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Conectividad funcional estática y efectiva dinámica en personas con Síndrome de Down en relación con el rendimiento cognitivo

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CONECTIVIDAD FUNCIONAL ESTÁTICA Y EFECTIVA DINÁMICA EN PERSONAS CON SÍNDROME DE DOWN EN RELACIÓN CON EL RENDIMIENTO COGNITIVO

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"Todo hombre puede ser, si se lo propone, escultor de su propio cerebro".

Santiago Ramón y Cajal.

Índice

Resumen

Antecedentes: El Síndrome de Down (SD) es una alteración génetica que causa discapacidad intelectual. Se han realizado pocos estudios sobre conectividad funcional y dinámica utilizando señales de fMRI (Imagen de Resonancia Magnética Funcional) en estado de reposo, específicamente, sobre la estructura y densidad relevante de la red por defecto en estado de reposo (DMN). Aunque se ha informado de datos sobre este tema en individuos adultos con SD (edad > 45 años), no se han estudiado las propiedades de la DMN en individuos jóvenes con SD. De igual manera, los indicadores de complejidad en el campo de la conectividad funcional y su posible relación con variables del funcionamiento cognitivo son escasos. Por otro lado, de acuerdo a las pruebas emergentes se sugiere que la red de conectividad funcional no sea un proceso estático en el tiempo, sino una conectividad dinámica que muestra los cambios en los patrones de actividad neuronal a lo largo del tiempo de registro. **El propósito** de esta tesis de doctorado es en principio, estimar la red de conectividad funcional, posteriormente; analizar cómo algunos indicadores de complejidad estimados en las subáreas que constituyen la DMN son predictores del resultado neuropsicológico para evaluar el rendimiento cognitivo y finalmente, utilizar los modelos de ecuaciones estructurales (SEM), para estimar los componentes dinámicos de la red de conectividad efectiva a través de los efectos (recursivos y no recursivos) entre las regiones de interés (ROIs), teniendo en cuenta cómo se comporta la conectividad dinámica efectiva en personas con SD en comparación con un grupo de control de la población en general (edad < 36 años). **Método:** Se reclutó una muestra de 22 jóvenes con SD entre 16 y 35 años (M = 25,5 y SD = 5,1) en varios centros para personas con discapacidad intelectual (ID). Además de los datos sociodemográficos, se evalúo con las pruebas Kaufman Brief Test of Intelligence (KBIT) y Frontal Assessment Battery (FAB), posteriormente se grabó una sesión de fMRI en estado de resposo durante un período de seis

minutos con un escáner 3.T Philips Ingenia. Un grupo de control de 22 personas, emparejadas por edad y sexo, fue obtenido del Proyecto Conectoma Humano (para comparar las propiedades de las redes entre los grupos), luego se hizo un análisis estadístico que incluyera una parte de la DMN con 6 ROI´s. Los **resultados:** por un lado, se obtuvieron los valores de las 48 ROI que configuraron la DMN, y se estimaron los gráficos de conectividad para cada sujeto, el gráfico de conectividad promedio para cada grupo, la agrupación, los efectos significativos en las ROI y la red de conectividad funcional promedio. Se encontraron diferencias significativas de los indicadores de complejidad entre los grupos: el grupo control mostró menos complejidad y menos varianza de las distribuciones de estos indicadores que el grupo con SD, sin embargo; el grupo con SD mostró relaciones signficativas y negativas entre algunos indicadores de algunas de las redes de la DMN con las puntuaciones de desempeño cognitivo. También se encontró que los patrones de conectividad dinámica son diferentes en ambos grupos, las redes de las personas con SD son más complejas y con efectos más significativos y dinámicos asociados con la ROI 3 y 4 relacionadas con áreas parietales superiores en ambos hemisferios cerebrales como eje de asociación e integración funcional. **Conclusiones**: Se identificó una mayor densidad de activación en el grupo SD en las redes DMN ventral, sensoriomotora y visual, aunque en el marco de una amplia variabilidad de patrones de conectividad en comparación con la red del grupo de control, lo cual amplía nuestra comprensión del patrón de las redes de conectividad funcional y la variabilidad intrasujeto en SD. Además, en cuanto a la conectividad efectiva dinámica, el grupo con SD se caracterizó por tener redes DMN más complejas y con una relación inversa entre la complejidad y el rendimiento cognitivo según las estimaciones de los parámetros negativos. Por tanto, se hace evidente que la correcta clasificación de estos grupos, especialmente en competencia cognitiva, es un buen paso inicial para proponer un biomarcador en el estudio de la complejidad de la red.

Palabras clave: fMRI, Estado de Reposo, síndrome de Down, red por defecto en estado de reposo, conectividad funcional y conectividad dinámica efectiva

Abstract

Background: Down Syndrome (DS) is a genetic disorder that causes intellectual disability. Few studies have been conducted on functional and dynamic connectivity using fMRI (Functional Magnetic Resonance Imaging) signals in the resting state, specifically on the relevant structure and density of the default network in the resting state (DMN). Although data on this topic have been reported in adult individuals with DS (age > 45 years), the properties of DMN in young individuals with DS have not been studied. Similarly, indicators of complexity in the field of functional connectivity and its possible relationship to variables of cognitive functioning are scarce. On the other hand, according to emerging evidence, it is suggested that the network of functional connectivity is not a static process in time, but dynamic connectivity that shows changes in the patterns of neuronal activity over the time of recording. The purpose of this PhD thesis is, in principle, to estimate the functional connectivity network, later on; to analyze how some indicators of complexity estimated in the subareas that constitute the DMN are predictors of neuropsychological outcome to assess cognitive performance and finally, to use structural equation models (SEM), to estimate the dynamic components of the effective connectivity network through the effects (recursive and non-recursive) between the regions of interest (ROIs), taking into account how effective dynamic connectivity behaves in people with DS compared to a control group of the general population (age < 36 years). Method: A sample of 22 young people with DS between 16 and 35 years old (M = 25.5 and DS = 5.1) was recruited in various centres for people with intellectual disabilities (ID). In addition to the sociodemographic data, they were evaluated with the Kaufman Brief Test of Intelligence (KBIT) and Frontal Assessment Battery (FAB), and then an fMRI session was recorded in a resting state for six minutes with a 3.T Philips Ingenia scanner. A control group of 22 people, matched by age and sex, was obtained from the Human Connectome Project (to

compare the properties of the networks between the groups), then statistical analysis was done that included a part of the DMN with 6 ROI's. The results: on the one hand, the values of the 48 ROI that configured the DMN were obtained, and the connectivity graphs for each subject, the average connectivity graph for each group, the grouping, the significant effects on the ROI and the average functional connectivity network were estimated. Significant differences in complexity indicators were found between the groups: the control group showed less complexity and less variance in the distributions of these indicators than the group with DS, however; the group with DS showed significant and negative relationships between some indicators of some of the DMN networks with cognitive performance scores. It was also found that the patterns of dynamic connectivity are different in both groups; the networks of people with DS are more complex and with more significant and dynamic effects associated with ROI 3 and 4 related to upper parietal areas in both brain hemispheres as an axis of association and functional integration. Conclusions: A higher density of activation was identified in the SD group in the ventral, sensorimotor and visual DMN networks, although within a wide variability of connectivity patterns compared to the control group's network, which broadens our understanding of the pattern of functional connectivity networks and the intra-subject variability in SD. Furthermore, in terms of dynamic effective connectivity, the SD group was characterized by more complex DMN networks and an inverse relationship between complexity and cognitive performance according to estimates of negative parameters. Therefore, it becomes evident that the correct classification of these groups, especially in cognitive competence, is a good initial step to propose a biomarker in the study of network complexity.

Keywords: fMRI, resting-State, Down Syndrome, Default Mode Network, Connectivity Functional and Connectivity Effective Dynamic

Listado de Abreviaturas

Abreviaturas en inglés

AAIDD: American Association on Intellectual and Developmental Disabilities

AAL: Automated anatomical labelling

AD: Alzheimer's Disease

APA: American Psychological Association

AIC: Akaike Information Criteria

AC-PC: Anterior Commissure-Posterior Commissure

BOLD: Blood Oxygenation Level Dependent

DF: Degree of freedom

dFC: dynamic Functional Connectivity

DMN: Default Mode Network

DMNv: Default Mode Network ventral

DMNa: Default Mode Network anterior

DSQIID: Demencia Screeening Questionnaire for Individuals with Intellectual Disabilities

DS: Down syndrome

DTI: Diffusion tensor imaging

FAB: Frontal Assessment Battery

FC: functional connectivity

fMRI: functional Magnetic Resonance Imaging

FLAIR: Fluid-Attenuated Inversion Recovery

FOV: Field of View

FSL: FMRIB Software Library v5.0

FWHM: Full width at half maximum

ICA: Independent Component Analysis

ID: intellectual disability

IQ: Intellectual Quotient

JFD: Jenkinson's Framewise Displacement

KBIT: Kaufman Brief Test of Intelligence

MCI: Mild Cognitive Impairment

MNI152: Montreal Neurological Institute 152 template brain

MRI: Magnetic Resonance Image

NIfTI: Neuroimaging Informatics Technology Initiative

PC: partial correlation

PCA: Principal component analysis

ROIs: Region Of interest

rs-fMRI: resting-state functional Magnetic Resonance Imaging

RSN: resting state network

SEMs: Structural Equation Models

SPM12: Statistical Parametric Mapping

TE: Time of Echo

TFE: Turbo field Echo

TR: Time of Repetition

WISC-V: Wechsler Intelligence Scale for Children -V

WS: Small-World

Abreviaturas en castellano

DTA: Demencia tipo Alzheimer

SD: síndrome de Down

EEG: Electroencefalograma

Evs: variables explicativas

GLM: Modelo Lineal General

Md: mediana

PET: Tomografía por emisión de positrones

RHD: Respuesta Hemodinámica

RMf: Resonancia Magnética funcional

SM: red sonsoriomotríz en resposo

TR: tiempo de repetición

T1: Tiempo de relajación o recuperación

T2: Tiempo de relajación o degradación

V: red de procesamiento visual en reposo

Capítulo 1.
Introducción

Introducción

1.1 Señal cerebral y la Imagen por Resonancia Magnética Funcional

La Imagen por Resonancia Magnética Funcional (fMRI, por sus siglas en inglés) es una técnica de neuroimagen descubierta hace apróximadamente veintinueve años, cuando se sustrajo por primera vez dos mapas de volumen sanguíneo de una imagen cerebral proveniente de inyecciones secuenciales de gadolinio con la técnica eco planar (EPI), la cual recolectaba datos en series temporales de volumen sanguíneo cerebral antes y durante la estimulación visual (Belliveau et al., 1991). Este estudio marcó un hito en el comienzo del uso de la resonancia magnética para mapear la actividad funcional del cerebro humano. Posteriormente, un grupo de investigación de Minnesota obtuvieron los primeros resultados exitosos de la resonancia magnética funcional usando la señal cerebral proveniente de los cambios de contraste dependiente de la oxigenación de la sangre endógenea (BOLD) (Cohen & Schmitt, 2012; Rosen & Savoy, 2012).

En la actualidad se considera la fMRI tiene mucha aceptación por ser una técnica no invasiva y por tener tanto una resolución temporal como espacial superior a otras técnicas de neuroimagen descubiertas hasta ahora. Existen dos grandes campos de aplicación de la fMRI, la investigación básica de los procesos cognitivos y la práctica clínica.

En cuanto a la investigación básica, los estudios de neuroimagen han supuesto una verdadera revolución en el estudio de las funciones cognitivas (Young, 2016). En los últimos años, se ha aumentado considerablemente los estudios de señal cerebral usando diversas técnicas de registro (Electroencefalograma EEG, Tomografía por emisión de positrones PET, Imagen por Resonancia Magnética MRI e Imagen por Resonancia Magnética Funcional fMRI), mostrando una nueva forma de entender el funcionamiento cerebral (Medaglia et al., 2015; Yildirim & Büyükiscan, 2019). Ciertamente, gracias a la evolución tecnológica en el estudio del cerebro se tienen al alcanze

medidas mucho más fiables del funcionamiento cerebral y se superan algunas limitaciones propias de los paradigmas clásicos de evaluación psicológica de las funciones cognitivas.

En cuanto a la práctica clínica, se utiliza principalmente para el planteamiento prequirúrgico, con el objetivo de tener mayor precisión en la representación cortical de las funciones neurológicas e identificar la lesión a tratar, lo que permite establecer una trayectoria quirúrgica que posibilite la preservación de dichas funciones y la calidad de vida del paciente (Mao & Berns, 2002).

La técnica de registro a la que se hace referencia en este trabajo es la fMRI, cuyo propósito es estudiar la función cerebral más allá de la localización anatómica, en una resolución de 3mm y con una serie de volúmenes en 3D. A continuación se expone el registro de señal cerebral usando esta técnica.

1.1.1. Registro de señal cerebral con fMRI.

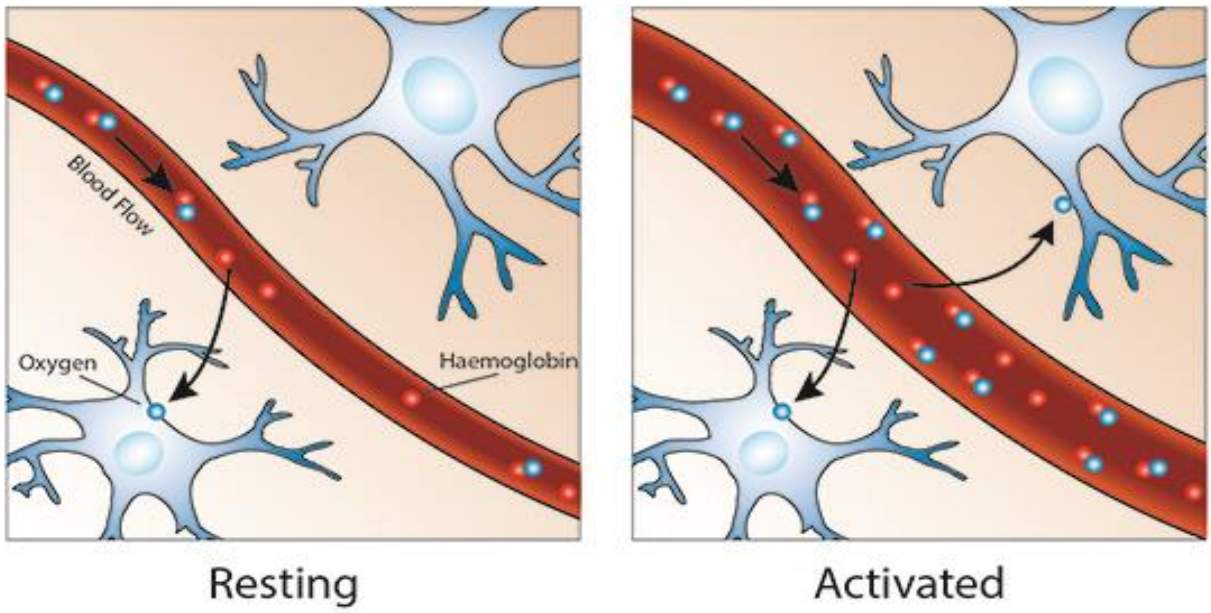
El escáner de resonancia magnética está compuesto por un tubo cilíndrico que contiene un electroimán muy potente que puede variar de acuerdo con la intensidad del campo de teslas. El campo magnético que genera cuando el sujeto está dentro del escáner, afecta los núcleos magnéticos de los átomos de hidrógeno en el agua (H_2O). Normalmente estos núcleos están orientados al azar, pero bajo la influencia del campo magnético, estos se alinean con la dirección del campo. Al momento de apuntar a la misma dirección, las pequeñas señales magnéticas de los núcleos individuales se suman de manera coherente, lo que resulta en una señal suficientemente grande como para medirla. Cuanto mayor es el grado del campo, mayor es el grado de alineación (López-Bonilla, 2013).

Se estima el funcionamiento cerebral a partir de la habilidad de medir la señal que se genera de la actividad neuronal en una región específica (Sell, 2007).

Como podemos ver en la Figura 1, cuando la actividad neuronal aumenta, por una demanda energética, incrementa el flujo sanguíneo de oxihemoglobina (sangre oxigenada con propiedades diamagnéticas) hacia las regiones de mayor actividad neuronal; posteriormente disminuye la concentración de la sangre (desoxihemoglobina con propiedades paramagnéticas), provocando que esta diferencia entre la oxi y dexosihomoglobina sea un índice indirecto del grado de actividad neuronal en esa área, conocido como oxigenación dependiente de la sangre (BOLD).

Figura 1

Diagrama del Efecto BOLD



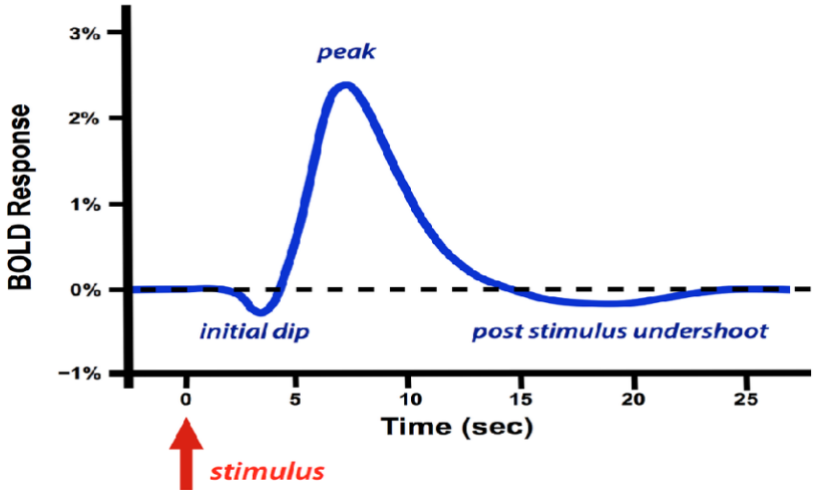
Nota: El gráfico representa la actividad neuronal en estado de reposo y en activación ante el efecto BOLD. Adaptado de *Magnetic Resonance Imaging of Brain Function*, por Stuart C. 1997, (https://bit.ly/3hXyUps).

Las características de esta señal, descritas por Ogawa et al. (1990), muestran que esta suele ser pequeña y variable por el tiempo de duración, además de tener ruido en magnitud como en variabilidad. El cambio en la señal BOLD está asociado a un proceso neuronal breve que se le

conoce como respuesta hemodinámica (RHD). Ésta consiste en una disminución momentánea de la oxigenación de la sangre inmediatamente después de que aumenta la actividad neuronal, provocando una "caída inicial (*initial dip*)". Posteriormente le sigue un período en que el flujo sanguíneo aumenta, satisface la demanda de oxígeno y compensa el aumento de ésta. El flujo sanguíneo alcanza un punto máximo después de unos 6 segundos y luego vuelve a bajar a la línea base, a menudo acompañado de un sub-impulso post-estímulo.

Figura 2

Ejemplo de respuesta hemodinámica en señal cerebral tras un único y breve estímulo



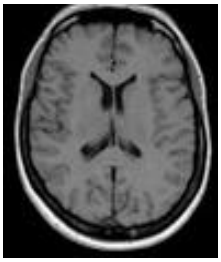
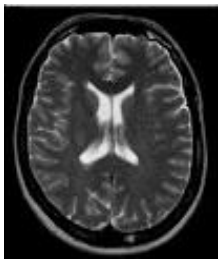
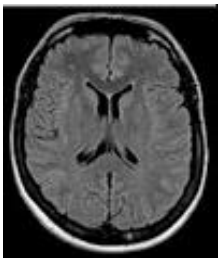
Nota: Adaptado de *BOLD and Brain Activity* [Fotografía], por Elster, 2018 (https://bit.ly/30ew61s).

A la par de generarse la señal BOLD están presentes los valores del tiempo de relajación que dependen de las propiedades magnéticas del medio en el que se encuentran los núcleos de hidrógeno. Cuando se apaga el pulso electromagnético se recupera la magnetización de los átomos de hidrógeno (llamados al conjunto de éstos spins), que tienen una magnitud y una dirección determinada. Al haber una ausencia de campos externos, los spins apuntaran a direcciones aleatorias, como suele ser su estado original y recuperan la magnetización longitudinal, llamado tiempo de relajación

longitudinal T1. Las imágenes que suelen obtenerse con el registro de T1 se identifican por tener un buen detalle de apreciación anatómico, con sustancia blanca hiperintensa en relación con sustancia gris. El tiempo de relajación transversal o el T2 es la constante de tiempo que pierden los átomos de hidrógeno en procesar todos al mismo tiempo el componente transversal de la magnetización. El tipo de imágenes generadas por T2 muestra la sustancia blanca hipointensa con respecto a la sustancia gris. También suelen llamarle FLAIR (*Fluid Attenuated Inversión Recovery*) (Thulborn et al., 1982) cuando a esta imagen se le separa del agua y suele mostrar lesiones patológicas como los edemas (Armony et al., 2012). En la Tabla 1 se presentan los registros que se obtienen a través de diferentes secuencias de imágenes cerebrales.

Tabla 1

Tipos de registro y secuencias de imagen cerebral.

Estructura	Imágenes T1	Imágenes T2	Imágenes FLAIR
Hueso	Hipointenso	Hipointenso	Hipointenso
Grasa	Hiperintensa	Hiperintensa	Hiperintensa
Líquido Cefalorraquídeo LCR	Hipointensa	Hiperintensa	Hipointensa
Sustancia blanca	Levemente hiperintensa	Hipointenso	Hipointenso
Sustancia gris	Isointensa	Isointensa	Isointensa
			

Nota. Se muestra la imagen que se adquiere en los tres planos anatómicos, con imágenes potenciadas (adquiridas) en T1, T2 y FLAIR. Adaptado de *Imágenes diagnósticas [Fotografía], por Facultad de Medicina, Departamento de Imágenes Diagnósticas,* 2014, (https://bit.ly/2XwceFp).

El análisis de la señal BOLD requiere de métodos de procesamiento mejorados como principios físicos y análisis estadísticos complejos, que permitan la extracción robusta y eficiente de información útil de las señales de tiempo.

1.1.2. Análisis de datos

Los datos que se obtienen de los cortes cerebrales de las imágenes de cada participante, se transforman en volúmenes cerebrales compuestos de voxels (abreviación inglesa de *volumetric pixel*, objeto cúbico unitario en un cuerpo tridimensional con coordenadas X, Y, y Z; que configura la unidad básica de análisis de cada imagen cerebral).

