. Researchers suggest the use of approaches similar to those used for facilitating learning in children with ADHD: to use learning settings where children are allowed to move, as they can learn better that way; to use problems that are closer to their daily lives, i.e. related to social status and dominance; and to use shifting tasks (Hartanto et al., 2016; Sarver et al., 2015). Holding in mind such a focus on resilience and on alternative talents when dealing with stress-exposed children, appears an important complement to the classical approach focused on deficits and on preventing the damages. To underly that adversities can generate strength, and permit a broader range of handling possibilities than expected, could help many children make sense of their hard histories and good use of them.

5.6 Limitations

Our studies are cross-sectional, therefore do not permit to infer on causalities between measures of inflammation and those of psychopathology. Yet, the exploratory post-hoc Path-Analysis run in study 1, supported a putative causal effect of stress over both psychopathology and inflammatory marker, and of immune and inflammatory markers over psychopathology.

While the size of the inpatient group is relatively large, the size of the other two samples is limited, especially that of the offspring group. This may have hindered reaching statistical significance in some comparisons.

In the study of Lupus offspring, we did not measure some relevant antibodies, in particular the anti-phospholipids (aPL) antibodies, implied in neurodevelopmental disorders in SLE offspring (É Vinet et al., 2014) and possibly also in neurological manifestations in their carriers (De Maeseneire et al., 2014). Assessment of pregnancy and delivery conditions was run retrospectively from mothers' recollections, as laboratory data about mothers' immune/inflammatory profile and medical treatment during pregnancy were missing.

Regarding stress measures, we used collective and not specific measures, and did not assess directly parental-child bond, or family atmosphere, but used proxies such as family disruption and maternal psychopathology to infer on possible family stressors. As reviewed in §5.2 though, both family disruption (Tan et al., 2018) and maternal depression (T. G. O'Connor et al., 2019) can represent emblematically the degree of familiar distress experienced by the children. Also, we assessed measures of past stress, and therefor in the inpatient group, we did not account for the possible effects of the acute stress linked to the hospitalization itself. To do this, it would be appropriate to repeat the measures in acute outpatients. Besides, we used solely stress subjective measures, which could be integrated with biological indices, related e.g. to cortisol or catecholamine production (Wosu et al., 2013).

Our work was intended as explorative. Regarding this dissertation itself, a disproportion may emerge between the extension of the reviewed literature, and the simplicity of the original research. We think that the original investigation, though limited in subjects and time extension, assessed and linked several different areas of research, and naturally lead to the topics reviews and discussed. It is our hope that the results of the work, and the review they have induced, may generate useful suggestions for future works.

6 CONCLUSIONS

This thesis aims at increasing knowledge about links between inflammation, autoimmunity, psychosocial stress and psychiatric conditions in adolescent population. It analyzed immune assets in a group of child and adolescent inpatients and in one of offspring of women with SLE.

The results suggest that:

- Psychopathology appears associated with inflammation already from early ages, and the pattern is suggestive of an activation of innate immunity, especially monocytes and their cytokines.
- Offspring of women with SLE present inflammatory changes, alterations in their immune system and neuropsychological tests, and a higher rate of psychopathology than expected. It cannot be concluded whether these changes have been caused by in-utero exposure to maternal immunity, whether they reflect a family trend to immune dysregulation, or whether they are the result of exposure to psychosocial stress.
- An antibody described as neurotoxic in Lupus patients had higher titers in both inpatients and offspring, than in healthy controls. The interpretation of this finding warrants further investigation.
- Psychosocial stress appears related with inflammatory markers and psychopathology in psychiatric patients, and with neurocognitive alterations in the offspring of women with SLE. Some of the measures used to estimate stress, such as disruption of the family structure and maternal depression, show the importance of parental support, parental well-being and family climate, for offspring well-being.
- Results advocate for a more routinary evaluation of inflammation in psychiatric patients and at-risk populations. Some of the measures proposed, although relatively new, have an efficient profile
- Results underscore the influence of daily, familiar stressors on the stress perceived by psychiatric patients, and the importance of routinely incorporating measures of parental-child bond, in the study and treatment of young subjects. Results support also interventions aiming at improving parent-child and familiar interactions

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