Cuando ya se tienen las imágenes con las que se trabajará, se comprueba que tengan la misma orientación del campo magnético, de forma que todas estén reorientadas. El propósito que se persigue en esta etapa es determinar las regiones de la imagen en las que la señal cambia con o sin presentación de estímulos. Este análisis de datos requiere de técnicas no dirigidas que hagan pocas suposiciones sobre los tiempos de activación de las respuestas esperadas. Necesitan idealmente ser robustos, así como precisos y exactos.

El análisis de datos de cualquier experimento de fMRI consta de 3 etapas. La Figura 3 lo describe de manera general. En la primera parte existen etapas de pre-procesamiento, que pueden aplicarse a los datos para mejorar la detección de eventos de activación. En segundo lugar, está el análisis estadístico para detectar los voxels de interés que muestran una respuesta de activación en la señal BOLD. Se toma en cuenta el ruido en las imágenes, así como la variabilidad biológica entre los individuos. Comúnmente suelen utilizar el Modelo Lineal General (GLM), por ser extremadamente flexible, útil tanto para análisis individuales y grupales, así como con estadísticos

paramétricos y no paramétricos. Finalmente, las imágenes de activación son mostradas junto con los valores de probabilidad por la confianza estadística per sé.

Existe un esquema que representa el modelo general estadístico y que se conoce como Modelo Lineal Masivo, esquematizado en Friston et al. (2007) y posteriormete adaptado por Guàrdia-Olmos, Peró-Cebollero, & Fauquet (2014). En el incluyen tres procesos ordenados:

- Preproceso de los datos (maximizar la calidad de los datos)
- Definición del modelo estadístico (en función del diseño empleado, la presencia de covariantes, número de grupos, etc.)
- Estimación de los contrastes estadísticos y su significación clásica o bayesiana (depende de las hipótesis formuladas).

Figura 3

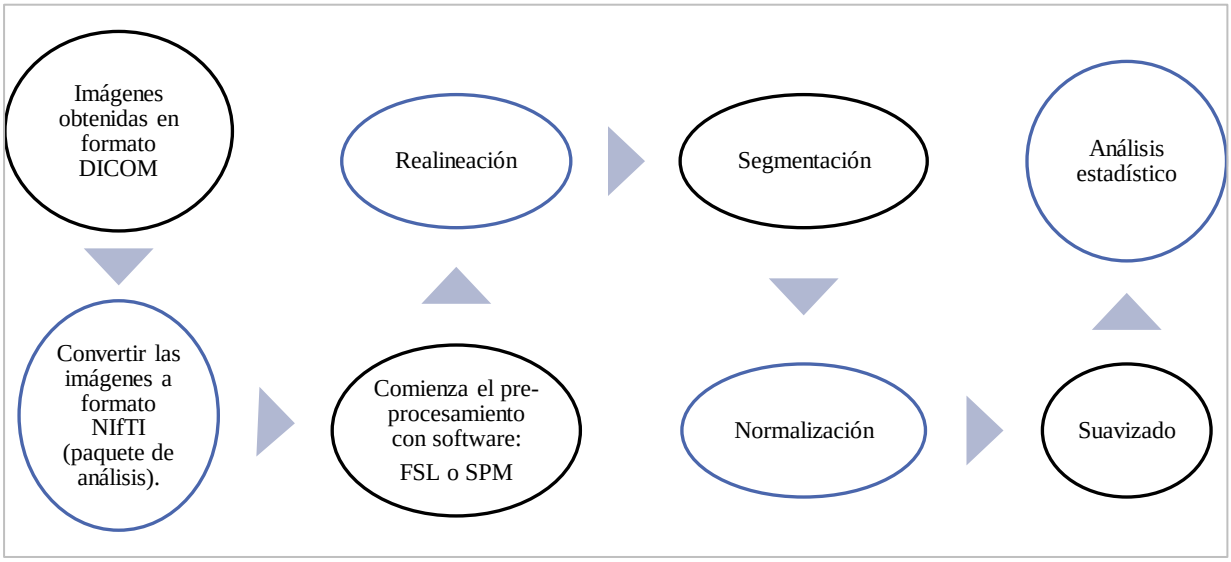
Pasos para el proceso de análisis de datos

Nota: Se requiere de una preparación de las imágenes llamada preprocesamiento, posteriormente un análisis estadístico de acuerdo al interés del estudio y por último una inferencia estadística que responda a la hipótesis del estudio.

En la Figura 4, el gráfico representa la secuencia del preprocesamiento de manera más detallada, primero se obtienen las imágenes del estudio de fMRI en DICOM, luego se convierten a NIfTI, se elige un software para el preprocesamiento y una vez que se tienen se hace realineación, segmentación, normalización y suavizado para proceder al análisis estadístico.

Figura 4

Secuencia del preprocesamiento de imágenes



Nota. Digital Imaging and Comunnications in Medicine DICOM, The Neuroimaging Informatics Technology Iniatitive NIfTI, FSL (FMRIB Software Library v5.0), SPM12 (Statistical Parametic Mapping https://www.fil.ion.ucl.ac.uk/spm/software/spm12/).

1.1.3. Modelo Lineal General

En neuroimagen se suele hacer este tipo de análisis estadístico GLM a nivel de grupo (también nombrado análisis de nivel superior o de segundo nivel). El propósito que tiene es hacer un análisis grupal que pruebe hipótesis, tales como si hay respuesta consistente en todos los individuos, o si las respuestas se relacionan con otras cantidades de interés.

Este análisis debe tener en cuenta las estimaciones de las cantidades de interés, el ruido (o variación) dentro de los datos de cada sujeto, así como las variaciones en las cantidades entre sujetos que se deban a diferencias biológicas.

El GLM para el análisis a nivel de grupo suele utilizar regresores o variables explicativas (EVs) para modelar los efectos entre los sujetos y que estos puedan ser comparados entre grupos. En neuroimagen se utiliza por la flexibilidad para utilizar muchos tipos de pruebas estadísticas. Los resultados de cualquiera de estas pruebas adoptan la forma de mapas que muestran los vóxeles que son estadísticamente significativos.

Otro motivo para hacer el análisis estadístico en la neuroimagen con GLM, es por la aplicación de métodos de corrección de comparaciones múltiples, siempre que se realice un análisis de vóxeles (es decir, una prueba estadística separada en cada vóxel). Esta ventaja hace que el número de vóxeles, que en neuroimagen es enorme (típicamente cientos de miles, o más) pueda acercarnos a hacer inferencias, sin caer en falsos positivos (Jenkinson & Chappell 2018).

El GLM puede estar incorporado a un paquete de software de neuroimagen, como es el caso del FSL (FMRIB Software Library v5.0) y del SPM12 (Statistical Parametic Mapping https://www.fil.ion.ucl.ac.uk/spm/software/spm12/).

1.1.4. Análisis estadístico de Componentes Principales, Análisis de Componentes Independientes y Modelos de Ecuaciones Estructurales en estado de reposo.

Estas son técnicas metodológicas para detectar y cuantificar los diferentes tipos de conectividad, que bien pueden ser: conectividad estructural, conectividad funcional y conectividad efectiva. Cada una de ellas tiene sus respectivas técnicas matemático-estadísticas.

En la conectividad estructural, conectividad funcional y conectividad efectiva se suele hacer Análisis de Componentes Principales (PCA), Análisis de Componentes Independientes (ICA), de voxel semilla y meta-análisis. No obstante, especificamente en la conectividad efectiva por las interacciones psicofisiológicas, se suele emplear el ánalisis con el modelo dinámico causal, modelos autorregresivos multivariantes y el Modelo de Ecuaciones Estructurales (SEM). Los métodos basados en PCA/ICA son especialmente útiles cuando no se conoce qué regiones están implicadas en una tarea determinada o no se conoce la conectividad estructural que pueda estar implícita. Para lo concerniente a este estudio se explicarán solo PCA e ICA y SEM.

El PCA es una herramienta estadística que permite reducir la dimensionalidad entre voxel, de manera tal que descompone una matriz de imágenes en componentes. Esta matriz es una tabla bidimensional de números ordenados en filas y columnas que se utilizan, entre otros usos, para describir sistemas de ecuaciones lineales (Rogers et al., 2007). El objetivo de esta herramienta es analizar mejor las regiones de interés (ROIs), como la cantidad de voxel que se activan tanto en estudio de resting o de tareas, puesto que se comportan en una serie temporal. Por tanto, este método consiste en transformar los datos a un nuevo sistema de coordenadas definido por las direcciones de mayor varianza de los datos. Las imágenes propias pueden capturar las características intrínsecas de los datos que se manifiestan en múltiples regiones que constituyen una amplia red funcional y el vector propio de cada componente mostrará la actividad de la red a través del tiempo (de la Iglesia-Vayá et al., 2011).

EL ICA no es una técnica de reducción de dimensionalidad, es una técnica estadística de separación de fuentes ciegas, es decir, que no pueden ser directamente observadas, por lo que se consideran que se observan *n* combinaciones lineales de *n* fuentes independientes. El propósito de

usarla es separar la señal y tratar de eliminar el ruido. El modelo ICA se puede expresar de forma matricial:

$$x = As$$

donde la matriz *x* recopila los datos observados, en este estudio son las imágenes obtenidas por fMRI, la matriz *A* es la matriz de coeficientes, la matriz *s* representa las fuentes originales.

Cuando se aplica el modelo, sólo la matriz *x* es conocida y a partir de ella se debe estimar *A* y *s*. Este modelo considera que los componentes son estadísticamente independientes y tienen una distribución no-gaussina.

Aunque existen algunas variaciones del método (Calhoun et al., 2003; Beckmann & Smith, 2004), se suele aplicar mientras se hace el preprocesamiento con FSL o SPM. Es especialmente apropiada a la hora de obtener las redes de conectividad intrínsecas como la red por defecto en estado de reposo (DMN, Default Mode Network) que es una red de regiones cerebrales interactuantes que están activas en estado de reposo y se inactiva con tareas cognitivas dirigidas al espacio externo.

Por otra lado, existe SEM que de acuerdo a Ruiz et al. (2010) "son modelos estadísticos multivariantes que permiten estimar el efecto y las relaciones entre múltiples variables" (p. 34). Son menos restrictivos que los modelos de regresión y permiten incluir errores de medida tanto en las variables criterio (dependientes) como en las variables predictoras (independientes). También son denominados modelos confirmatorios, puesto que tienen como fin "confirmar" mediante el análisis de la muestra las relaciones propuestas en la teoría explicativa que se haya decidido utilizar (Ruiz et al., 2010).

El uso de SEM se ha vinculado a la estimación de redes de conectividad efectiva dinámica, sobre todo para establecer la direccionalidad de las relaciones en las ROI seleccionadas. La mayoría

de estas contribuciones se han hecho dejando de lado la visión de la conectividad dinámica. Por ejemplo, Guàrdia et al. (2018a) muestran redes de conectividad efectiva en pacientes diabéticos y en un primer meta-análisis Guàrdia et al. (2018b) muestran los parámetros estimados por SEM en redes de conectividad sin componentes dinámicos.

Sin embargo, la idea de una conectividad dinámica efectiva es todavía poco explorada, y en el campo de los modelos SEM, aún menos. La reciente aparición de la biblioteca GIMME por R (Group Iterative Multiple Model Estimation) abre una opción interesante en el uso de la SEM en la conectividad dinámica efectiva (Gates & Molenaar, 2012; Gates et al., 2017). Los antecedentes muy iniciales sobre esta cuestión pueden identificarse como los propuestos por Zhang et al. (2020) en el campo de las redes dinámicas y el lenguaje, sobre la base de una cartografía previa de Beltz & Gates, (2017). Sin embargo, los autores de la biblioteca R proponen comprender los componentes de las redes dinámicas a partir del estudio del impacto estimable del número de efectos cortos que se pueden identificar.

Desde un punto de vista aplicado, hay algunos trabajos en conectividad dinámica que es importante mencionar. En primer lugar, Chen et al. (2018) con pacientes con Deterioro Cognitivo Ligero (DCL); Threlkeld et al. (2018) con pacientes con Lesión Cerebral Traumática (LCT); Park et al. (2018) mostrando un procedimiento para la estimación de la línea base en estudios de conectividad dinámica; Sharaev et al. (2016) con sujetos de control y estudio de pequeñas redes; Xu et al. (2016) estudiando el efecto del metilfenidato en sujetos sanos; Tang et al. (2016) estudiando el efecto del consumo de tabaco en sujetos sanos; Li et al. (2017) con pacientes deprimidos; y finalmente, Xu et al. (2017) estudiando la conectividad dinámica en gemelos.

Todos los estudios mencionados anteriormente citados y el conocimiento sobre la conectividad funcional se pueden resumir de la siguiente manera: a) hay pruebas de una relación

entre las propiedades topológicas de las redes cerebrales complejas, básicamente funcionales, y ciertas medidas del rendimiento cognitivo (Dosenbach et al., 2007; Bassett et al., 2009; van den Heuvel et al., 2009; Hagmann et al., 2010; Crossley et al., 2013; Lin et al., 2014); b) la conectividad funcional de la (DMN) está asociada a la función cognitiva del cerebro (Buckner et al., 2008; Bonnelle et al., 2012; Kucyi & Davis, 2014); c) la conectividad funcional de la red cerebral no es un proceso estático en el tiempo (Chang & Glover, 2010; Cocchi et al., 2011; Handwerker et al., 2012; Tagliazucchi et al., 2012; Chen et al., 2013; Hutchison et al., 2013a; Hutchison et al., 2013b; Kucyi et al., 2013; Lee et al., 2013; Leonardi et al., 2013; Thompson et al., 2013; Allen et al., 2014; Tagliazucchi & Laufs, 2014) d) Las nuevas pruebas sugieren que la conectividad cerebral funcional dinámica puede indicar cambios en los patrones de actividad neuronal que subyacen en aspectos críticos de la cognición o en la información clínicamente relevante (Tagliazucchi et al., 2012; Park & Friston, 2013; Hutchison et al., 2013a; Allen et al., 2014; Calhoun et al., 2014; Kucyi & Davis, 2015; Tagliazucchi & Laufs 2014); e) la conectividad dinámica se asocia con el estado mental interno tanto en reposo como durante la ejecución de una tarea (Fornito et al., 2012); y f) existe evidencia de la variabilidad de las redes de conectividad funcional dinámica. La variabilidad está asociada a las estrategias de seguimiento no dirigidas que las personas suelen hacer en reposo (Kucyi & Davis, 2014). Las subregiones de la DMN muestran una actividad de variabilidad decreciente cuando hay una mejor resolución de las tareas cognitivas (Garrett et al., 2011; Liang et al., 2013). Así pues, un aumento de ese seguimiento no dirigido estaría vinculado a un peor desempeño de la tarea durante los estímulos de la misma y cabría esperar que ello se tradujera también en una mayor complejidad de la red de conectividad, ya sea dinámica o estática.

La comparación más sencilla en términos cognitivos radica en el análisis de las redes de conectividad funcional dinámica de sujetos sanos en comparación con personas con un

funcionamiento cognitivo comprometido; por ejemplo, la población con síndrome de Down (SD). Estos estudios deben controlar estrictamente la selección de la edad de los participantes para evitar la presencia de la enfermedad de Demencia tipo Alzheimer (DTA) u otras enfermedades cognitivas. El uso de la fMRI en el SD ha proporcionado datos notables que justifican un estudio más profundo del funcionamiento del cerebro en esta población. Básicamente, los trabajos anteriores muestran que en el SD hay un aumento de la conectividad entre redes (es decir, hiperconectividad) caracterizada por una conectividad positiva incluso en las regiones que en los grupos de control son negativas; como consecuencia, hay una clara disminución de la anticorrelación (Anderson et al., 2013; Vega et al., 2015; Wilson et al., 2019).

Teniendo en cuenta los estudios citados, uno de los propósitos de este estudio fue establecer las redes de conectividad efectiva y dinámica de un grupo de SD y otro de control, emparejados por edad y género, utilizando SEM. En un paradigma de estado de reposo y sólo en una parte del DMN (6 ROI's). También se identificó si hay un patrón diferente entre ambos grupos y, finalmente, se evaluó la posibilidad de usar esos patrones para discriminar entre grupos.

Debido a los resultados y a la evidencia de los trabajos mencionados, se formularon las siguientes hipótesis: a) Las personas con SD mostrarán patrones de conectividad en la red DMN mucho más complejos que los que caracterizan al grupo de control y b) Los modelos SEM de cada grupo mostrarán estos efectos y se confirmará que podría ser un biomarcador que informe sobre un proceso fisiológico o fisiopatológico que este alterando la funcionalidad de la red.

1.2 Conectividad Funcional Estática y Conectividad Efectiva Dinámica

La conectividad funcional parte de un constructo estadístico, en donde se relacionan redes neuronales especialmente remotas que muestran cierta interrelación. Es determinada a través de la

dependencia estadística, que se puede calcular a partir de medidas de correlación o covarianza. Por tanto, hace suposiciones acerca de la biología subyacente e hipotetiza que las diferencias de conectividad se traduzcan a déficits neurocognitivos, en donde si existe una adecuada conectividad es porque hay una activación reducida en un área del cerebro; en cambio en donde existe pobre conectividad, habra una activación elevada por el sobre esfuerzo.

La conectividad funcional se hace entre todos los elementos del sistema, independientemente si todos están conectados o no pero que son altamente dependientes en el dominio temporal. Cabe decir que no hace referencia a efectos direccionales específicos de causa-efecto, o a un modelo estructural implícito. Con este enfoque, es posible medir las variaciones en la imagen de la intensidad de la señal, asociadas a los cambios hemodinámicos presentes en BOLD y llevados a cabo durante el estado de reposo. Las redes funcionales generadas bajo estas condiciones se denominan redes "resting-state", de las cuales se sabe que aproximadamente un 60-80% del consumo metabólico del cerebro se debe a la actividad intrínseca de estas redes (de la Iglesia-Vayá et al., 2011).

Los principales análisis para estudiar la integración funcional utilizaban PCA para descomponer los datos no correlacionados mutuamente, ni en el espacio ni en el tiempo. Sin embargo, ahora el uso de *ICA* facilita que se describa la actividad en una red, cuando no se conoce qué regiones están implicadas en una tarea determinada o la conectividad estructural implícita (Goldman & Cohen 2003; Kiviniemi et al., 2003; Greicius et al., 2004).

Por tanto, con la conectividad funcional estática se supone que las relaciones de las redes de conectividad son constantes en todo momento, que hay una estacionariedad espacial y temporal a lo largo del período de medición de la duración del registro; esto puede ser conveniente si se quiere evitar hacer un análisis complejo y con una excesiva simplificación.

Existe otra forma de considerar la conectividad funcional y es desde una perspectiva dinámica, en donde toda la serie temporal de la señal filtrada puede ser objeto de ser fraccionada siguiendo un criterio de maximización de una función externa que explique la variabilidad de la señal a lo largo del registro (Hoppensteadt & Izhikevich 1999).

La conectividad funcional dinámica es más prominente en estado de reposo, durante la cual la actividad mental no tiene restricciones, puesto que está bien establecido que los individuos participan libremente en varios tipos de actividad mental durante los períodos de descanso (Delamillieure et al., 2010). Por ejemplo, al indicar a los participantes que dentro del resonador mantengan los ojos cerrados, abiertos o fijos, alteran el contenido espectral de la actividad espontánea y los patrones de conectividad funcional en los núcleos subcorticales, la corteza sensorial y las regiones del modo predeterminado (McAvoy et al., 2008; Yan et al., 2009; Wu et al., 2010).

Diversas investigaciones (Chang & Glover, 2010; Kiviniemi et al., 2011; Hutchinson et al., 2012), han demostrado que la conectividad funcional dinámica en estado de reposo muestra la naturaleza variable en el tiempo tanto de la fuerza de conectividad como de la direccionalidad, si es positiva o negativa. Lo cual puede generar una nueva comprensión de las diferencias de conectividad funcional encontradas en enfermedades neuropsiquiátricas como la Enfermedad de Demencia tipo Alzheimer (Jones et al., 2012), el autismo (Starck et al., 2012) y la esquizofrenia (Sakoğlu et al., 2010).

Para el análisis estadístico en la conectividad funcional dinámica, se suele usar el método de las ventanas de tiempo deslizante o móviles (Allen et al., 2014; Hutchison et al., 2013; Hindricks et al., 2016; Yaesoubi, Allen, Miller & Cahoun, 2015; Chang & Glover, 2010) que consiste en dividir de las imágenes funcionales, los volumenes cerebrales registrados durante la sesión de fMRI en estado de reposo, en ventanas móviles que sean útiles para calcular la variación temporal del registro

de la señal. Sin embargo, Hutchison et al. (2013) puntualiza que la validez de los resultados extraídos del análisis mediante ventanas móviles puede estar afectado por la elección de la longitud de la ventana, así como por la elección de los parámetros del filtro de banda de la señal y el impacto de las fuentes de ruido.

1.3 Teoría de Redes Complejas

1.3.1 Red por defecto en estado de reposo DMN

A principios del siglo XX se creía que el cerebro era eléctricamente activo sólo durante una tarea que requiriera atención o actividad física. No se concebía la idea que a partir de estar en reposo sin ninguna actividad en concreto, el cerebro hiciera conexiones importantes y no sólo de plasticidad cerebral, sino de trabajo neuronal por medio de redes.

Es así, como la neuroimagen, al buscar en la conectividad funcional la descripción de la relación entre los patrones de activación neuronal de las regiones cerebrales que anatómicamente están separadas, identifica la comunicación funcional que hay entre las regiones.

Por ello, a partir de las investigaciones pioneras como la de Biswal et al. (1995), se concibe que nuestro cerebro es una red, que tiene regiones distribuidas espacialmente, pero vinculadas funcionalmente y que comparte información entre sí. Prueba de ello, es la detección de las primeras fluctuaciones espontáneas en el cerebro de redes distribuidas espacialmente dentro de la corteza motora primaria durante el reposo, calculando las correlaciones temporales en todo el cerebro con el curso del tiempo y a partir del vóxel semilla (Beckmann et al., 2005).

Marcus Raichle et al. (2001), por su parte y con estudios relacionados a estas fluctuaciones, identificó que el mayor gasto de esa energía se encuentra en el estado de reposo, al señalar que solo el peso corporal es del 2%, gasto cardíaco y flujo sanguíneo 15%, consumo de oxígeno 20% y

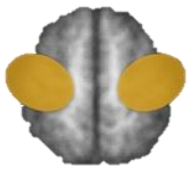
glucosa 25%. Además, sus hallazgos demostraron que existe un conjunto de regiones cerebrales que se activan, pero qué con la ejecución de una tarea, la actividad en esa red disminuye; esa red a la que hacen referencia y que se mide a través de la señal BOLD la denominaron Default Mode Network (DMN).

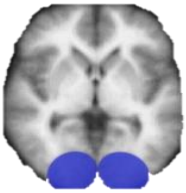
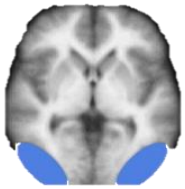
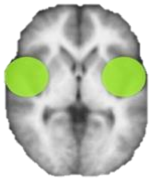
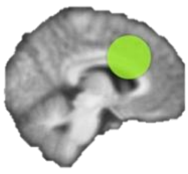
Posteriormente y de acuerdo a varios estudios que reprodujeron los resultados pioneros, identificaron altos niveles de conectividad funcional en diversas regiones de otras redes funcionales conocidas como: red visual primaria, red auditiva y redes cognitivas de orden superior (Biswal et al. 1997; Cordes et al. 2002; Damoiseaux et al. 2006; De Luca et al., 2005; Fox & Raichle, 2007; Grecius et al., 2003; Lowe et al., 2000; Van den Heuvel et al., 2008a).

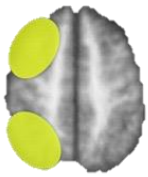
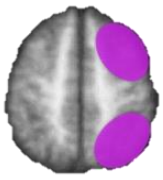
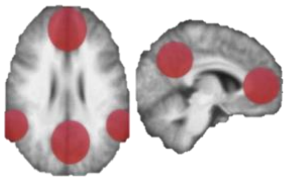
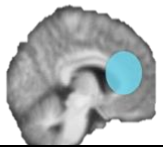
Actualmente hay más de ocho redes en estado de reposo, que cubren más del 80% de la corteza cerebral. Tabla 2.

Tabla 2

DMN y hallazgos de subredes

Red	**Autores que las refieren en sus estudios**	**Regiones cerebrales involucradas**	**Ilustración**
Motor Primaria	Biswal et al. 1995 Beckmann et al. 2005 De Luca et al. 2006 Damoiseaux et al. 2006 Salvador et al. 2005a Van den Heuvel et al. 2008a	Activación giro pre y poscentral, desde la fisura de Silvio hasta la pared media de la fisura interhemisférica.	

Visual Primaria	Beckmann et al. 2005 De Luca et al. 2006 Damoiseaux et al. 2006 Salvador et al. 2005[a] Van den Heuvel et al. 2008a	Surco bilateral de la calcarina, regiones extraestriadas mediales, pero no laterales, como el giro lingual, división inferior de la corteza del precuneo, núcleo geniculado lateral del tálamo conectado con el lóbulo occipital.	
Visual extra-estriada	Beckmann et al. 2005 De Luca et al. 2006 Damoiseaux et al. 2006 Salvador et al. 2005[a] Van den Heuvel et al. 2008a	Lóbulo occipital que se extiende hacia la unión occipito-temporal, abarcando regiones no primarias de la corteza visual. Activación dorsal en regiones parietales superiores.	
Bilateral Insular-temporal corte cingular anterior	Beckmann et al. 2005 De Luca et al. 2006 Damoiseaux et al. 2006 Van den Heuvel et al. 2008a	Abarca la activación cortico-auditiva primaria y secundaria, giro de Heschl plano polar y plano temporal, giro temporal superior y cortex insular posterior, activación adicional en corteza cingular anterior, supramarginal anterior al giro y tálamo.	 

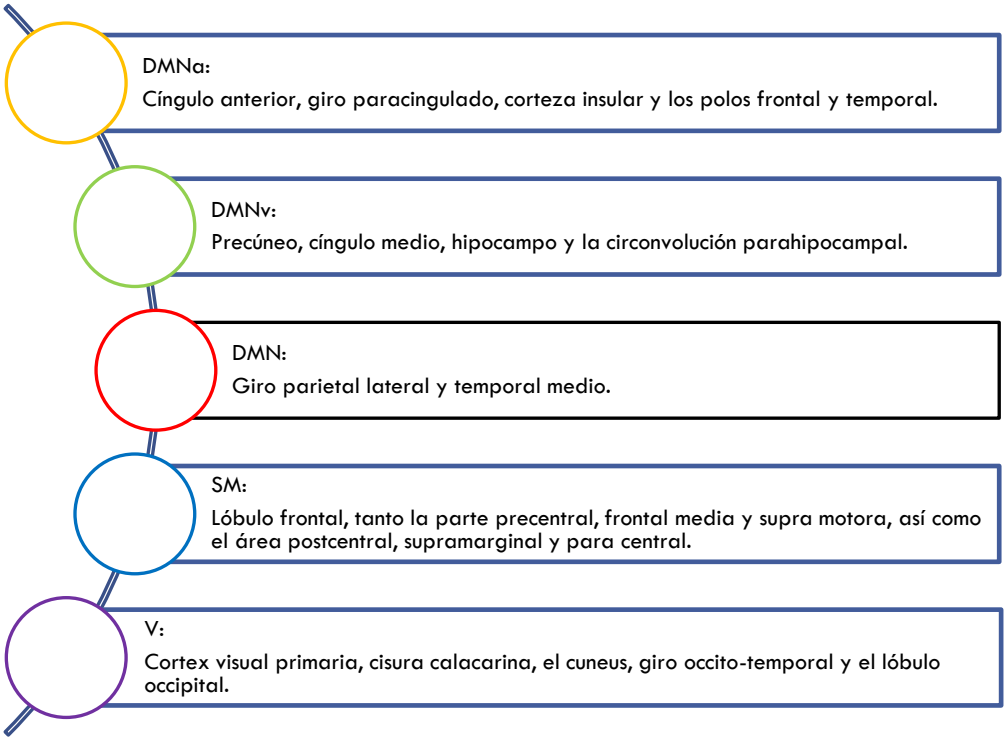
Hemisferio izquierdo fronto-parietal	Beckmann et al. 2005 De Luca et al. 2006 Damoiseaux et al. 2006 Van den Heuvel et al. 2008a	Frontal medial y orbital izquierdo. Parietal superior, giro temporal medio y cíngulo posterior	
Hemisferio derecho fronto-parietal	Beckmann et al. 2005 De Luca et al. 2006 Damoiseaux et al. 2006 Van den Heuvel et al. 2008a	Frontal medial y orbital derecho. Parietal superior, giro temporal medio y cíngulo posterior.	
Default Mode Network	Beckmann et al. 2005 Damoiseaux et al. 2006 Van den Heuvel et al. 2008a	Precuneus, media frontal, corteza inferior parietal y lóbulo temporal medial.	
Frontal	Damoiseaux et al. 2006 Van den Heuvel et al. 2008a	Giro fronto medial y giro frontal superior.	

Nota: Las redes en estado de reposo que se presentan son de acuerdo a estudios que aun teniendo diferentes protocolos de adquisición de imágenes y métodos de medición, coinciden en encontrar redes en estado de reposo funcionalmente vinculadas en el cerebro.

De entre todas las aproximaciones a la conectividad funcional con fMRI en estado de reposo, cabe destacar los trabajos recientes dedicados a la estimación de la DMN, que a través de una categorización más general, muestran cinco redes: Corteza Prefrontal Medial, Estructuras Temporales Inferiores, Corteza Cingulada Posterior, Precuneo y Giro Angular Bilateral (Spreng & Andrews-Hanna, 2015), las cuales se dividen en subredes: DMN anterior (DMNa), DMN ventral (DMNv), DMN posterior (DMN), sensoriomotora (SM) y la red visual (V) (Farras-Permanyer et al., 2019) Ver Figura 5.

Figura 5

Subredes de la DMN



Nota: Default Mode Network anterior (DMNa), Default Mode Network ventral (DMNv), Default Mode Network posterior (DMN), Sensoriomotora (SM) y Visual (V). Los colores de los círculos son representativos de cada una de las subredes, posteriormente en los resultados de los estudios se identificaran así.

Todas las regiones que participan en todas las redes funcionales interactúan continuamente entre sí, cuando el cerebro está en reposo, con la misma jerarquía funcional que controla toda la acción y la cognición del cerebro.

De acuerdo con estudios de Gusnard & Raichle (2001), la DMN al tener altos niveles de conectividad tanto funcional como estructural, así como altos niveles de actividad metabólica en situación de reposo, se puede encontrar en personas sanas. Por tanto, la importancia de la detección de la DMN está asociada a estados de salud en estado de reposo y las excepciones a esta activación

se asocian a patologías con profunda afectación cognitiva, como es el caso de la Demencia Tipo Alzheimer (DTA) (Sinai et al., 2016; Yi et al., 2015).

Además, existe la evidencia de que la relación entre la conectividad funcional frente a la conectividad estructural en estado de reposo, es la interconexión de tractos de materia blanca en la corteza cingular posterior y en el lóbulo temporal medial (Greicius et al., 2009), en concordancia, las regiones que muestren mayor nivel de conectividad estructural a su vez tendrán un mayor nivel de conectividad funcional (Hagmann et al., 2008; Honey et al., 2007, 2009).

1.3.2 Teoría de grafos

Ante el análisis que se hace en conexiones funcionales específicas entre regiones cerebrales concretas, recientemente se busca ahora explicar cómo se organizan las conexiones funcionales entre las regiones cerebrales, a través de la teoría de grafos.

Es una rama de las matemáticas que se remonta al siglo XVIII. Contribuye a trazar un mapa del cerebro desde la estructura a la función, a través de examinar la topología de redes complejas que puede revelar información importante sobre la organización local y mundial de las redes cerebrales funcionales (Bullmore & Sporns, 2009; Sporns et al., 2004; Stam et al., 2009 y Stam & Reijneveld, 2007).

Una red compleja (compuesta por muchas partes, que tienen su propia estructura interna y una función determinada), se define como un conjunto de nodos o vértices (nodes o vertex) unidos entre ellos mediante aristas o enlaces (edges o links).

Una red compleja es un grafo, el cuál es identificado como: $G = (V, E)$, siendo V el conjunto de nodos que refleja las regiones cerebrales y E las conexiones funcionales entre estas regiones cerebrales.

Los nodos de la red son las representaciones de somas de neuronas individuales o de áreas de volumen cerebral y los aristas o enlaces son la correlación que existe entre los nodos, pueden representarse como un pequeño número de regiones cerebrales a gran escala basadas en una plantilla cortical predefinida, que de acuerdo al propósito del análisis se puede interpretar como áreas de Brodmann, voxeles o regiones de interés (ROIs).

El nivel de conectividad funcional entre dos regiones se calcula como el nivel de correlación entre las dos regiones cerebrales.

El cálculo del nivel de conectividad funcional entre todos los pares de nodos posibles y la determinación de la existencia de una conexión funcional, mediante el uso de un umbral de corte predefinido o mediante un enfoque ponderado, da lugar a una representación gráfica de la red cerebral funcional y permite examinar su organización mediante la teoría de grafos.

Lo que permite caracterizar los aspectos de la conectividad son las métricas en redes que estudian la integración (estimar la facilidad con que las regiones cerebrales se comunican normalmente y se relacionan), la segregación (cuantifican la presencia de grupos de regiones cerebrales densamente interconectados, llamados clústeres o módulos) y las métricas de centralidad (miden la importancia relativa de un nodo o arista dentro de la arquitectura de la red). Existen otras métricas como la densidad, el Small World, la entropía y la complejidad que también pretenden conocer a profundidad las redes complejas. Ver Tabla 3.

Tabla 3

Algunos indicadores de la teoría de grafos estimados para determinar las características de cada red analizada.

Métricas	Descripción	Fórmulas
Integración funcional (FI)		
Numero de comunidades	Número de comunidades independientes detectadas en un grupo específico de ROIs. Estimación del número máximo de agrupaciones estadísticamente significativas en relación con una red aleatoria.	
Media de path-length	El path length de un nodo i (L_i) es el número medio de aristas que se deben cruzar para ir del nodo i al resto de nodos de la red.	$Li = \sum_{i \epsilon N} \left(\frac{1}{n-1} . \sum_{j \epsilon N, j \neq i} dij \right)$ Donde N es el número total de nodos de la red, n es el número de nodos implicados y d_{ij} es el shortest path length entre el nodo i y j.
Desviación estándar de path-length	El characteristic path length es una medida global de la red, es decir, que solo hay un valor para la red entera. Consiste en la media del path length de cada nodo de la red. Proporciona información sobre el nivel de conectividad global de la red y sobre cómo puede integrarse información eficiente entre los diversos sistemas.	$L = \frac{1}{N} \sum_{i \epsilon N} Li$
Segregación funcional (FS)		
Clustering Coeficiente Global	Es el valor medio del coeficiente de clustering, es decir, la fracción de triángulos de alrededor de un nodo y	$C = \frac{\sum \Gamma i}{\sum ki(ki-1)}$

	es equivalente a la fracción de vecinos del nodo que son vecinos entre ellos. Indica el nivel de conexión local de un gráfico.	
Número de triángulos	Se trata del número de triángulos conectados que se pueden estimar dentro de una red en un espacio euclidiano.	$G = (V, E)$ Es una pareja ordenada en la que *V* es un conjunto no vacío de vértices y *E* es un conjunto de aristas. Donde *E* consta de pares no ordenados de vértices tales como $\{x, y\} \in E$, entonces se dice que *x* e *y* son adyacentes.
Otras medidas		
Densidad	La densidad de la red (D) es el número de aristas existentes en el grafo en proporción al número total de posibles aristas.	$D = \frac{K}{N(N-1)}$ Donde K es el número de aristas existentes en la red y N es el número total de nodos en la red.
Small World (WS)	Redes que presentan un coeficiente de clustering mayor que lo esperado por azar y que, además, tienen un corto path lenght característico.	$S = \frac{Cnorm}{Lnorm} = \frac{C/Crandom}{L/Lrandom}$ Se dice que una red representa este tipo de organización si el índice calculado es superior a 1.
Entropía	Es una medida dentro de la conectividad efectiva que mide el flujo de información dirigida.	Estimation of Von Neumann index H(X) = E(I(X)) – expected information of a random variable. I(X) = ln[1/P(X)] and so H(X)=-E(ln[P(X)].

Complejidad	Es el número de nodos y los pasos alternativos que existen entre redes específicas.

Nota: Algunos de estos indicadores fueron seleccionados de Rubinov & Sporns (2010) para fines del estudio y son: coeficiente de agrupación (clustering-coefficient), la longitud característica del recorrido de un grafo (characteristic path-lengt), grado de un nodo (connectivity degree), entropía, número de triángulos, número de comunidades, complejidad, y redes del mundo pequeño (small-word).

La teoría de grafos propone que el cerebro humano no solo es una red aleatoria, sino una organización topológica de Small Word altamente eficiente y rentable, organizada de manera optimizada hacia un alto nivel de eficiencia local y global a través de los diferentes subsistemas de la red cerebral (Rubinov & Sporns, 2010).

Capítulo 2.
Personas con síndrome de Down

Personas con síndrome de Down

2.1 Características generales

El síndrome de Down (SD por sus siglas en español y DS por sus siglas en inglés) es la causa genética que más comúnmente se conoce por su condición y está asociada con la discapacidad intelectual, además de estar caracterizado por una variedad de hallazgos clínicos adicionales. Ocurre en aproximadamente 1 de 800 nacimientos en todo el mundo (Marylin & Bull, 2020). En México la incidencia es de aproximadamente uno por 691 nacimientos al año (Sistema Nacional para el Desarrollo Integral de la Familia [DIF], 2020). En España la incidencia cada vez es menor, actualmente 150 corresponden a personas con SD al año (Pascual, 2019).

Hay una considerable variación fenotípica entre los sujetos, y la discapacidad intelectual es más comúnmente moderada, pero va de leve a grave, mientras que la función social suele ser alta en relación con el par cognoscitivo. Existe incidencia y presentación del SD según el origen étnico y la región geográfica (Marylin & Bull, 2020); los apoyos, recursos y accesos a los servicios de atención tanto hospitalaria como educativa son fundamentales, sin dejar de lado el aspecto cultural de inclusión.

En 1866 se hizo la descripción del síndrome por John Langdon Down (Down, 1867), un médico de Cornwall (Inglaterra), sin embargo, no fue hasta 1932 cuando Davenport sugirió que las irregularidades cromosómicas podrían originar ciertas formas de discapacidad intelectual, entre ellas el síndrome de Down. En 1956, con las técnicas disponibles se pudo establecer con carácter definitivo que el número normal de cromosomas humanos es de 46, y un año más tarde Jérôme Lejeune descubrió que en el síndrome de Down existía un cromosoma extra perteneciente a la pareja de cromosomas 21 (HSA21) (Lejune et al., 1959), con lo cual se constató la diferencia cromosómica de la afección. (Allen et al., 1961; Gautier, 2009).

La causa del SD es una tercera copia del cromosoma 21, llamado trisomía 21. Esta es producida por una disyunción, con la presencia de 47 cromosomas, o por translocación de un cromosoma 21 adicional a otro cromosoma. Las características clínicas no difieren entre las dos causas de la trisomía 21. Existen otros dos diagnósticos genéticos que suelen estar asociados con menos características clínicas de SD, una de ellas es el mosaicismo de la trisomía 21 y otro la trisomía parcial 21. Tabla 4.

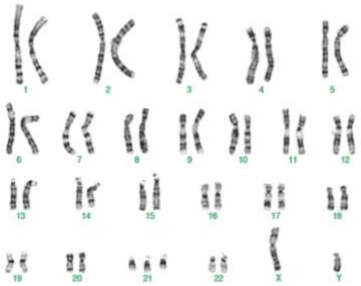
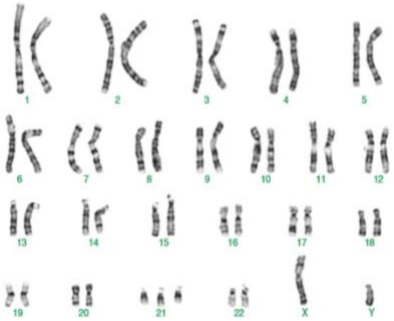
Desde el primer trimestre de gestación, con el seguimiento prenatal, se puede solicitar el abordaje diagnóstico, asesoramiento genético y vigilancia hasta el nacimiento (DPSD, 2010).

No obstante, el diagnóstico confirmatorio suele ser postnatal, con el apoyo de un examen físico y de un clínico experimentado que reconozca las características fenotípicas, así como las enfermedades comórbidas que suelen estar acompañadas, como la hipotonía muscular.

El examen físico es apoyado por el estudio del careotipo pediátrico, que se aplica al mes de nacimiento para identificar el tipo de aneuploidía cromosómica que asevere la existencia del síndrome de Down.

Tabla 4

*Base cromosómica del síndrome de Down**

Características cromosómicas	Descripción	Porcentaje de casos	Careotipo*
Disyunción meiótica	Ocurre en el óvulo en el 95% de los casos y el riesgo aumenta con la edad de la madre.	96%	
Traslocación	Normalmente se produce con un cromosoma 21 unido al cromosoma 14, 21 o 22. En la traslocación del 14/21, 1 de cada 3 casos involucra a un portador paterno; en el 90% de esos casos, el portador es la madre; En la traslocación del 21/21, 1 de cada 14 casos involucra a un portador paterno; en el 50% de esos casos, el portador es el padre.	3-4%	
Mosaicismo	El número de células afectadas varía de una persona a otra; hay menos complicaciones médicas y a menudo la discapacidad intelectual es menos grave que en los casos	1-2%	

	caracterizados por el mosaicismo.	
Trisomía parcial	La duplicación de un segmento delimitado del cromosoma 21 está presente.	<1%

Nota: *La información procede de Hook (1982) en relación con la no disyunción y traslocación de la meiótica, Papavassiliou et al. (2015) en relación con el mosaicismo, y Pelleri et al. (2016) con la trisomía parcial, en Bull, M. J. 2020. Las figuras son de Tolmie (2013).

Las características fenotípicas más comunes del Síndrome son: fisuras palpebrales inclinadas hacia arriba, puente nasal plano, pliegues en la nuca, pliegue palmar único de flexión, clinodactilia del quinto dedo e hipotonía. En algunos casos, tienen comorbilidad con hipertensión arterial, hipotiroidismo, trastornos de las vías respiratorias (apnea obstructiva del sueño), reflujo gastroesofágico, obesidad, trastornos muscoesqueléticos (dislocación de la cadera), enfermedades cardíacas (Marylin & Bull, 2020) y tienen características histopatológicas de la enfermedad de demencia tipo Alzheimer (DTA) después de los 40 años (Wiseman et al., 2015), que los hace tener un mayor riesgo en desarrollarla en comparación con la población en general.

En cuanto a la esperanza de vida, en 1973 era de 30 años y desde el 2002 es de 60 años (Glasson et al. 2014). La causa más común de muerte en la infancia y la edad adulta son las infecciones respiratorias, en parte relacionada con las inmunodeficiencias. La demencia contribuye a la mortalidad en algunos estudios (Marylin & Bull, 2020).

2.2 Neuropsicología en personas con síndrome de Down

Desde una visión fisiológica y neuroanatómica, se identifica que el cerebro de personas con DS tiene como consecuencia de la alteración genética, afectaciones estructurales que varían en

cuanto a la intensidad entre un individuo u otro. Lo que hace manifiesto posibles trastornos cognitivos. Ver Tabla 5.

Tabla 5

Alteraciones cerebrales en el síndrome de Down

Nivel de alteración	Descripción	Consecuencia
Cerebral	Cortical: disminución en el tamaño del lóbulo frontal, amígdala e hipocampo	Fallos en memoria operativa a largo plazo de tipo semántico, disfunción ejecutiva, menor capacidad de atención, así como de cambiar de tarea, con mayor tendencia a la conducta repetitiva.
	Subcortical: hipoplasia en cerebelo	Hipotonía, retraso en la coordinación motora, alteraciones en la marcha, dificultades del habla (problemas de artículación e inteligibilidad como disartria atáxica).
Neuronal	Neurogenésis imperfecta	Hipocelularidad en determinadas líneas celulares, así como del tamaño global de las neuronas (en el número de expansiones dendríticas.
	Apoptosis	Simultanea iniciación de procesos de muerte neuronal.
Neuroquímico	Neurotransmisores alterados	Dopamina, taurina, histamina y GABA. Niveles bajos en aspartato, glutamato, serotonina y noradrenalina en diversas áreas del cerebro adulto.

Nota: Como consecuencia de la alteración génetica (un cromosoma de más en el par 21), genera de forma ascendente una disminución o alteración desde una base a nivel neuroquímico, en los neurotransmisores que repercute a nivel neuronal y por ende a nivel cerebral (Flórez et al. 2015).

Estas anomalías encontradas en las personas con SD, trae como consecuencia procesos cognitivos afectados, como lentitud en la velocidad del aprendizaje, coeficiente intelectual de moderado a severo, con un cociente intelectual (CI) de 50 a 70 (Parker et al., 2010), que declina con la edad y que se manifiesta cuanto más exigentes sean las tareas a ejecutar, algunos problemas en memoria explícita verbal a corto plazo, más que en memoria implícita, pobre codificación de la información, alteraciones en su capacidad de recuperación o evocación, déficit de atención y en lenguaje hay retraso en el desarrollo en aspectos fonológicos y sintácticos del habla como en la articulación e imitación vocal.

En personas con SD se ha demostrado que, debido a las características interindividuales, existe una variabilidad en el deterioro cognitivo (Nieuwenhuis-Mark, 2014) y que se manifiesta en función de las exigencias de la tarea a realizar y del instrumento de evaluación (Stanton & Coetzee, 2004).

Los déficits cognitivos encontrados en personas con SD, especialmente en las funciones verbales o ejecutivas, se asocian con un bajo rendimiento en la inteligencia verbal y, por lo tanto, están asociados con deterioros del lenguaje (Næss et al., 2011) y funcionamiento ejecutivo (Lanfranchi et al., 2010). Esto se ha asociado con el desarrollo deteriorado de la corteza prefrontal y puede ser una indicación de AD (Rowe et al., 2006). Sin embargo, no hay ninguna referencia a los estudios que identifican las redes que pueden estar involucradas en este proceso.

2.3 Discapacidad Intelectual en personas con síndrome de Down

De acuerdo a Schalock (2011) y posteriormente la AAIDD (American Association on Intellectual and Developmental Disabilities), la discapacidad intelectual es un estado individual que se caracteriza por presentar limitaciones significativas tanto en el funcionamiento intelectual como en la conducta adaptativa, que puede ser originada antes de los 18 años de edad. Además refiere que se tienen que tener en cuenta cinco premisas para definirlo, las cuales son: 1) considerar las limitaciones en el contexto de ambientes comunitarios ordinarios en personas con edad y cultura iguales, 2) tener en cuenta la diversidad cultural y lingüística, así como las diferencias en la comunicación, como en aspectos conductuales, motores y sociales, 3) identificar las capacidades que coexisten con las limitaciones, 4) identificar el perfil de necesidades de apoyo y 5) mantener apoyos personalizados apropiados durante un largo período. Ante esto, la discapaciad viene determinada más por el contexto en el que se desenvuelve, que no por una baja inteligencia.

Por otro lado, converge el concepto de inteligencia, definada como la capacidad mental general que comprende las siguientes funciones: razonamiento, planificación, solución de problemas, pensamiento abstracto, comprensión de ideas complejas, el aprendizaje con rápidez y el aprendizaje a partir de la experiencia (Gottfredson, 1997).

La inteligencia comienza por ser una función biológica, por lo que cada persona nace con un límite o techo intelectual determinado por la herencia (Flórez et al., 2015), que mucho dependerá del contexto y de la estimulación cognitiva para potencializarla.

En recientes estudios de neuroimagen, se ha identificado que la inteligencia esta incrustada no solo en una red cerebral única, sino más bien en una organización compleja de redes cerebrales comunicantes (Ponsola et al., 2016). La inteligencia es el resplado de una variedad de mecanismos

neuronales complejos que involucran una red interactiva de registros, particularmente en ganglios basales, corteza prefrontal y parietal (Jiang et al., 2020).

En cuanto a las personas con SD, hay estudios que han examinado las relaciones cerebrales específicas, como el tamaño en comparación con controles emparejados por edad y rendimiento en pruebas de inteligencia y lenguaje; revelando que en personas con DS la inteligencia en general y el dominio de conceptos lingüísticos se correlacionan negativamente con el volumen del giro hipocampal, pero que esto no guarda relación con el tamaño total del cerebro ni con variables cognitivas (Raz et al., 1995; Menghini et al., 2011).

La estimación de la edad mental en la población de SD ha sido ampliamente estudiada y también es muy controvertida debido tanto a la ausencia de instrumentos específicos para este fin como al uso del CI para definir el grado de discapacidad intelectual (Dierseen, 2012 y Lanfranchi et al., 2015). Dado que es una medida que implica el registro del rendimiento cognitivo, puede enmascarar déficits específicos debido a su naturaleza tan heterogénea.

En los últimos años, ha habido un creciente interés en facilitar este cálculo, puesto que, en la última versión de la prueba de referencia mundial para la estimación de cociente intelectual en niños (WISC-V), se ha incorporado la planificación del cálculo de la edad mental de una manera fácil y sin complicaciones. Sin embargo, en el caso en que nos encontramos, con una muestra de personas con discapacidad intelectual, las dificultades para encontrar una prueba válida y fiable para la estimación de la edad mental son muchas (Edgin et al., 2010 & Hamburg et al., 2019). Entre ellos se encuentran el efecto de base, el hecho de que se centra en evaluar sólo las habilidades del lenguaje, la baja sensibilidad de las medidas para detectar algunos efectos, la poca flexibilidad de uso en todas las culturas e idiomas, la aplicación en un rango de edad cronológica que no conduce

directamente a un ajuste para la edad mental y, por último, la falta de validación psicométrica en poblaciones con discapacidades del desarrollo (Edgin et al., 2010).

Inicialmente, se ha propuesto el uso de WISC-V para la estimación del cociente intelectual en la población adulta con SD. El objetivo que buscan es aliviar el efecto del suelo y esperar que un valor de cociente intelectual de aproximadamente 70 puntos pudiera representar una gran parte de la población. Sin embargo, a pesar de las facilidades mostradas por la prueba WISC-V para la evaluación de las subescalas implicadas en las tareas de cálculo mental, no parece adecuado para la evaluación integral de personas con SD por diversas razones, pero dos en particular: 1) existe una dificultad para entender los elementos con un alto contenido verbal; y 2) es una prueba con un rango de edad muy limitado (entre 5 y 16 años). Por lo tanto, creemos que la estimación de la edad mental debe abordarse desde otra perspectiva (Ripoll, 2001).

En un estudio de Hamburg, et al. (2019), se llevó a cabo una revisión sistemática de la literatura sobre las diferentes pruebas de cociente intelectual para adultos con SD, y de todas ellas la que se identificó con menos problemas de efecto suelo fue la prueba KBIT, incluso para poblaciones muy extremas (por ejemplo, con demencia). Por lo tanto, la prueba KBIT fue elegida porque amplía el rango de edades cronológicas y porque implica menos tiempo para la aplicación, en vista de que, sólo hay dos subescalas: inteligencia verbal (con el vocabulario expresivo y definiciones subprueba) y la inteligencia no verbal (con la subprueba matrices), que se encuentra dentro del rango estimado de tiempo de concentración (aproximadamente 30 minutos), lo cual reduce la fatiga de la persona evaluada.

2.4 Demencia tipo Alzheimer y en personas con síndrome de Down

Es característico de las personas con SD que el envejecimiento sea prematuro, aunque su esperanza de vida esté en aumento. Lo que lo hace evidente es el declive en funciones cognitivas que posterior a los treinta años se suelen presentar como signos de alarma incipiente: déficit en comprensión verbal, aislamiento social, pérdida de interés y mayor fatiga para realizar tareas (Ghezzo et al., 2014). El argumento son los signos neuropatológicos que aparecen avanzada la edad de los cuarenta años: deposición de placas amiloides seniles y ovillos neurofibrilares en amígdala, hipocampo, áreas de asociación de la corteza frontal, temporal y parietal (Holland & Oliver, 1995). Por tanto, el deterioro cognitivo está presente en circuitos neuronales de estructura fronto-subcortical y temporal, en particular en la corteza prefrontal dorsolateral (flexibilidad mental), cíngulo anterior (pérdida de interés como el letargo) y en áreas fronto- mediales (generación de palabras).

La DTA es el paso posterior del deterioro cognitivo y está presente a los sesenta años de edad aproximadamente, a consecuencia de la triplicación y sobre expresión del gen β-amiloide que se sintetiza a partir de la proteína precursora amiloide (APP) (Ghezzo et al., 2014; Handen, 2020).

La importancia del diagnóstico diferencial radica en identificar que hay tres trastornos comunes que por su presencia podrían enmascarar la demencia, como coexistir con ella: depresión, hipotioridismo y disfunciones visuales o auditivas (Evenhuis, 1992). Para poder discernir ante esto y saber si cumple con los criterios diagnósticos de demencia, se puede aplicar la prueba DSQIID (Dementia Screening Questionnaire for individuals with intellectual disabilities) (Deb et al., 2007). Que entre sus bondades esta identificar predictores de demencia a partir de 20 ítems. Además, cuenta con una excelente fiabilidad, sensibilidad, especificidad entre evaluadores (Deb et al., 2007b; Parmenter, 2008).

Asi, Burt et al. (2000), sugieren que la mejor práctica para diagnosticar la demencia en personas con SD es: establecer una línea base del funcionamiento premórbido a la edad de 35 años y luego seguimiento con reevaluaciones anuales.

2.5 Default Mode Network en personas con síndrome de Down

En una revisión sistemática para evaluar la actividad cerebral en personas con DS (Carbó-Carreté et al., 2020), identificaron que no existe un establecimiento regular y estable típico en la conectividad funcional. Mancho-Fora et al. (2020) identificaron que en personas mayores sanas (< 75 años), hay menos conectividad dentro de la red, pero más entre las subredes que componen la DMN. Utilizaron indicadores de menor segregación, modularidad y eficiencia local. Los resultados obtenidos se asociaron con una mala función ejecutiva, memoria y velocidad de procesamiento (Andrews-Hanna et al. 2007). Esto refleja una pérdida progresiva de especialización dentro de las redes cerebrales relacionadas con funciones superiores (Antonenko & Flöel, 2014). En estudios de sujetos con diabetes tipo 1 y fMRI con una tarea (Gallardo-Moreno et al., 2015), no se encontraron diferencias en el rendimiento de las tareas en comparación con los sujetos de control, aunque sí encontraron una mayor conectividad cerebral en ciertas áreas donde esto podría interpretarse como un mecanismo compensatorio. En un estudio más reciente (Pedersini et al., 2020), al estudiar a pacientes con hemianopsia, atribuyeron a un mecanismo neuroplástico que los cerebros dañados se caracterizan por una reorganización de toda la red cerebral, expresada por ser menos segregada y con ganglios funcionales mal integrados. Estos efectos complejos también se han observado en sujetos con síndrome de Down (Anderson et al., 2013).

En vista de lo anterior, se han identificado patrones de relaciones negativas entre indicadores de complejidad de la red en conectividad funcional y variables de rendimiento cognitivo e indicadores de estado de salud, edad cronológica o estados de deterioro cognitivo como deterioro

cognitivo leve (MCI). Estos resultados sugieren que menos estructuras complejas se asocian con mejores estados de salud o rendimiento cognitivo. Se esperaría que este efecto resulte en el caso de SD, sin embargo; la gran variación detectada en las estructuras de DMN en la población con SD nos lleva a creer que este efecto se verá algo borroso por el efecto de las enormes diferencias individuales en la determinación de la red DMN entre sujetos. Por lo tanto, cabe esperar que la red DMN y sus subredes presenten valores en los indicadores de complejidad que, en el caso de las personas con SD, dificultan la obtención de relaciones estadísticamente muy relevantes (en términos de tamaño de efecto convencional) entre esos valores y el rendimiento cognitivo. El comportamiento bien conocido del efecto suelo en las pruebas psicométricas aplicadas a esta población contribuirá a estas consideraciones, así como a las dificultades experimentales que entraña el registro de señales fMRI en SD (Figueroa-Jiménez et al., 2020, Shehzad et al., 2009, Anderson et al., 2011).

Capítulo 3.
Justificación y objetivos del estudio

Justificación

Los estudios de neuroimagen han significado una verdadera revolución en el estudio de las funciones cognitivas. En los últimos años, los trabajos que utilizan señales cerebrales (EEG, PET, IRM o fMRI, entre otros) han aumentado considerablemente y han proporcionado una nueva forma de entender la función cerebral (Medaglia et al., 2015). Esto se debe a varias razones, aunque fundamentalmente podemos destacar la evolución tecnológica que permite medidas mucho más fiables del funcionamiento del cerebro y la necesidad de superar los paradigmas clásicos de evaluación psicológica de las funciones cognitivas.

Este tipo de estudio se ha aplicado a una multitud de poblaciones diferentes, tanto a nivel muy básico como aplicado (Chiesa et al., 2017). Entre estos últimos, los estudios con poblaciones de especial importancia clínica han abierto una nueva forma de entender el funcionamiento cognitivo asociado a determinados síndromes o diagnósticos clínicos y al declive causado por el envejecimiento. Son innumerables los estudios que pueden vincularse a esta idea (Karmiloff-Smith et al., 2016; Yildirim & Büyükiscan, 2019).

Sin embargo, una excepción a esto se encuentra en los trabajos con poblaciones o muestras con discapacidad intelectual (ID), especialmente cuando se utilizan señales de fMRI. En un examen sistemático, Carbó-Carreté et al. (2020) identificaron sólo 9 trabajos, de los cuales 7 utilizaron el paradigma de la tarea y 2 utilizaron la técnica del estado de reposo (rs-fMRI).

Por lo tanto, debemos abordar la baja producción de estudios de fMRI en personas con ID y más específicamente, en personas con SD. Creemos que la razón principal de esta situación es que se trata de una técnica de registro aún reciente, aplicada sobre todo a poblaciones con una incidencia más amplia. Sin embargo, se está extendiendo gradualmente a poblaciones adicionales, como las personas con SD. Las dificultades asociadas a este tipo de registro en esta población se centran en

1) la presencia de movimientos excesivos durante el registro, 2) la dificultad de configurar grupos de control, 3) bajos niveles de CI que impiden la realización de paradigmas con tareas más elaboradas por su nivel de comprensión, y 4) según nuestra experiencia, la falta de conocimiento y recelos por parte de los tutores legales y de las propias personas con SD para participar (Pujol et al., 2015).

Entre todos los enfoques de estudio de la conectividad cerebral con fMRI en estado de reposo, cabe destacar los trabajos dedicados a la estimación de la (DMN) (Wilson et al., 2019; Anderson et al., 2013). La cual según Horn et al. (2014), muestra altos niveles de conectividad tanto funcional como estructural y altos niveles de actividad metabólica en reposo en personas sanas (Gusnard & Raichle, 2001). Por lo tanto, la importancia de la detección de la DMN se asocia a condiciones de salud en reposo, y las excepciones a esta activación se asocian a patologías con un profundo deterioro cognitivo, como la demencia de tipo Alzheimer (DTA) (Yi et al., 2015; Sinai et al, 2016). Por tanto, parece importante establecer el funcionamiento de la DMN en las personas con SD, ya que tal estructura, hasta donde sabemos, sólo ha sido estudiada recientemente por Vega et al. (2015) y Wilson et al. (2019). El primer trabajo analizó las diferencias en la conectividad funcional del estado de reposo entre y dentro de la red para siete redes funcionales en los grupos de SD en comparación con el grupo de TD (típicamente en desarrollo) y el grupo de WS (Síndrome de Williams). Los resultados sugieren una diferencia global en la conectividad entre las redes en el grupo de SD en comparación con los controles a través de muchas regiones del cerebro.

El segundo trabajo (Wilson et al., 2019) mostró diferencias estadísticamente significativas entre un grupo de personas con SD en comparación con un grupo de control sano. En particular, los autores señalan que la activación de la corteza prefrontal media es mayor en los controles sanos y que el

efecto opuesto se presenta en la red de giro temporal medio, en la que la activación en los individuos con SD es algo mayor que en los controles sanos.

Es importante aclarar que cuando hablamos de una mayor activación en un área específica del cerebro, queremos decir que los valores de la señal son mayores en esa área en comparación con el otro grupo. Es obviamente un efecto de activación neuronal que la señal del fMRI detecta. Este último trabajo (Wilson et al., 2019) es especialmente importante ya que analizó una muestra de personas con SD en ausencia de beta-amiloide cerebral y, por lo tanto, libres de la deficiencia cognitiva asociada al SD. Sin embargo, en las muestras de personas con SD, el deterioro cognitivo sigue estando presente debido a la discapacidad intelectual. De hecho, ambos trabajos fueron realizados con adultos (rango de edad 30-55 años), y no hay pruebas obtenidas en personas más jóvenes.

Por otro lado, estudios en cuanto a indicadores de complejidad de la red en relación a variables del funcionamiento cognitivo, son poco frecuentes, específicamente si estos indicadores estimados se estudian en las subáreas de la red DMN, mucho menos se conoce si pueden ser predictores del resultado neuropsicológico para evaluar el cociente intelectual y el rendimiento cognitivo.

Ahora bien, es de interés estimar si la red desde el enfoque de la conectividad efectiva dinámica, con Modelos de Ecuaciones Estructurales (SEM), puede resultar ser un biomarcador al compararlo con un grupo control en el estudio de la complejidad de la red que informe sobre diferencias en la funcionalidad de la red.

Objetivos del estudio

Ante este panorama, poco explorado sobre todo en personas jóvenes con SD, el objetivo general de esta tesis doctoral conformada por tres estudios es: estimar los patrones de conectividad funcional y efectiva dinámica en un grupo de jóvenes con Síndrome de Down y otro control en situación de reposo, a través de indicadores de complejidad de la amplia red DMN en relación a pruebas neuropsicológicas y al estudio de redes de sistemas complejos.

Este objetivo general se desglosa en los siguientes objetivos específicos:

1. Estimar la red de conectividad funcional basada en DMN en estado de reposo en personas con SD.
2. Estimar indicadores de complejidad de la red DMN para explorar y describir el comportamiento del patrón de conectividad funcional que presentan los jóvenes con SD.
3. Analizar la relación entre algunos indicadores de complejidad de las subáreas que constituyen la amplia red DMN y las puntuaciones obtenidas en pruebas neuropsicológicas adaptadas para la evaluación del coeficiente intelectual y el rendimiento cognitivo en el marco de la fluidez verbal y el funcionamiento ejecutivo.
4. Describir la variación existente en las subáreas de la DMN de 48 regiones obtenidas del atlas AAL de 90 ROI utilizando descriptores del comportamiento de cada una de las redes DMN dentro del ámbito del estudio de redes de sistemas complejos.
5. Establecer las redes de conectividad efectiva dinámica de un grupo con SD y otro control, apareado por edad y género, usando SEM, y en situación de reposo y mediante el estudio de una parte de la DMN (6 ROI´s).
6. Identificar si existe un patrón diferente entre ambos grupos y, valorar la posibilidad de usar esos patrones para discriminar entre grupos.

Los 3 estudios que a continuación se presentan explican las redes de conectividad funcional estática y conectividad efectiva dinámica desde la óptica, de la neuropsicología y de las neurociencias en general. Los hallazgos se revelan con rigurosidad científica y con el uso de un vocabulario técnico sin excesos, para lo cual se ha añadido un glosario de terminología al inicio de la tesis. Por otro lado, cabe decir que estos estudios se presentan en formato completo y en idioma inglés tal cual se enviaron a publicar, el primero ha sido aceptado y los otros dos estan en revisión por la revistas.

Capítulo 4.

Studio 1: Resting-state Default Mode Network connectivity in young patients with Down syndrome.

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Studio 1:

Resting-State Default Mode Network Connectivity in Young Individuals with Down Syndrome.

Introduction

There is no doubt that neuroimaging studies have instigated a real revolution in the study of cognitive functions. In recent years, works using brain signals (EEG, PET, MRI, or fMRI, among others) have increased considerably and have provided a new way of understanding brain function (Medaglia et al., 2015). There are several reasons for this, although we can fundamentally highlight the technological evolution that allows much more reliable measures of brain functioning and the need to overcome classical paradigms of psychological assessments of cognitive functions.

This type of study has been applied to a multitude of different populations, both at a very basic level and an applied level (Chiesa et al., 2017). Among the latter, studies with populations of special clinical importance have opened a new way of understanding the cognitive functioning associated with certain syndromes or clinical diagnoses and the decline caused by aging. Countless studies can be linked to this idea (Karmiloff-Smith et al., 2016; Yildirim & Büyükiscan, 2019).

In relation to the different brain signals, the one that has been of most interest in the last ten years is the functional magnetic resonance imaging (fMRI) register. The reason for this preference may be because the fMRI signal allows the generation of representational and mathematical models of brain function, and though it is a somewhat cumbersome record, it is not as invasive as in other signals (Mak et al., 2017). In fact, the increase from the first work in 1994 to date has followed a growing monotonic function (Alegria et al., 2016; Engel et al., 1994; Fox et al., 2015).

However, an exception to this is found in works with populations or samples with intellectual disability (ID), especially when using fMRI signals. In a systematic review, Carbó-Carreté et al. (2020) identified only 9 papers, of which 7 used the task paradigm and 2 used the resting-state technique (rs-fMRI).

Therefore, we must address the low production of fMRI studies in people with ID and more specifically, in people with DS. We believe that the main reason for this situation is because this is a still recent registration technique, applied mostly to populations with a wider occurrence. However, it is gradually being extended to additional populations, such as people with DS. The difficulties associated with this type of recording in this population are centered on (a) the presence of excessive movement during recording, (b) the difficulty in configuring control groups, (c) low IQ levels that prevent the realization of paradigms with more elaborate tasks due to their level of understanding, and (d) according to our experience, the lack of knowledge and misgivings on the part of legal guardians and people with DS themselves (Pujol et al., 2015).

Among all the approaches to study brain connectivity with resting-state fMRI, the works dedicated to the estimation of the default mode network (DMN) should be highlighted (Anderson et al., 2013; Wilson et al., 2019). As is widely known, the DMN is a network of networks that is generally activated in a resting-state paradigm. The DMN is an anatomically defined brain area that usually activates when individuals are not centered in any external environment (Buckner et al., 2008). Specifically, it presents high intrinsic activity during resting-states without specific task engagement (Beckmann et al., 2005). There is some controversy regarding the act of recording the signal with eyes open or closed. This simple fact has generated various studies to assess the effect of eyes open or closed (Agcaoglu et al., 2019).

The DMN is configured by five networks characterized by the medial prefrontal cortex, medial temporal low structures, posterior cingulate cortex, precuneus, and angular gyrus bilaterally (Spreng & Andrews- Hanna, 2015). According to Horn et al. (2014), the DMN shows high levels of both functional and structural connectivity and high levels of resting metabolic activity in healthy people (Gusnard & Raichle, 2001). The importance of detecting the DMN is therefore associated with health conditions at rest, and the exceptions to this activation are associated with pathologies with profound cognitive impairment, such as Alzheimer's Disease (AD) (Sinai et al., 2016; Yi et al., 2015).

In view of the abovementioned factors, it seems important to establish the functioning of the DMN in people with DS since such a structure, to our knowledge, has only recently been studied by Vega et al. (2015) and Wilson et al. (2019). The first paper analyzes the differences in between- and within-network resting-state functional connectivity for seven functional networks in DS groups in comparison with TD (typically developing) and WS group (Williams syndrome). The results suggest a global difference in between-network connectivity in DS group compared with controls across many brain regions. The second paper (Wilson et al., 2019) shows statistically significant differences between a group of people with DS compared to a healthy control group. In particular, the authors point out that the activation of the medial prefrontal cortex is greater in healthy controls and that the opposite effect is present in the middle temporal gyrus network, in which the activation in DS individuals is somewhat greater than that in healthy controls.

It is important to clarify that when we speak of increased activation in a specific area of the brain, we mean that the signal values are higher in that area compared to the other group. It is obviously a neuronal activation effect that the fMRI signal detects. This last work (Wilson et al., 2019) is especially important since it analyzed a sample of DS people in the absence of brain beta-amyloid

and, therefore, free of the cognitive impairment associated with ATD. However, in samples of people with DS, cognitive impairment is still present because of intellectual disability.

In fact, both works were done with adults (age range: 30–55 years), and there is no evidence obtained in younger people. As these are adults with ATD, the covert diagnostic effect of ATD-associated DMN alteration cannot be avoided (Rubenstein et al., 2020). This effect is avoided when evaluating younger DS persons. Thus, studies of the DMN in younger DS individuals will allow analysis of the network with fewer effects not directly associated with DS.

The main objective of this study was to estimate the functional connectivity network based on the DMN in a resting state in young people with DS in comparison with the brain connectivity network in a group of healthy individuals with no DS. Second, we propose to estimate different indicators to explore and describe the behavior of the pattern of functional connectivity networks in the DS group and control group.

Materials and methods

Participants:

The initial sample was composed of a total of 35 persons with DS between 16 and 35 years of age (M=24.7 and SD=5.5), and 26.5% were women (n = 9). The sampling was opportunistic, and recruitment took place through contact with different associations dedicated to DS in the state of Jalisco (México) (63.6% of participants) and in Spain (36.4%). The inclusion criteria were as follows: a) age between 16 and 35 years old and b) formal diagnosis of DS including evidence of karyotyping results. The exclusion criteria were a) evidence of other comorbid diagnoses implying cognitive dysfunction, b) inability to obtain consent from legal caregivers, and c) the presence of medication affecting cognitive functions and d) the presence of translocation or mosaicism.

After recording the fMRI signal, ten of the subjects were eliminated due to excessive movement during the recording, and some of them were even removed for the same reason after having repeated the recording. Records with movement greater than ±2 degrees (or greater than half voxel size) were eliminated and not included in this paper analysis and therefore, not statistically analyzed. Thus, the final sample for which fMRI was analyzed was composed of a total of 22 persons with DS, with the following observed age distribution: M = 25.5 and SD = 5.1. The distribution of the final sample consisted of 8 people from Mexico and 14 from Barcelona, the average age was M = 25.6 (SD = 5.2) and 22.7% were women (n = 5). In relation to the degree of severity, it revealed that 4.5% had a limited intellectual disability, 36.4% had mild intellectual disability, 40.9% had moderate intellectual disability and finally, 18.2% had profound intellectual disability. This classification appears in the official report that each DS person presented at the time of incorporation into the study and limited intellectual disability it's connected with the borderline zone so this category don't appears in ICD-10 categories (Codes F70-F79). All the DS group were right-handed.

A control group (n=22) was included to compare the indicators of complex networks analyzed in DS population. These subjects were obtained from the Human Connectome.

Project (http://www.humanconnectomeproject.org/), specifically from the open access dataset Autism Brain Imaging Data Exchange I (ABIDE I). The ABIDE I is an image repository comprised by 17 international sites and collect structural and rest fMRI scans from people with Autism Spectrum Disorder and healthy control groups. All data, including the phenotypic datasets and the protocol of acquisition parameters, are available in http:// http://fcon_1000.projects.nitrc.org/indi/abide/abide_I. Only the control group of ABIDE I dataset was used and the subjects were selected to be matched with DS sample by chronological age

(M=24,68; SD=4.90; maximum 2 year of difference in some subject) and gender (22.7% were women). No statistical differences were found in relation to age (t = 0.568; df = 42; $p_{bilateral}$ = .573).

Instruments:

The data from this work, only for DS group, are part of a larger protocol in which the relationship between the brain signal (fMRI) and various variables connected with cognitive performance, quality of life and physical activity are studied in DS population. In this case, for the following study, only some instruments were used to check that the inclusion criteria were met. In all cases, the following assessment and measurement elements were administered:

The Dementia Screening Questionnaire for Individuals with Intellectual Disabilities (DSQIID) has an internal consistency estimated with α by a Cronbach value of .91 (Deb et al., 2007). It was used to rule out signs of dementia.

Ad hoc questionnaires were used to assess the clinical and educational history, and the following variables were collected: age, sex, place of residence and degree of intellectual disability. This questionnaire can be used for research purposes only and can be obtained by requesting it from the authors.

Procedure:

For the DS group, informed consent was obtained from each participant prior to the first neuropsychological screening session in accordance with the Declaration of Helsinki. All the phases of the protocol were approved by the ethics committee of the Bioethics Committee of the University of Barcelona (Spain) and the University of Guadalajara (México). In accordance with this document, informed consent was obtained from the parents of each person with DS and from the persons with DS themselves. In the case of DS people, our protocol included a part in which the tasks that we

would perform were explained in detail to each person and confirmation of the understanding of this part by the person with DS was required. In addition, a medical report was obtained for each participant to rule out incompatibilities with the scanner register. All participants were evaluated in two registration sessions by previously trained researchers. The administration sequence was the same for all subjects, and the scales referenced above were administered first to avoid fatigue bias. All questionnaires were heteroadministered. The DSQIID scale was completed by the parents of the people with DS, while the sociodemographic record was obtained from the people with DS, and all the assessments were administered during the same day. Data were collected from March 2018 to July 2019.

MRI image acquisition and preprocessing:

After the administration of the scales, the participants underwent the fMRI recording sequence in the following order: T1-weighted, T2-weighted, FLAIR and 6- minute resting-state. Two system models 3 T Philips Ingenia scanner (Phillips Healthcare) were used (one located at the Clinical Laboratory, Integral Medical Diagnostic Center of Guadalajara's RIO Group Center in Jalisco, and the other at the Pasqual Maragall Foundation in Barcelona). A T1-weighted turbo field echo (TFE) structural image was obtained for each subject with a 3-dimensional protocol (repetition time [TR] = 2300 ms, echo time [TE] = 2980 ms, 240 slices, and field of view [FOV] = 240 x 240 x 170). The image acquisition was in the sagittal plane. For the functional images, a T2*-weighted (BOLD) image was obtained (TR = 2000 ms, TE = 30 ms, FOV = 230 x 230 x 160, voxel size = 3 x 3 x 3 mm, 29 slices). The image acquisition was in the transverse plane. During scanning, the participants were instructed to relax, remain awake, and keep their eyes open and fixed on a cross symbol on the screen.

The structural imaging data were analyzed using an FSL (http://www.fmrib.ox.ac.uk/fsl/, RRID:SCR_002823) preprocessing pipeline adapted under authorization from Diez et al. (2015), with its parameters adjusted to fit our experimental data, including a motion correction procedure to solve the undesired head movements in the fMRI sessions. T1-weighted images were reoriented to match the same axes as the templates, and a resampled AC-PC aligned image with six degrees of freedom (df) was created. All nonbrain tissue was removed to obtain an anatomical brain mask that would be used to parcel and segment the T1-weighted image data. The use of DARTEL templates was ruled out since some previous analyzes did not identify significant differences in relation to the use of general templates (Jacola et al., 2011). The final step involved registering our structural imaging data to normalized space using the Montreal Neurological Institute reference brain based on the Talairach and Tournoux coordinate system (Ashburner & Friston, 1999). Finally, during the fMRI recording, a caregiver of the DS person evaluated was present inside the scanner room, dedicated to their care to reassure the DS persons and thus avoid unnecessary movements or aberrant behaviors or lack of adherence to rejection instructions. He was only present in the room without interacting with the person evaluated, but we found that the mere presence of caregivers or parents greatly reduced aberrant movement or distractions.

Regarding the control group, the acquisition was performed in different institutions of the United States. As in the case of the DS group, all the participants performed fMRI recording sequence: T1, T2, Flair and between 6- and 9-minutes resting-state. The repetition time (TR) in all cases was 2000 ms and the voxel size was different for every protocol. Moreover, due to the extra minutes in resting, in all the cases in the control group, the number of volumes was greater than in the DS group (oscillating between 240 volumes and 300). Therefore, we used only the first 220 volumes corresponding to the ones used in the DS group.

Regions of Interest:

For both groups, the automated anatomical labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) was used to define the regions of interest (ROIs). This atlas contains 45 cortical and subcortical areas in each hemisphere (90 areas in total and available by request). To acquire the full signal of a given ROI, it is necessary to compute an average over the entire time series of all the voxels of a given brain area following the AAL atlas. In relation to the objective of the present study of the brain connectivity patterns in Down syndrome, we select only regions involved in the DMN network. These regions were divided into anterior, ventral and posterior subnetworks based on the classification proposed by Huang et al. (2015). The anterior DMN (DMNa) subnetwork included the anterior cingulate, paracingulate gyrus, insular cortex, and frontal and temporal poles. The ventral DMN (DMNv) subnetwork included the precuneus and middle cingulate, hippocampus and parahippocampal gyrus. The posterior DMN (identified as simple DMN) subnetwork included the lateral parietal and middle temporal gyrus. Additionally, the sensorimotor (SM) has been included, which consists of the frontal lobe; the precentral, mid-frontal and supra-motor areas; and the postcentral, supra-marginal and para-central areas. Likewise, the visual network (V) is composed of the primary visual cortex, the calcarine fissure, the cuneus, the occipitotemporal gyrus and the occipital lobe (Farras-Permanyer et al., 2019). The table 6 shows the entire ROI's list.

Statistical Analysis

Once the images were preprocessed, correlation matrices were obtained between the 48 ROIs for each subject evaluated and group. To avoid the aberrant effect of values in some especially high or low ROIs (outliers), the jackknife correlation was estimated. There are other simulation possibilities in estimating statistical significance, but for small samples it is still recommended. This technique

consists of calculating all the correlation coefficients between all the possible ROI pairs if one of the observations is excluded on each occasion.

The average of all the correlations for each ROI pair attenuates the effects of the outliers. Each jackknife correlation coefficient is estimated using the following expression:

$$\theta_{(ROIi,ROIj)} = Jackknife\ Correlation\ Mean\ (ROIi, ROIj) = \frac{1}{n}\sum_{k=1}^{n} r_i$$

where r_i is Pearson's correlation between each pair of ROIs and n is the sample number in which the correlations in each pair have been estimated by extracting the record (volume) i. The SE of each average was also estimated from the expression:

$$SE = \sqrt{\frac{n-1}{n}\sum_{i=1}^{n}(r_i - \theta)^2}$$

Table 6

Relationship of ROIs for the construction of the DMN and subnetworks considered according to the AAL90 atlas.

	DMN		DMN anterior		DMN ventral		Sensorimotor		Visual
Roi	Region name	Roi	Region name	Roi	Region name	Roi	Region name	Roi	Region name
59	Parietal_Sup_L	29	Insula_L	35	Cingulum_Post_L	1	Precentral_L	43	Calcarine_L
60	Parietal_Sup_R	30	Insula_R	36	Cingulum_Post_R	2	Precentral_R	44	Calcarine_R
61	Parietal_Inf_L	31	Cingulum_Ant_L	37	Hippocampus_L	7	Frontal_Mid_L	45	Cuneus_L
62	Parietal_Inf_R	32	Cingulum_Ant_R	38	Hippocampus_R	8	Frontal_Mid_R	46	Cuneus_R
85	Temporal_Mid_L	87	Temporal_Pole_Mid_L	39	Parahippocampal_L	19	Supp_Motor_Area_L	47	Lingual_L
86	Temporal_Mid_R	88	Temporal_Pole_Mid_R	40	Parahippocampal_R	20	Supp_Motor_Area_R	48	Lingual_R
				55	Fusiform_L	57	Postcentral_L	49	Occipital_Sup_L
				56	Fusiform_R	58	Postcentral_R	50	Occipital_Sup_R
				65	Angular_L	63	Supramarginal_L	51	Occipital_Mid_L
				66	Angular_R	64	Supramarginal_R	52	Occipital_Mid_R
				67	Precuneus_L	69	Paracentral_Lobule_L	53	Occipital_Inf_L
				68	Precuneus_R	70	Paracentral_Lobule_R	54	Occipital_Inf_R

This allows for the estimation of confidence intervals for each correlation coefficient. Selecting between the correlation coefficient obtained with the whole sample or the one obtained through Jackknife estimation depends on the bias value obtained. The bias is defined by the following expression:

$$Bias = (n - 1) * (\theta - \hat{r})$$

For each correlation between ROI's the value of Bias was obtained and when this was close to 0 the average Jackknife value was used. In cases where Bias was different from 0, the value of the lower limit of the confidence interval was used, to avoid the probability of type I error. To perform these analyses, the dist R library (3.6.3) was used and all correlations were positivized. Once the matrices were configured for each DS person, the binary matrix for each one was also obtained. Pearson's correlations with degrees of significance lower than $p < .001$ were considered significant to reduce type I error again.

To further analyze the density of the functional connectivity networks for each participant, we studied the structures that arose in the whole-brain analysis, including the DMN areas described in table number 1. The same binarization criterion was applied to this new matrix. All the correlation matrices thus estimated were transformed to Z-scores by means of the Fisher transformation:

$$z = \frac{1}{2} \ln \left(\frac{1 + r}{1 - r} \right)$$

All the two matrixes were binarized using degrees of significance lower than $p < .001$ were considered significant to further reduce type I errors. The Z matrices were used as a main matrix to estimate distance between ROI's and the binarized matrices were used as an adjacent matrices to estimate each network. To further analyze the density of the functional connectivity

networks for each participant and for the entire sample, we studied the structures that arose in the whole-brain analysis, including only the DMN areas described in above mentioned Table 6.

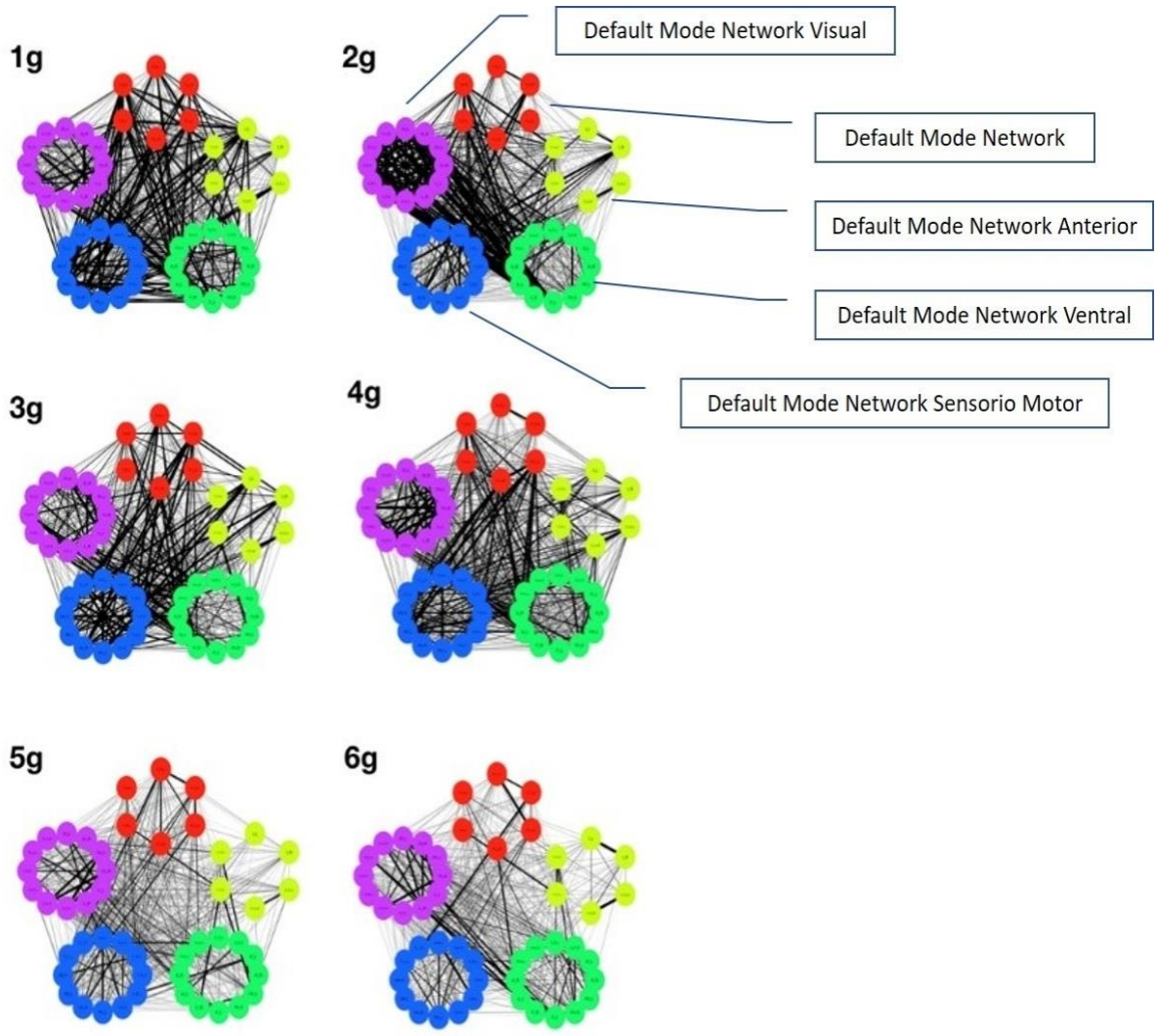
Graph plots from each z_i correlation matrix were built through the qgraph package for R (Epskamp et al., 2012). The results and maps obtained from these results were displayed by BrainNetViewer (Xia et al., 2013). Database is disponible upon request to the authors.

Results

Figure 6 shows a representation of the functional connectivity network of six of the 22 DS subjects. The simple visual inspection of the networks shows a very variable behavior, and a certain continuum can be identified in terms of the density of the connectivity network. We selected some of the characteristic networks of subjects with high (1g and 2g) connectivity in the global DMN, of those with medium connectivity (3g and 4g) and finally of those with low connectivity intensity (5g and 6g). They were obtained from the values of correlation coefficients transformed to Fisher's z_i values, establishing a threshold of p <.001. Figure 6 shows the networks of these selected subjects.

Figure 6

Representative graphs of high connectivity (1g and 2g); medium connectivity (3g and 4g) and low connectivity (5g and 6g).



Note: The number of each ROI is listed in table 6.

The simple graphical inspection of Figure 6 indicates a wide variability in the connectivity density of the DMN network in the sample of DS persons, and they did not show a regular pattern regarding the connectivity density. It was not necessary to reproduce this analysis in the control group, since the evidence of variability in the directed networks in the DS group was sufficient to try to study both groups using the average correlation matrix. According to this situation, we chose to show the analyses performed with the average

correlation matrix representative for each group. To do so, Figure 7 shows the correlogram between the 48 ROIs constituting all DMN networks (corrplot library of R), and Figure 8 shows the average connectivity network established from the average correlation matrix (qplot library of R).

Figure 7

Average correlation matrix correlogram for each group.

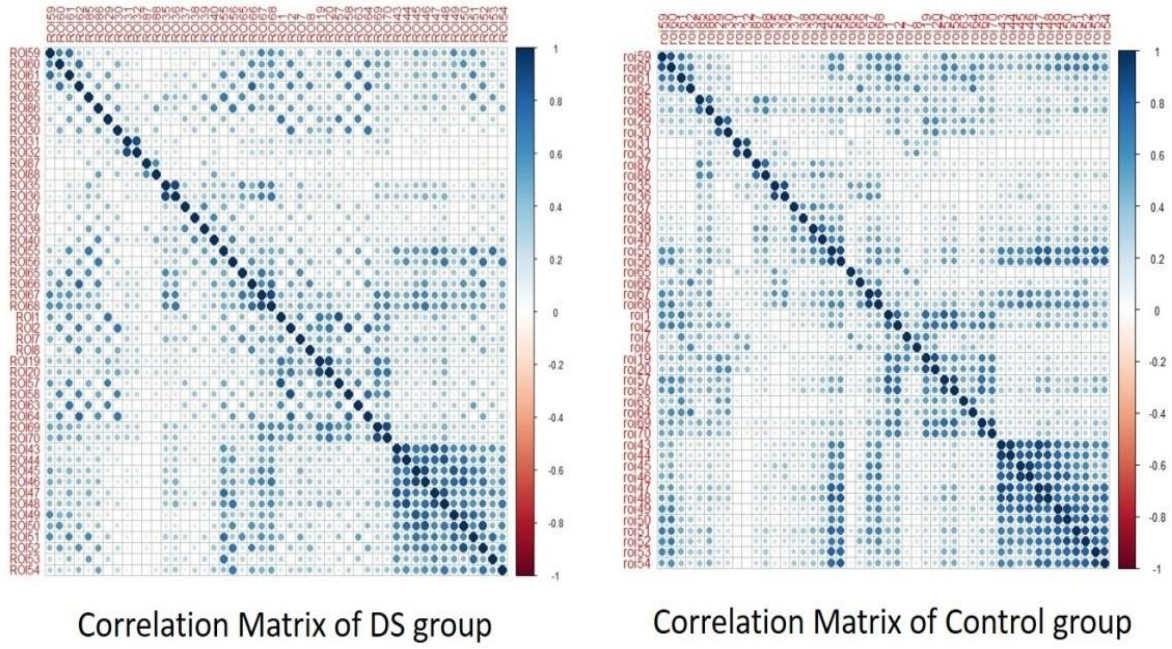
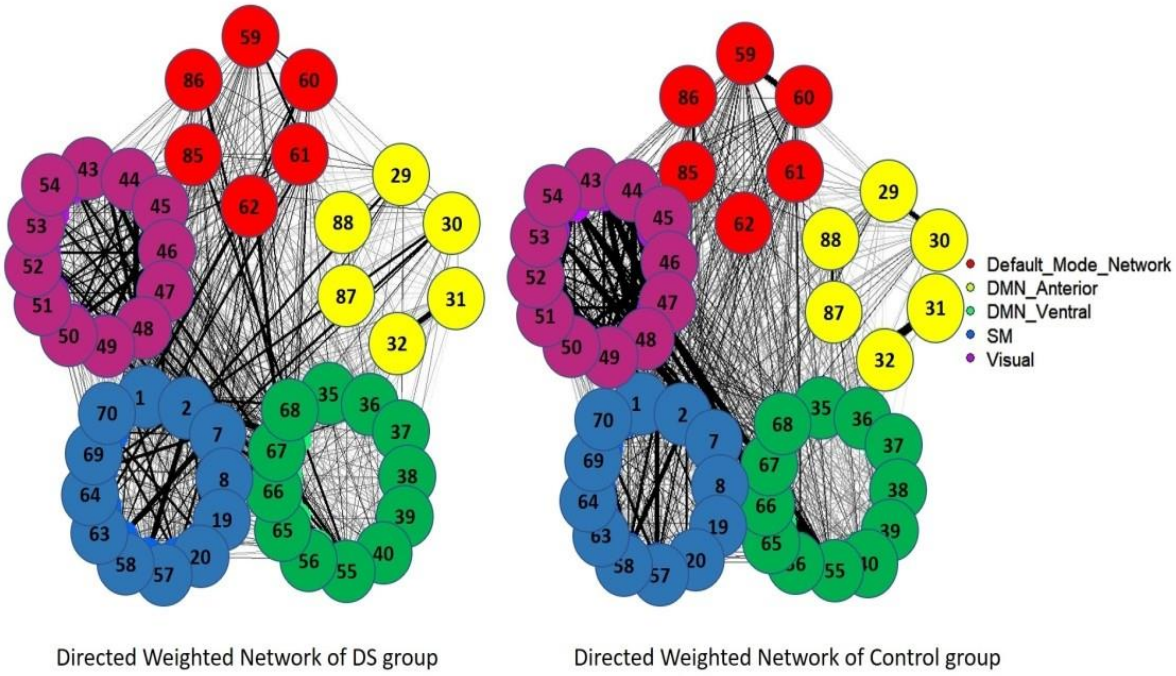


Figure 7 indicates very moderate average connectivity levels in both groups except in some subnetworks (such as the visual network). The visual inspection of the correlograms shows a higher similarity between global correlation values. As previously stated, Figure 8 shows these effects more clearly through the estimation of the corresponding directed network for each group.

Figure 8

Average graph of functional connectivity on the DMN network for people with DS, estimated from Fisher's transformed zi values.

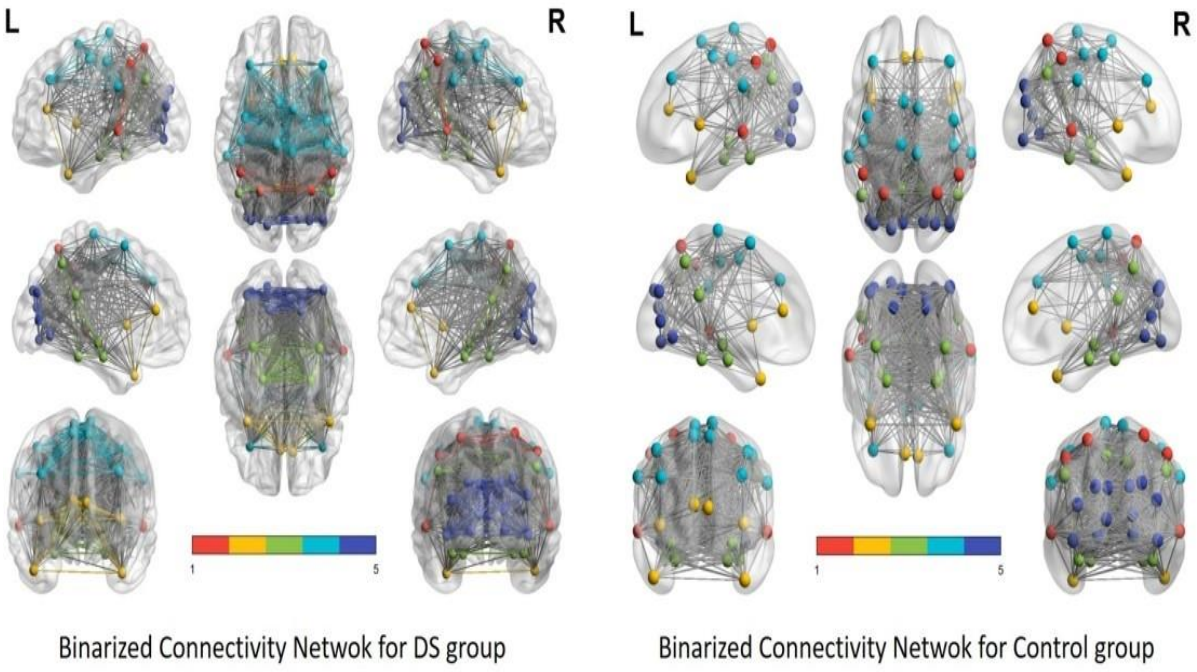


Note: Red: DMN posterior; yellow: DMN anterior; green: DMN ventral; blue: Sensoriomotor and purple: Visual. The number of each ROI is listed in table 6.

From these values, the binary functional connectivity matrix for each group was obtained, and the results were presented using BrainNetWiewer. Figure 9 shows the results obtained after this procedure.

Figure 9

DMN network of binary functional connectivity in people with DS.

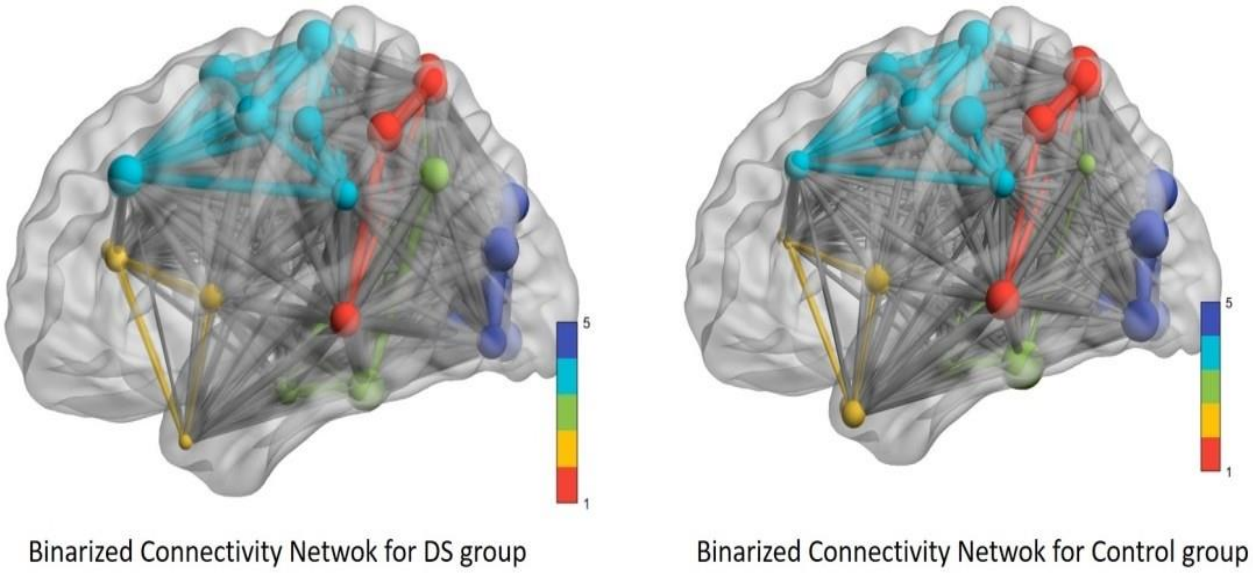


Note: Red: DMN posterior; yellow: DMN anterior; green: DMN ventral; blue: Sensoriomotor and purple: Visual.

The graphical representation of the functional connectivity network was also obtained from the heavy matrix and using the degree of each ROI to establish its connection level with the rest of the ROIs. Figure 10 shows these networks for both groups.

Figure 10

DMN network of heavy functional connectivity in people with DS.



Note: Red: DMN posterior; yellow: DMN anterior; green: DMN ventral; blue: Sensoriomotor and purple: Visual. The size of the ROI is proportional to the connectivity they present, and the edges between ROIs are proportional to the zi transformation between them.

Finally, to provide the data corresponding to the importance of each DMN ROI in relation to network connectivity, we present in Table 7 the path length values for each ROI estimated from the weighted global matrix for each group and ordered from highest to lowest connectivity with the rest of the regions in the DS group to facilitate the interpretation.

Table *7*

Degree (weighted) for each ROI, ordered from the highest value to the lowest in DS group.

AAL90 atlas			DS Group	Control Group
DMNv	68	Precuneus_R	23.21	10.64
	67	Precuneus_L	22.56	11.17
Visual	48	Lingual_R	22.34	9.74
	46	Cuneus_R	21.06	8.16
	47	Lingual_L	20.93	9.33
	45	Cuneus_L	20.25	10.58
SM	69	Paracentral_Lobule_L	20.22	7.53
	70	Paracentral_Lobule_R	20.01	7.59
Visual	44	Calcarine_R	19.47	3.78
	51	Occipital_Mid_L	19.39	3.85
	50	Occipital_Sup_R	19.16	6.72
DMNv	66	Angular_R	18.92	7.82
SM	19	Supp_Motor_Area_L	18.67	5.87
DMNv	55	Fusiform_L	18.66	5.97
Visual	52	Occipital_Mid_R	18.65	6.57
SM	20	Supp_Motor_Area_R	18.64	6.88
Visual	43	Calcarine_L	18.63	8.16
	54	Occipital_Inf_R	18.37	9.05
DMNv	56	Fusiform_R	18.22	11.59
SM	7	Frontal_Mid_L	18.13	11.46
DMN	61	Parietal_Inf_L	17.80	5.54
Visual	49	Occipital_Sup_L	17.78	7.48
DMN	62	Parietal_Inf_R	17.75	10.97
	59	Parietal_Sup_L	17.70	11.49
SM	1	Precentral_L	17.68	10.12
DMN	60	Parietal_Sup_R	17.46	11.06
DMNv	36	Cingulum_Post_R	16.78	7.32
SM	2	Precentral_R	16.66	6.87
	8	Frontal_Mid_R	16.35	9.43
DMNv	35	Cingulum_Post_L	15.89	9.01
DMN	86	Temporal_Mid_R	15.52	9.99
DMNv	65	Angular_L	15.36	10.27
SM	57	Postcentral_L	15.31	7.19
	58	Postcentral_R	15.30	7.89
DMNv	40	Parahippocampal_R	15.13	10.01
DMN	85	Temporal_Mid_L	14.88	9.37
Visual	53	Occipital_Inf_L	14.86	9.97

SM	64	Supramarginal_R	14.74	9.63
	63	Supramarginal_L	13.07	10.01
DMNa	29	Insula_L	12.10	9.86
DMNv	39	Parahippocampal_L	11.76	11.33
DMNa	30	Insula_R	11.74	11.54
	31	Cingulum_Ant_L	11.74	10.41
	32	Cingulum_Ant_R	10.24	9.76
DMNv	38	Hippocampus_R	8.86	11.40
	37	Hippocampus_L	8.77	10.23
DMNa	87	Temporal_Pole_Mid_L	6.03	10.31
	88	Temporal_Pole_Mid_R	5.77	10.26

Note: DMN: posterior; DMNa: anterior; DMNv: ventral; SM: Sensoriomotor.

In addition, we carried out a secondary analysis to assess whether the origin of the samples from Mexico or Spain could have generated some type of bias. No statistically significant result was obtained indicating the absence of differences between subsamples. We used nonparametric test to avoid the heteroscedasticity between groups and small sample. The significance was between .432 to .876 in Mann-Whitney test.

Discussion

The results obtained in the analysis of the functional connectivity networks of the DMN networks in people with DS have shown a wide variability in the density of connectivity that each participant presents and an average result in which greater intra network connectivity is shown in the motor–sensory network and in the visual network. The rest of the connections between ROIs are statistically significant but of lesser intensity. The study of the networks and the degree of each ROI indicate that, in fact, the motor sensor network and the visual network present higher values of connection intensity, while the DMNa and DMNv networks present lower intensity of connections than the rest, although the latter are presented in a very disaggregated way. The connectivity network for the control group indicates a similar network to that described in the case of the DS group but with lower intensity connection values (edges) between ROIs.

First, our results show that the intensity of functional connections between the ROIs that make up the DMN and between the subnetworks that can be identified are extremely variable and present in a certain continuum and that especially in our sample, there is no generalized interruption of the DMN, as was reported by Wilson et al. (2019) in older people with DS. The individualized graphs indicate such a level of variability that the graphs and average results should be analyzed with caution. This effect is not different from that reported in similar studies in other populations (Smitha et al., 2017), including networks estimation in healthy people (Farras-Permanyer et al., 2019). More interesting is the average network estimate obtained from the average correlation matrix. In this case, the result indicates that as mentioned previously, the DMN of people with DS is characterized by greater connectivity in the DMNv network related to visuospatial processing and the coding of information through the visual and auditory pathways, as well as the sensorimotor and visual areas since they have the highest degree within the ROIs as opposed to the DMNa in charge of emotional processing, mood control, and the subsequent DMN network related to information recognition. The control group shows the same connections found for the DS group, as expected, but with lower intensity levels than the DS group.

This is consistent, to some extent, with the work of Pujol et al. (2015), which refers to greater connectivity in the ventral brain system as opposed to the anterior brain system. Therefore, our results indicate a profile of connectivity in young people with DS that, unlike the profile of young people without DS, reports less functional connectivity and/or correlative strength within the DMN between the medial prefrontal cortex, that is, the DMNa, and the posterior cingulate cortex, also known as the DMNv, which progressively decreases as age increases. This is congruent with what is reported in the same line by Mak et al. (2017).

People with DS showed somewhat different functional connectivity networks than expected in the DMN according to the average graph in comparison with the control group.

They showed greater self-referential mental activity based on the strength of the association obtained in the DMNv, although in a somewhat fragmented way, as did the processing of the visual area and the control of involuntary movements of the sensorimotor area in a resting state. During the recognition of spatially oriented stimuli, the system that understands speech located in a DMN subarea and social and emotional association processing carried out by the DMNa showed little functional connection strength.

We should, however, look for some reasonable explanation for the overactivation of the sensory–motor and visual areas. It seems plausible to assume that the people with DS evaluated moved their upper and lower extremities and, in addition, had abnormalities with eye tracking during recording, which could generate these differences. Similarly, given the morphological characteristics of people with DS such as decreases in the cerebellum, prefrontal cortex, hippocampus, and circumvolution of the temporal lobe and with networks and circuits exhibiting less extension and a lower organizational capacity (Flórez et al., 2015), it may be complementary to the previous description to explain the overactivation detected in the average graph; this presents greater connectivity in the aforementioned subnetworks, little symmetry between subnetworks, and low intensity of functional association between the DMN subnetworks.

This work presents some limitations to consider. First, the sample size is limited, the control group is drawn from general databases, and therefore, they have not been recruited in the strict sense, and DSQIID was not studied for its psychometric properties for its Spanish version. The inclusion of a control group, being a relevant contribution, does not stop presenting difficulties in interpreting the results due to differences in brain morphology between groups. Despite this, it has been included to better establish network properties in the DS group. Finally, it should be noted that this work should be complemented with an exhaustive analysis of the cognitive functions of DS people to assess possible links of the

properties of the connectivity network with the distributions of the cognitive performance tests.

The results obtained and their interpretation led us to conclude that the DMN network in the DS population can be affected by the difficulty of recording with interfered movements (motor and visual) and a clear asymmetry between subnetworks. Obviously, the lack of this type of effects in the control group must be attributed to the absence of alterations in the network, both in cerebral and behavioral terms, in non-DS people.

Likewise, we can establish that there is clear intrasubject variability that shows very different behavior in terms of the density of connectivity detected in the participants. This behavior is not exclusive to the sample used in this study since the variability in the non-DS populations is similar. However, it seems necessary to further study density-modifying variables that can explain part of the observed variation. It will be necessary to study whether the effect of more neurostructural mechanisms or the effect of external variables (e.g., cognitive factors including the level of cognitive response or possible cognitive reserve effects or more psychological aspects such as quality of life) could explain this phenomenon. Complementarily, the relationship that DS has, for example, with organically based health conditions such as hypothyroidism and congenital heart disease, as well as with the use of medications, should be investigated. Similarly, longitudinal studies could allow to analyze the network properties of the DMN network from the follow-up of young to elderly subjects and to evaluate the possibility that this network becomes an early biomarker of ATD.

Capítulo 5.

Studio 2: Complexity analysis of the Default Mode Network using Resting-State fMRI in Down Syndrome: relationships highlighted by a neuropsychological assessment.

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Studio 2:

Complexity analysis of the Default Mode Network using Resting-State fMRI in Down Syndrome: relationships highlighted by a neuropsychological assessment.

Introduction

Down syndrome (DS) is one of the most frequent diagnosis in the intellectual disability field and is characterized by a specific cognitive phenotype due to alterations in hippocampal structure (Pennington et al., 2003). The neuropsychological DS profile is characterized by alterations in motor abilities, language (morphosyntax), verbal short-term memory and explicit long-term memory; in contrast, visuospatial short-term memory and implicit long-term memory are usually preserved (Næss et al., 2011; Vicario, 2006). These patterns in DS were described in a recent systematic review (Gandy et al., 2020). In this review, the authors concluded that these dysfunctions were related to chronic health conditions, basically to sleep disorders. In addition to these sleep disorders present in DS, another important issue addressed in the DS population related to neuropsychological aspects is Alzheimer's Disease (Wilcock & Griffin, 2013; Hartley et al., 20215 and Lott & Head, 2019). Although the presence of dementia in this population becomes apparent at approximately the fifth decade of live (Head et al., 2007) the indicators of Alzheimer's disease are expected ten years before, tha is, at approximately 40 years old (Oliver et al., 1998).

Interest in neuropsychological and cognitive functions in people DS has promoted the development of assessment tools specifically designed for this population, such as the TESDAD battery (de Sola et al., 2015) and the Arizona Cognitive Test Battery (ACTB) (Edgin et al., 2010; Edgin et al., 2017). Moreover, in recent years, there has been a growing interest in introducing the neuroimaging techniques to study neuropsychological aspects in people with

DS, mainly in studies related to Alzheimer's disease and dementia (Powell et al., 2014; Lao et al., 2020).

In relation to neuroimaging techniques the use of functional magnetic resonance imaging (fMRI) is increasingly used to study brain connectivity in people with intellectual disability (Carbó-Carreté et al., 2020). The use of fMRI is becoming more common in brain connectivity studies, because it allows the understanding and analysis of the brain as a complex network (Strogatz, 2001; Newman, 2003; Bocaletti et al., 2006). From this perspective, the brain is understood as a system organized by nodes and the connections established between them that provide functional or structural information (Bullmore & Sporns, 2009). This discipline has its origins in the mathematical graph theory with the aim to quantify and defining how the brain is organized (Farahani et al., 2019). There are two main groups of measures to study brain networks; first, through indicators of functional segregation that define local network communities; second, measures addressed to assess functional integration. These latter indicators explain the global communication between the segregated groups, that is, how these networks are coordinated and share information (Rubinov & Sporns, 2010; Sporns, 2013).

Graph theory has been used in studies of resting-state fMRI (rs-fMRI) to provide a better comprehension of brain connectivity in neurological or psychiatric diseases (Wang et al., 2020; Khazaee et al., 2015; Alaerts et al., 2015). In rs-fMRI, when the person is required to maintain closed eyes or look at fixed points, a specific network of the brain is activated, called default mode network (DMN) (Buckner et al., 2008; Gusnard & Raichle, 2001). This network is characterized by high levels of functional and structural connectivity and by high levels of resting metabolic activity in healthy people (Gusnard & Raichle, 2001). A recent study (Figueroa-Jiménez et al., 2020) evaluated DMN properties in young DS people in comparison with a control group. The results showed that there were higher levels of overactivation in the ventral, sensorimotor and visual DMN networks, although these effects occurred with high

levels of heterogeneity of connectivity patterns. However, it is not clear whether this heterogeneity in cognitive performance variables.

In the present study, the principal goal was to provide knowledge regarding DMN function in the DS population and analyse whether complexity in the brain network could be related to cognitive performance. A complex system is defined by the study of phenomena in which multiple sources of information regardless of the operation of a single source of information. A complex system, therefore, requires simultaneous and multiple information at a certain point in time. There is no strict definition of this concept, since its application to various scientific fields makes it difficult. However, there is a wide degree of agreement in considering the quantification of complexity as indicators of (1) How hard is to describe? (2) How hard is to create? and (3) What is its degree of organization? (Lloyd, 2001).

In DS, DMN connectivity to other areas of the brain is different from that in the non-DS population (Anderson et al., 2013; Vega et al., 2015; Wilson et al., 2019). Moreover, based on graph theory analysis, the clustering coefficient was higher in the DS group than in the control group (Anderson et al., 2013). Nevertheless, Carbó-Carreté et al. (2020), in a systematic review to assess brain activity in people with DS, identified that there is no typical regular and stably established functional connectivity. In addition to the studies on brain connectivity in people with DS, the published research regarding AD (Alzheimer Disease) has become a framework for our work because, as mentioned, it is one of the most important issues being addressed in this population based on their early appearance and types of neuropsychological alterations presented. Based on AD and graph theory studies, (Supekar et al., 2008), it was shown that the characteristic path length (functional integration measure) and the clustering coefficient (functional segregation measure) were low. Thus, the small-world, defined by the optimal balance between these two measures (Sporns & Honey, 2006) indicated brain connectivity. Nevertheless, a recent study (Xu et al., 2020) examined the topological attributes of the small-

world in patients with subjective cognitive decline (SCD; a clinical stage before the diagnosis of AD). The SCD sample presented global efficiency values lower than normal controls, while characteristic path length and modularity were higher. However, increased characteristic path length values and decrease global efficiency suggested a reduction in abilities related to information communication of the whole brain (i.e., integration function) in the SCD sample. However, the increased values of modularity in SCD suggested that, in this population, local communication, and information transmission (segregation function) were improved.

Some studies in healthy population have also presented results that provide interesting data to define our objectives. For instance, it was shown in healthy older people (< 75 years) that there was less connectivity within the network but more connectivity among the subnetworks that make up the DMN (Mancho-Fora et al., 2020). They used indicators of lower segregation, modularity and local efficiency. The results obtained were associated with poor executive function, memory and processing speed (Andrews-Hanna et al., 2007). All this reflects a progressive loss of specialization within the brain networks related to higher functions (Antonenko & Flöel, 2014).

Based on the published works mentioned, the aim of this paper was to explore the observed distribution of complexity indicators in a DS group in comparison with a matched control group. Our expectation is that some of the descriptive measures of the connectivity networks show more erratic observed distributions in the group of people with DS Moreover, we analyzed the relationship between some of those complexity indicators in the subareas that constitute the DMN and the scores obtained on neuropsychological tests. Given the dispersion that we expected to find in the group of people with Ds, the relationships with neuropsychological performances will be specific and not systematic.

Materials and methods

Participants:

The sampling was non-random and was performed through contact with different associations dedicated to DS in the State of Jalisco (México) (53.2% of participants) and Barcelona, Spain (46.8%). The initial sample comprised a total of 32 persons with DS between the ages of 16 and 35 (M=24.7 and SD=5.49) of whom 28.12% were women (number of women = 9). The inclusion criteria applied were a) age between 16 and 35 years old and b) a diagnosis of DS. The exclusion criteria were a) evidence of other diagnostic comorbidities involving cognitive dysfunction with AD; b) inability to obtain legal consent from guardians; and c) the presence of medication affecting cognitive function.

The diagnosis proportions of intellectual disability of 29 participants with DS referred by the tutors (the remaining could not be accredited), were 3.4% borderline intellectual disability, 52.2% mild intellectual disability, 37.9% moderate intellectual disability and 3.4% profound intellectual disability. This classification appeared in the official report that each DS person presented at the time of incorporation into the study and limited intellectual disability relates to the borderline zone, so this category does not appear in the ICD-10 categories (Codes F70-F79). A total of 84.4% of the participants with DS were right-handed, and 6.3% of the participants with DS were ambidextrous (n=32).

Written informed consent was obtained from every individual before taking part in the study, in accordance with the Declaration of Helsinki and with approval of the institutional ethics committee. Moreover, this procedure was approved by the Bioethics Committee of the University of Barcelona (03/10/2017).

Regarding the fMRI signal recording, ten participants with DS recorded an excess of movement greater than ±2 degrees (or greater than half a voxel size) and were eliminated, and some of them were eliminated even repeating the recording session, since the second session

also showed excess movement. The final sample was ultimately composed of a total of 22 persons with DS, with an observed age distribution of M = 25.55 and a standard deviation (SD) = 5.119. The distribution of the sample by sex was 22.7% female. In the final sample, the maximum movement was 1.2 degrees, and the average was 0.72% degrees (SD = 0.11).

A control group was added, matched (one by one) by age and sex with the DS group. Subjects were selected who were within the range of movement used in the group of people with DS, movements of a maximum of ±2 degrees (M = 0.92; SD = 0.09) and only subjects whose protocol contained the absolute absence of pathology ere included that compromised their cognitive performance or any type of chronic disease or medication. The images of this second sample were obtained from the Connectome Project (http://www.humanconnectomeproject.org/) during July of 2020 with the same image properties that the DS group. For each control participant, we obtained the structural T1 and T2 images and whole-brain resting-state fMRI signals during the same period as the DS group. In all the individuals int the control group, the number of volumes was greater than in the DS group (between 240 and 300 volumes). Therefore, we used only the first 220 volumes corresponding to those used in the DS group.

Instruments:

The DS data from this work are part of a larger protocol in which the relationship between brain signal (fMRI) and various variables connected with cognitive performance, quality of life and physical activity are studied. In all cases, the following elements of assessment and measurement were administered to determine if they met the criteria for inclusion and exclusion:

(1) Ad hoc questionnaires were used to assess the clinical and educational history, and the following variables were collected: age, sex, place of residence and degree of intellectual disability.

(2) Dementia Screening Questionnaire for Individuals with Intellectual Disabilities (DSQIID): with an internal consistency estimated with α by Cronbach's α of .91 (Deb et al., 2007). This questionnaire was useful for ruling out signs of dementia. As it only affected the application of the exclusion criteria, a version adapted to Spanish was used without a study of psychometric properties.

Neuropsychological evaluation:

- The protocol designed for the evaluation of the participants with DS to measure cognitive performance was integrated with the following neuropsychological tests:
- Frontal Assessment Battery (FAB): This consists of tasks exploring the functions of the frontal lobes through six subtests: similarities (concept formation), verbal fluidity (mental flexibility), motor series (programming), interference (carrying out conflicting instructions), control (inhibition of responses) and autonomy (independence from the external environment). The cut-off point for the frontal-subcortical deficit was 16-15, and the cutoff point for frontal-subcortical dementia was 13-12. The Frontal Assessment Battery scores correlated with the Mattis Dementia Rating Scale scores ($rho = 0.82$, $p < 0.01$) (Dubois et al., 2000).
- Intelligence Quotient (IQ) was assessed using the Kaufman Brief Test of Intelligence (KBIT), a screening test that evaluates crystallized intelligence (learning and problem solving) based on formal schooling and cultural experience, from two levels of conceptualization: verbal intelligence with an expressive vocabulary and definitions subtest; and nonverbal intelligence with a master's subtest. This test is valid for use by people from 4 to 90 years of age and generates standard scores (verbal, nonverbal and IQ composite) (Kaufman, 1990).

Regarding the control group, only the rs-fMRI image was analysed. These data are open and regulated by the Connectome Project regulations. The cognitive outcome assessment in the

control group was different from that in the DS group and impossible to compare. Therefore, to avoid confusing comparisons, the cognitive assessment in the control group was excluded. The inclusion criterion in the control group required that the technical characteristics of the acquisition of the images were the same as those used in the registration of the people in the DS group. This was done to guarantee the comparison between both groups of the structures of the connectivity networks between the two groups.

Procedure:

Each subject with DS and their guardians provided informed consent before the first neuropsychological evaluation session in accordance with the Declaration of Helsinki. The protocol was approved by the Bioethics Commission of the University of Barcelona. Additionally, a medical report was obtained from each participant to confirm that the MRI study was safe. All participants were evaluated in two registration sessions by previously trained researchers. The administration sequence was the same for all subjects, and the previously referenced scales were administered first to avoid fatigue bias. All the questionnaires were administered by the researcher. The sociodemographic information was obtained from the people with DS, and all of this information was collected on the same day. The DSQIID scale was completed by the guardians of the participants with DS.

MRI acquisition and preprocessing:

After administering the scales, the participants in the DS group had the fMRI recording sequences performed in the following order: T1, T2, Flair and 6-minute resting-state. Both Mexican and Spanish participants were recorded on similar scanners. Two Philips Ingenia 3.0T system models were used (one located at the Clinical Laboratory, Integral Centre of Medical Diagnosis of Guadalajara's Grupo Río in Jalisco and the other at the Fundació Pasqual Maragall

in Barcelona). A T1-weighted turbo field echo (TFE) structural image was obtained for each participant with a 3-dimensional protocol (repetition time [TR] = 2300 ms, echo time [TE] = 2980 ms, 240 slices, and field of view [FOV] = 240 x 240 x 170). The image acquisition was in the sagittal plane. For the functional images, a T2 weighted (BOLD) image was obtained (TR = 2000 ms, TE = 30 ms, FOV = 230 x 230 x 160, voxel size = 3 x 3 x 3 mm, 29 slices). The image acquisition was in the transverse plane. The characteristics of both scanners were identical, and a subsequent review of each recording was performed to check if there was any difference between the two recording facilities. No difference was found between the two, neither technologically nor procedurally. The guarantee the equality of records in both scanners, data from a reduced group of subjects was recorded to determine if there was any significant difference between the records of the same person in the two scanners. This procedure was performed prior to this work and did not show any relevant difference between scanners. During scanning, the participants were instructed to relax, remain awake, and keep their eyes open and fixed on a cross symbol on the screen. The data were collected during the period from March 2018 to July 2019.

In the case of the control group, the acquisition was performed in different institutions in the United States. The repetition time (TR) in all cases was 2000ms and the voxel size was different for every protocol. As mentioned above, the technical characteristics of both groups were the same and only open-eye resting-sate protocols were selected.

For the two groups, the structural imaging data were analyzed using an FMRIB Software Library (FSL) (FMRIB Software Library v5.0, Oxford, United Kingdom) preprocessing pipeline adapted under authorization from Diez, et al. (2015), with its parameters adjusted to fit our experimental data, including a motion correction procedure to solve the undesired head movements in the fMRI sessions. To obtaining the functional connectivity (FC) matrices, the fMRI images were preprocessed as follows. First, a slice time correction based on the TR of

the images acquisition was carried out to obtain thirty contiguous slices in the Anterior commissure-posterior commissure (AC-PC) plane. The input images were reoriented to match the template axes and motion correction was computed to coregister all the volumes with the central one so that all the voxels of the different volumes belonged to the same brain point. Then, all non-brain tissue was removed and, to get a better signal-to noise ratio, the volumes were smoothed with a 6 mm full width at half minimum (FWHM) isotropic Gaussian kernel. Also, intensity correction and band-pass filtering between 0.01 and 0.08 Hz were applied to the data. The resulting functional data images were registered and normalized to the standard Montreal Neurological Institute (MNI) space. Finally, the white matter and the cerebrospinal fluid effects were removed so that no other interference was added to the fMRI signal. The final step involved registering our structural data images to the normalized space using the Montreal Neurological Institute (MNI) reference brain based on the Talairach and Tournoux coordinate system (Ashburner & Friston, 1999).

Regions of interest:

The automated anatomical labelling (AAL) atlas (Tzourio-Mazoyer et al., 2002) was used to define the regions of interest (ROIs). This atlas contains 45 cortical and subcortical areas in each hemisphere (90 areas in total), which are alternatively interspersed (available by request) and described in Table 8. To acquire the full signal from a given ROI, it is necessary to compute an average over the entire time series of all the voxels of a given brain area following the AAL atlas. The specific values of each ROI were estimated from the application of Principal Components Analysis (PCA) with the strict selection of each group of voxels defined by the mask of each ROI. Given the objective of the present study regarding brain connectivity patterns, we identified only the DMN. These regions were divided into five subnetworks:

concentrated partial DMN, anterior, ventral, and two posterior subnetworks, sensorimotor and visual, all based on the classification proposed by Huang, et al. (2015).

Estimation of mental Age:

The estimation of mental age in the DS population has been widely studied and is also very controversial because of both the absence of specific instruments for this purpose and the use of Intelligence Quotient (IQ) to define the degree of the intellectual disability (Dierssen, 2012; Lanfranchi et al., 2015). Since it is a measure that involves the recording of cognitive performance, it can mask specific deficits due to its very heterogeneous nature.

In recent years, there has been a growing interest in facilitating this calculation, since, in the latest version of the world reference test for the estimation of IQ in children (WISC-V), the planning of the calculation of mental age in an easy and uncomplicated way has been incorporated. However, in the situation in which we find ourselves, with a sample of persons with intellectual disabilities, there are many difficulties in finding a valid and reliable test for the estimation of mental age are (Edgin et al., 2010; Hamburg et al., 2019). Among these difficulties are floor effects, test that focus on evaluating only language skills, low sensitivity of the measures to detect some effects, low flexibility for use across cultures and languages, applications, in a chronological age range that do not directly lead to adjustments for mental age and, finally, lack of psychometric validation in populations with developmental disabilities (Edgin, et al., 2010).

Initially, the use of WISC was proposed for the estimation of the IQ in the adult population with DS. The aim was to alleviate the floor effect and hope that an IQ value of approximately 70 points could represent a large part of the population. However, despite the facility of the WISC-V test for the evaluation of the subscales involved in the mental calculation tasks, it does not appear to be suitable for the integral evaluation of persons with ID for various reasons,

Table 8

Relationships of Regions of Interest (ROIs) for the construction of the Default Mode Network (DMN) and subnetworks considered according to the AAL90 atlas.

DMN		DMN anterior		DMN ventral		Sensorimotor		Visual	
Number in the AAL90 Atlas	**Region name**	**Number in the AAL90 Atlas**	**Region name**	**Number in the AAL90 Atlas**	**Region name**	**Number in the AAL90 Atlas**	**Region name**	**Number in the AAL90 Atlas**	**Region name**
59	Parietal_Sup_L	29	Insula_L	35	Cingulum_Post_L	1	Precentral_L	43	Calcarine_L
60	Parietal_Sup_R	30	Insula_R	36	Cingulum_Post_R	2	Precentral_R	44	Calcarine_R
61	Parietal_Inf_L	31	Cingulum_Ant_L	37	Hippocampus_L	7	Frontal_Mid_L	45	Cuneus_L
62	Parietal_Inf_R	32	Cingulum_Ant_R	38	Hippocampus_R	8	Frontal_Mid_R	46	Cuneus_R
85	Temporal_Mid_L	87	Temporal_Pole_Mid_L	39	ParaHippocampal_L	19	Supp_Motor_Area_L	47	Lingual_L
86	Temporal_Mid_R	88	Temporal_Pole_Mid_R	40	ParaHippocampal_R	20	Supp_Motor_Area_R	48	Lingual_R
				55	Fusiform_L	57	Postcentral_L	49	Occipital_Sup_L
				56	Fusiform_R	58	Postcentral_R	50	Occipital_Sup_R
				65	Angular_L	63	SupraMarginal_L	51	Occipital_Mid_L
				66	Angular_R	64	SupraMarginal_R	52	Occipital_Mid_R
				67	Precuneus_L	69	Paracentral_Lobule_L	53	Occipital_Inf_L
				68	Precuneus_R	70	Paracentral_Lobule_R	54	Occipital_Inf_R

but there are two reasons in particular: 1) there is a difficulty in understanding items with high verbal content, and 2) it is a test with a very limited age range (between 5 and 16 years). Therefore, we believe that the estimation of mental age should be approached from another perspective (Ripoll, 2001).

In a study by Hamburg, et al. (2019), a systematic review of the literature on the different IQ tests for adults with DS was conducted, and of all of them the one identified with the lowest problem involving a floor effect was the KBIT test, even for very extreme populations (e.g., with dementia). Therefore, the KBIT test was chosen because it extends the range of chronological ages and because it involves less time for application, as there are only two subscales: verbal intelligence (with the expressive vocabulary and definitions subtest) and nonverbal intelligence (with the matrix subtest), which falls within the estimated range of concentration time (approximately 30 min) and reduces the fatigue of the person evaluated.

However, this test does not allow the estimation of mental age. Our proposal was based on the following heuristic. First, direct scores were calculated for the two subtests (matrices and vocabulary), and the IQ of each participant with DS was calculated traditionally. Based on these direct scores, we located in the standardization scales to which age range this score would correspond, selecting the scale with the smallest difference between the population mean (IQ = 100) indirect score and the observed score. Once the scale with the smallest difference was located, the observed score was placed, and the age range to which it corresponded was identified. In all cases, the most favorable mental age (upper limit) within the range offered by the scales was selected. In the case that the direct score indicated a level lower than four years, the mental age was set at that age, assuming that this value is the floor of the test.

The limitations of this proposal are obvious. First, it would be ideal to have a test where the lower limit was less than four years and, second, there is an overestimation effect of mental age because the upper limit of the age confidence interval was used. However, this allows us to avoid the bias effects that could occur in subsequent statistical analyses by facilitating the incorporation of mental age as a relevant variable.

It should be noted that, even with these limitations, we believe that this is one of the most reliable tests for people with DS (Hamburg et al., 2019) and is supported by its regular use as an inclusion criterion (Esbensen et al., 2018; Key & Dykens, 2014; Pujol et al., 2015; Sinai et al., 2016; Vega et al., 2015).

Statistical Analysis:

For the two groups, the observed distributions of the indicators of the nondirected connectivity networks were analysed based on the ROIs of the five networks described in Table 8, as well as the global network that would freely incorporate the 48 ROIs defined. For each of the five smaller networks and the global network, the nondirected networks were estimated based on the partial correlations between nodes (ROIs), and the complexity indicators are shown in Table 9.

Table 9

List of estimated weighted indicators to determine the characteristics of each network analysed.

	Description	Calculations
	Functional Integration (FI)	
Number of communities	Number of independent communities detected in a group of specific ROIs. Estimated maximum number of statistically clusters significant in a random network.	
Mean of the path lengths	The path length of a node i (Li) is the average number of edges that must be crossed to go from node i to the remaining nodes in the network	$Li = \sum_{i \epsilon N} \left(\frac{1}{n-1} . \sum_{j \epsilon N, j \neq i} dij \right)$ where N is the total number of nodes in the network, n is the number of nodes involved and dij is the shortest path length between node i and j.
Standard Deviation of the path lengths	The characteristic path length is a global measure of the network, i.e., there is only one value for the entire network. It consists of the average path length of each node in the network.	$L = \frac{1}{N} \sum_{i \epsilon N} Li$
	Functional Segregation (FS)	
Global Cluster Coefficient	This is the average value of the clustering coefficient, which is the fraction of triangles around a node and is equivalent to the fraction of neighbours of the node that are neighbours among them.	$= \frac{\sum \Gamma i}{\sum ki(ki-1)}$
Number of triangles	This is the number of connected triangles that can be estimated within a network in Euclidean space.	$G = (V, E)$ An ordered pair in which V is a nonempty set of vertices and E is a set of edges. Where E consists of unordered pairs of vertices such as {x, y} E, then x and y are said to be adjacent.
	Other measures	
Density	The network density (D) is the number of edges in the network in proportion to the total number of possible edges.	$D = \frac{K}{N(N-1)}$ where K is the number of edges in the network and N is the total number of nodes in the network.
Small World (WS)	Networks that present a higher clustering coefficient than expected by chance and that, in addition, have a characteristic shortest path length.	$S = \frac{Cnorm}{Lnorm} = \frac{C/Crandom}{L/Lrandom}$

		A network is said to represent this type of organization if the calculated index is greater than 1.
Complexity	The number of nodes and alternative paths that exist within a specific network	

The selection of these indicators has followed two criteria: 1) the use of the most common and known indicators according to Rubinov (2010) and 2) previous recommendations the recommendations (Santarnecchi et al., 2017) regarding sensitive indicators for the description of a network. There are a multitude of possible alternative indicators, but neither the sample size nor the objectives of this paper focus on a comprehensive analysis.

In the DS group, each of the estimates of these indicators, for each subarea, was included as a predictor for the cognitive performance variables (FAB total score) and the standardized scores of the scale (vocabulary and matrices) KBIT in a specific study, as above mentioned, with de DS group.

For each criterion variable, the resulting multiple regression linear model was obtained from the best possible combination of linear predictors. The following statistical operations were performed on each model. Given the high variance in some of the predictor variables, a 5% cutoff for each tail was used to avoid the effect of extraneous values in such a small sample, and chronological age was included as a correction criterion in the estimation. Once these transformations were made, robust stepwise regression models were estimated using as an inclusion criterion the significance of the change in the coefficient of determination (R^2) and the adjustment value of the Akaike information criteria (AIC). The detection criterion of the best model was a significant change in R^2 with a p <0.01 and more than 10% reduction in the AIC value between successive steps.

Results:

Table 10 shows the basic statistics of the observed distribution of the criterion variables for the DS group. Table 11 shown the complexity indicators statistics for both groups described in Table 9. Estimates of the standard error of the mean have been obtained by bootstrapping with 10000 repetitions to reduce the effect of the small sample. Despite the small sample size, we believe that it is important to observe the behaviour of the indicators described to establish the individual and group differences concerning the connectivity networks studied.

Table 10

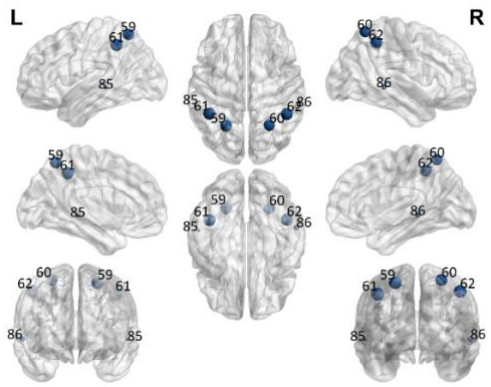
Descriptions of the observed distributions of the criterion variables.

Criteria Variables	Mean (Standard Deviation)	Bootstrap 95% CI	Symmetry	Kurtosis
Mental Age Vocabulary	6.11(2.51)	4.97 – 7.26	0.967	0.034
Mental Age Matrices	5.42(1.53)	4.72 – 6.12	1.032	0.843
FAB (Frontal Assessment Battery) Score	9.62(4,20)	7.71 – 11.53	0.215	0.681
Total Score Vocabulary	23.71 (13.91)	17.38 – 30.04	0.603	-0.452
Total Score Matrices	47.47(13.76)	41.21 – 53.74	-0.063	0.879

Table 11

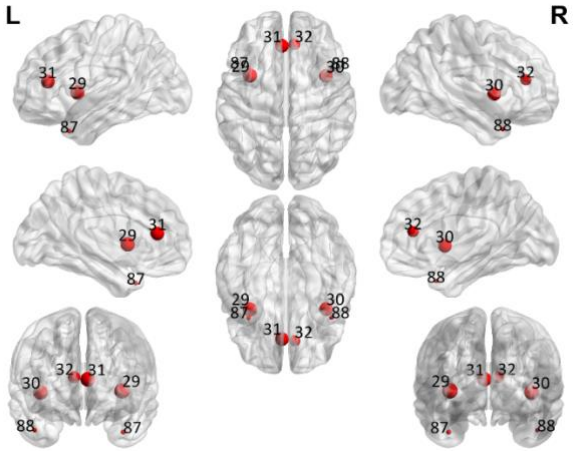
Descriptions of the observed distributions of the complexity indicators in each group in the five subnetworks and the entire network that make up the DMN and their distribution according to the AAL atlas. The number of ROIs coincides with the description Table 8. SD: standard deviation. DMN partial network (6 ROIs).

DMN partial network (6 ROIs)



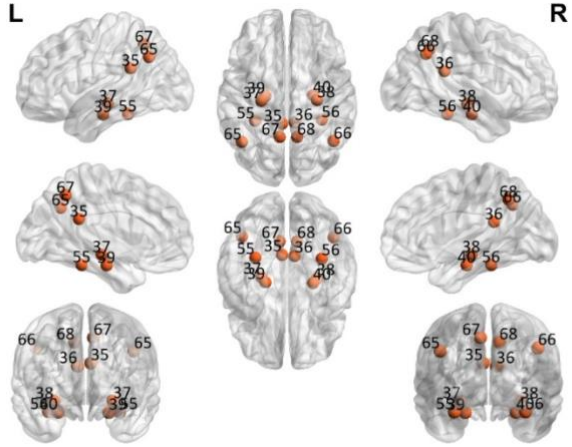
Network Indicators	DS Group		Control Group	
	Mean	SD	Mean	SD
Number of Communities	2.23	.922	0.001	0.0001
Mean of the weighted path	0.496	0.193	0.12	0.02
Standard Deviation of the weighted path	0.276	0.146	0.06	0.01
Density	0.768	0.101	0.001	0.0001
Small-worldness	1.027	0.088	0.0001	0.0001
Global Cluster Coefficient	0.317	.006	0.001	0.0001
Complexity	0.822	0.238	0.11	0.02
Segregation (triangles)	105.136	90.590	104.66	22.31

DMN Anterior (DMNa) partial network (6 ROIs).



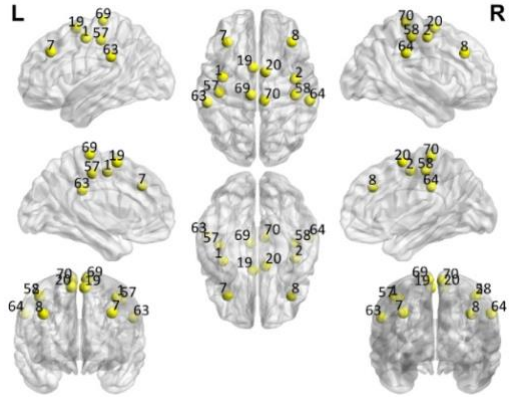
Network Indicators	DS Group		Control Group	
	Mean	SD	Mean	SD
Number of Communities	2.41	0.194	0.21	0.04
Mean of the weighted path	0.423	0.043	0.10	0.02
Standard Deviation of the weighted path	0.299	0.027	0.05	0.01
Density	0.768	0.021	0.0001	0.0001
Small-worldness	1.027	0.018	0.0001	0.0001
Global Cluster Coefficient	0.318	0.001	0.0001	0.0001
Complexity	0.868	0.046	0.11	0.02
Segregation (triangles)	109.181	18.035	103.14	21.98

DMN Ventral (DMNv) partial network (12 ROIs).



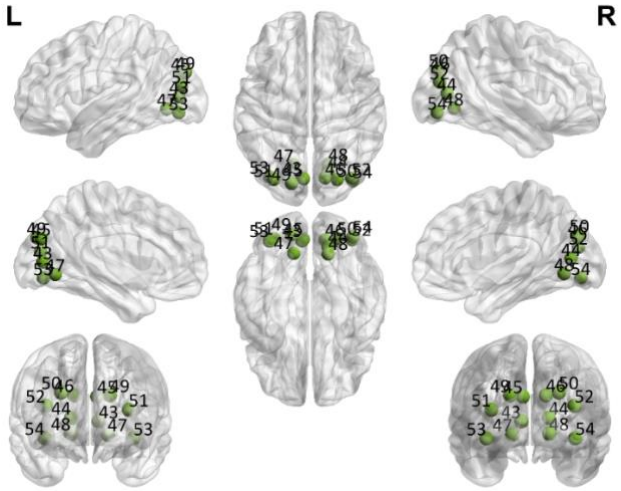
Network Indicators	DS Group		Control Group	
	Mean	SD	Mean	SD
Number of Communities	2.409	0.107	0.59	0.12
Mean of the weighted path	0.605	0.033	0.08	0.01
Standard Deviation of the weighted path	0.232	0.029	0.03	0.01
Density	0.454	0.001	0.001	0.001
Small-worldness	1.240	0.014	0.05	0.01
Global Cluster Coefficient	0.316	0.001	0.001	0.001
Complexity	0.871	0.031	0.071	0.0001
Segregation (triangles)	209.818	38.25	209.27	44.61

Sensorimotor (SM) partial network (12 ROIs).



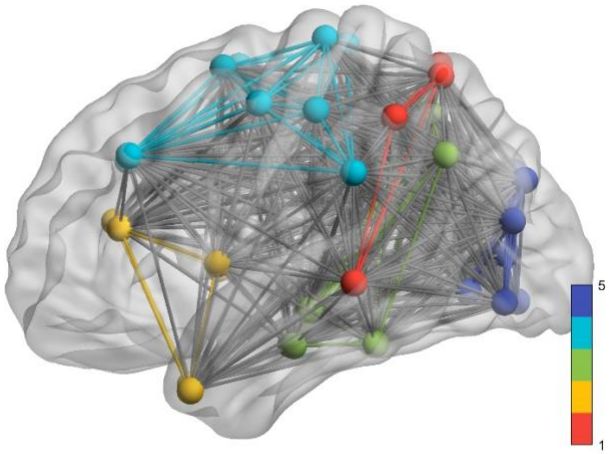
Network Indicators	DS Group		Control Group	
	Mean	SD	Mean	SD
Number of Communities	2.545	0.108	0.49	0.10
Mean of the weighted path	0.677	0.027	0.08	0.01
Standard Deviation of the weighted path	0.202	0.032	0.22	0.04
Density	0.454	0.001	0.001	0.001
Small-worldness	1.230	0.013	0.07	0.01
Global Cluster Coefficient	0.313	0.007	0.003	0.0008
Complexity	0.884	0.027	0.06	0.001
Segregation (triangles)	217.090	37.303	208.28	44.40

Visual (VIS) partial network (12 ROIs).



Network Indicators	DS Group		Control Group	
	Mean	SD	Mean	SD
Number of Communities	2.500	0.109	0.35	0.07
Mean of the weighted path	0.783	0.016	0.07	0.01
Standard Deviation of the weighted path	0.115	0.009	0.04	0.009
Density	0.454	0.001	0.0001	0.0001
Small-Worldness	1.271	0.011	0.06	0.001
Global Cluster Coefficient	0.316	0.005	0.002	0.0006
Complexity	0.930	0.011	0.04	0.008
Segregation (triangles)	220.001	37.549	199.05	42.43

GLOBAL NETWORK ANALYSIS (48 ROIs).



Network Indicators	DS Group		Control Group	
	Mean	SD	Mean	SD
Number of Communities	4.863	0.257	1.184	0.25
Mean of the weighted path	0.690	0.022	0.07	0.01
Standard Deviation of the weighted path	0.248	0.030	0.08	0.01
Density	0.152	0.020	0.001	0.0001
Small-Worldness	2.483	0.090	0.17	0.03
Global Cluster Coefficient	0.312	0.001	0.001	0.0003
Complexity	0.724	0.0617	0.03	0.008
Segregation (triangles)	865,76	201.190	837.19	178.49

Note: Purple: Visual. Blue: Sensorimotor. Green: ventral DMN (DMNv). Yellow: anterior DMN (DMNa). Red: DMN

To analyze the differences between the two groups, we chose the Mann-Whitney nonparametric test to avoid the effect of the reduced sample size and some anomalies observed in the symmetry and kurtosis of the distributions. The global and subarea results indicated that the median values in the DS group were systematically higher than in the control group. The unilateral significance of these statistical contrasts ranged from $p < 0.05$ to $p < 0.001$ using the Bonferroni correction to reduce the probability of making a type I error. These results indicated that the overall complexity levels of fMRI connectivity networks were much higher in the DS group than in the control group.

Likewise, the variance values of the complexity indicators for both groups were compared to assess the hypothesis of greater variability in the DS group. For this, the Levene test adapted to two groups was used, obtaining a clear significance (ranging from $p < 0.05$ to $p < 0.001$) showing that the variability in the complexity indicators in the DS group was greater than that in the control group.

It was only for the DS group, that the linear models relating the neuropsychological test performance with the complexity indicator values of each analyzed network were estimated, and these included the estimation of two mental ages. Table number 12 shows the results of the weighted least square (WLS) estimation to reduce the impact of small sample and Akaike information criterion (AIC) for each model. Table 12 shows the Pearson correlation between each predicted variable (FAB total score, vocabulary subtest score and matrices subtest score) and the complexity indices as regressors.

Table 12

Pearson correlations between variables.

COMPLEXITY INDICATOR	DMN Partial			DMN Anterior			DMN Ventral			Sensoriomotor			Visual			Observed distribution		
	FAB	VOC	MAT	FAB	VOC	MAT	FAB	VOC	MAT	FAB	VOC	MAT	FAB	VOC	MAT	FAB	VOC	MAT
Number of communities	0.221	0.333	.572**	-0.051	0.018	0.070	-0.026	0.110	0.328	-0.193	-0.238	0.375	0.172	0.247	0.510*			
Mean of the path lengths	-0.181	0.184	-0.172	0.065	0.372	0.000	-0.241	-0.024	-0.275	-0.190	0.016	-0.127	-0.362	-.435*	-0.500*			
SD of the path lengths	0.132	-0.164	0.002	-0.022	-0.188	-0.206	0.297	0.075	0.166	0.163	-0.047	0.001	0.376	.644**	0.491*			
Density	-0.007	-0.341	-0.182	-0.007	-0.341	-0.182	0.011	0.007	0.022	0.003	0.012	0.008	0.084	0.026	0.003			
Small-world	0.007	0.341	0.182	0.007	0.341	0.182	-0.143	-0.003	-0.167	0.155	0.012	0.090	0.317	.448*	0.197			
Global clustering coefficient	-0.105	0.022	0.033	0.017	-0.008	0.105	0.068	0.092	-0.311	0.131	-0.075	-0.207	0.245	0.325	0.091			
Complexity	-0.037	0.069	-0.008	0.042	-0.029	0.172	-0.175	-0.257	-0.139	-0.077	0.028	-0.267	-0.404	-.436*	-0.409			
Number of triangles	-0.365	-0.418	-0.457*	-0.352	-0.427	-0.453*	-0.359	-0.441*	-0.417	-0.397	-.438*	-.452*	-0.368	-0.416	-.438*			
Mental Age Vocabulary																0.653**	0.907**	0.189*
Mental Age Matrices																0.605**	0.693**	0.346

Note: FAB = FAB total score; VOC = vocabulary subtest score; MAT = matrices subtest score.
** p < 0.001 p <0 .05. In mental age vocabulary and matrices only the correlations with FAB, VOC and MAT were shown once.

Table 13 shows the estimated model significance, using WLS. To facilitate the statistical estimation processes, only those complexity indicators with statistically significant correlations with each of the three criterion variables were defined as regressors. In this way, some collinearity problems derived from an excessive number of regressors were reduced.

Table 13.

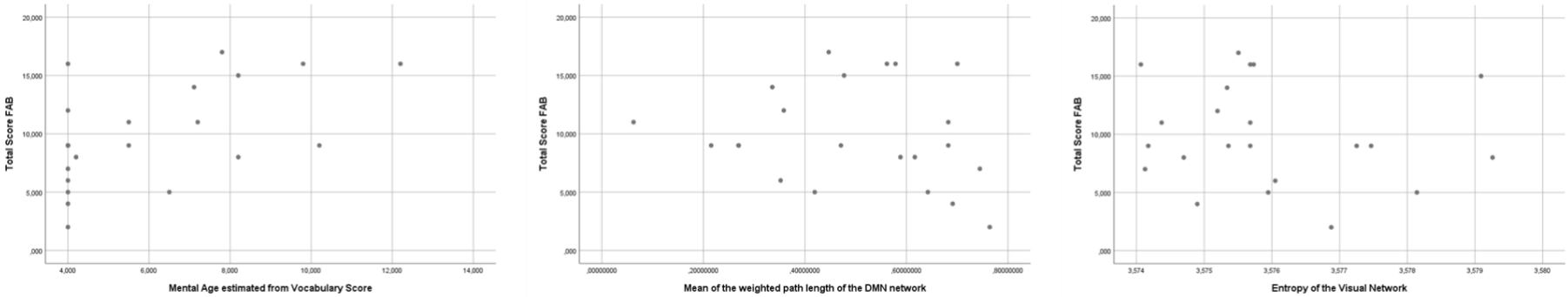
Parameter estimation (β_{ij}) for each of the criterion variables.

Criteria Variables	Predictor	Parameter	*p*	Effect Size		Observations
FAB total score	Mental Age estimated from the Vocabulary score	0.997	0.01	0.376	*AIC* = 124.367	Outliers subject number 11 (Cook Distance = 0.242)
	Mean of the weighted path length of the DMN network	-8.361	0.034	0.241		
Variables excluded	Step number 1: Number of communities in DMN partial; Number of triangles in the subnetworks DMN partial, DMN ventral, Sensorimotor and Visual; SD of the Variables excluded path length of DMN ventral, Small-world in DMN ventral; Number of communities in Sensorimotor network; mean and SD of the path lengths of Visual network;Small-world of the visual network, Global clustering coefficient of visual network; complexity of the visual network and Mental age derived from matrices subtest.					
Vocabulary subtest score	Mental Age estimated from the vocabulary score	5.156	<0.001	0.950	*AIC* = 112.556	Outliers subject number 16 (Cook's distance = 0.388) and 19 (Cook's distance = 0.264)
	Mean of the weighted path length of the Sensorimotor network	-15.069	0.004	0.026		
	Small-Worldness of the Visual network	25.226	0.029	0.013		
	Complexity of the DMN Ventral	-13.281	0.046	0.010		

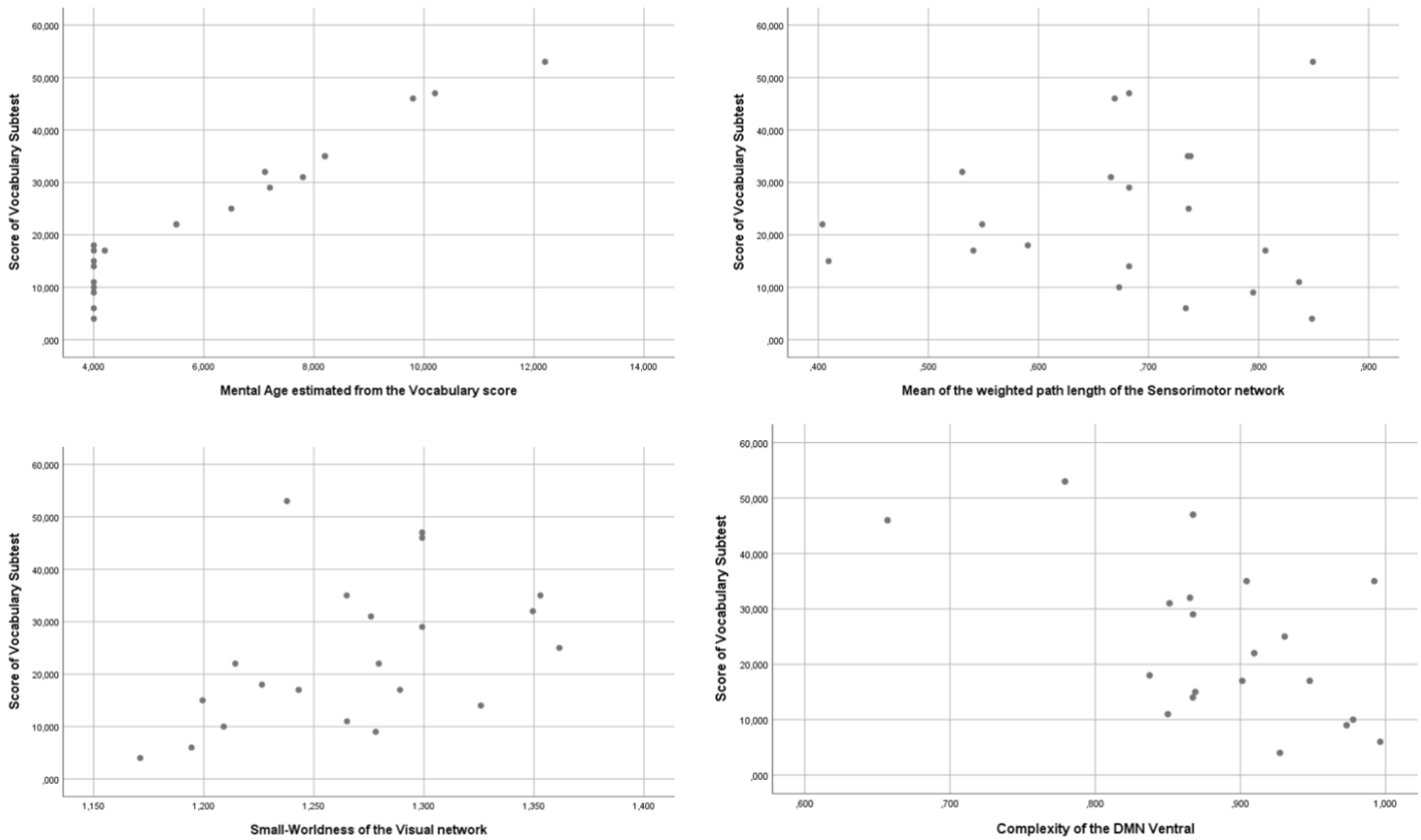
Variables excluded	Step number 1: Number of communities, Mean and SD of the path lengths and number of triangles of DMN partial; Mean and SD of the path lengths, density and Small-world of the DMN anterior; Number of communities of DMN Ventral; Number of communities of Sensorimotor and Visual networks. Step number 2: Density and Small-world of DMN partial; Number of triangles of DMN anterior; Complexity and Number of triangles of DMN ventral; Number of triangles of Sensorimotor network a Mental Age derived from Matrices Test. Step number 3: Mean and SD of path lengths of Visual network; Global clustering coefficient, Complexity and Number of triangles of Visual network.					
Matrices Subtest Score	Number of communities of the Visual Network	14.581	0.004	0.562	*AIC* = 168.857	Outliers subject number 7 (Cook's distance = 0.432)
	Number of communities of the DMN networks	-24.149	0.042	0.247		
Variables excluded	Step number 1: Mean of the path lengths, Density, Small-world and Number of triangles of DMN partial; SD of path lengths, Density, Small-world, Complexity and Number of Triangles of DMN anterior; all the indicators (except Density) of the DMN ventral; Number of communities, Complexity and Number of triangles of Sensorimotor network; Mean and SD of the path lengths, Small-world, Complexity and Number of triangles of Visual network. Step number 2: Mental age derived from vocabulary and matrices tests.					

Note. No statistically significant differences were found about the observed distribution of complex indicators or any other variables (including the criteria variables) and gender.

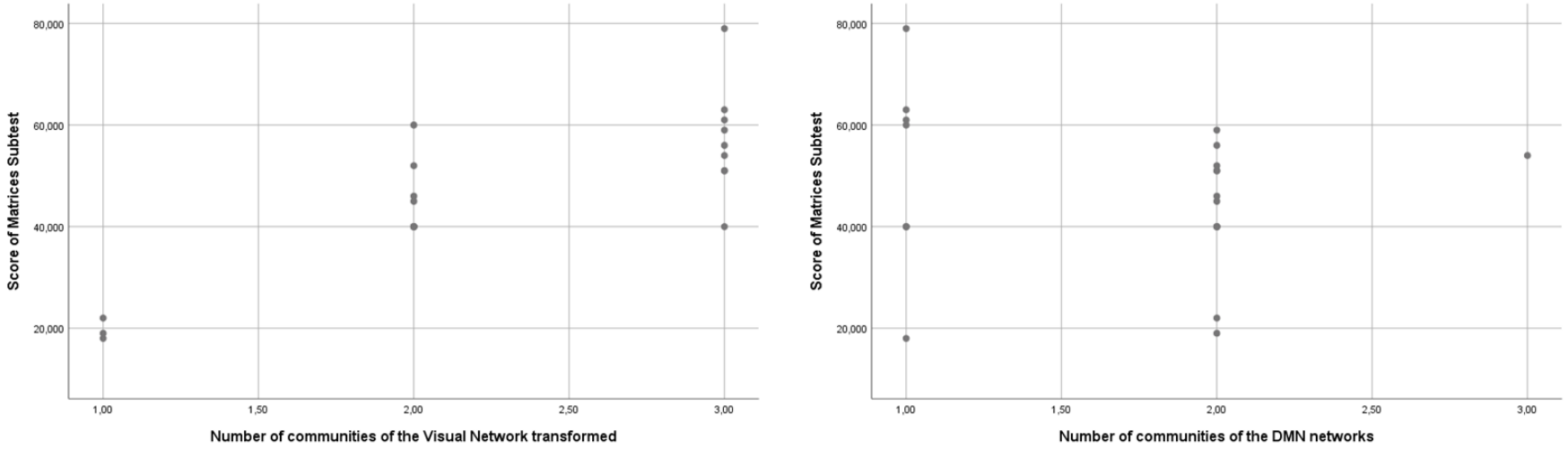
Figure 1.
Bivariate plots representing the statistically significant effects of the linear model in predicting neuropsychological scores.



Bivariate distribution plots of FAB total scores for each predictive variable



Bivariate distribution plots of the vocabulary subtest scores for each predictive variable.



Bivariate distribution plots of matrices subtest scores for each predictive variable.

Discussion

In the present study, we compare the complexity of the DMN (using common indicators of complexity (Rubinov & Sporns 2010) in the subareas that constituted the 48 ROIs extended network) (Table 8) in rs-fMRI paradigm between the DS group and a control group matched by sex and age. The results showed that the DS group had more complex networks in the different subnetworks identified as the DMN. Moreover, the observed distribution of those complexity indicators in the DS group revealed greater variability than in the control group.

Focusing on the networks complexity measures, the results obtained are similar to those presented in previous studies. In relation to segregation measures, the values were higher in persons with DS than in the controls in each subnetwork of the DMN. For instance, consistent with (Lloyd, 2013), the DS group showed higher global clustering coefficient values than the control group.

In relation to the results provided by studies on AD and people with SCD, the integration measures indicated some abnormalities. The increased values in the mean of the weighted path were similar to the results presented in (Xu et al., 2020); thus, we can also argue that in DS people the capacity to transmit and connect the information through the whole brain is altered. Nevertheless, related to (Xu et al., 2020) and specifically in their results on modularity, we were also able to affirm that the networks segregation function is increased in people with lower cognitive performance. In the current study, this increase in the DS population, can be identified through measures of the global clustering coefficients, complexity, and number of tringles. As expected, and reflected in Xu, et al. (2020); density was higher in subnetworks where the global clustering coefficient was higher, specifically in the DMN partial network and in the DMN anterior network.

In the DS group, we must highlight the peculiar behaviour of the observed distribution of all the variables since most of them were characterized by nonsymmetric distributions. Based

on the sample size used, these results are no more than initial descriptions. However, the differences in the estimation of the DMN subnetworks in people with DS are very large. The mean value in the number of communities in each subnetwork indicated the impossibility of assuming that each subnetwork was configured as a single directed network. This should be interpreted as an anomaly in the structure of the global DMN and its networks in terms of network complexity. It is sufficient to observe the average value of the number of communities in the global network (48 ROIs) (DS Group: M=4.86 SD=1.20; and control group M=1.184 SD=0.252; $p < 0.001$) and see how far it is from what is expected in the DMN (Figueroa-Jiménez et al., 2020).

All these results confirm the appraisals regarding the aberrant behavior of the connectivity networks in people with DS. This aberrant behavior can be summarized by saying that the networks show many connections between the ROIs, of a highly disaggregated nature and with a wide within-subject variability, so that it is feasible to think that this type of connectivity pattern may be associated with serious cognitive alterations. This statement is bases on the studies cited above that obtained similar results to ours in samples of people with AD. This level of congruence allows us to think about a certain pattern typical of the functional connectivity networks associated with severe cognitive deficit that should be verified with grater force with other interest groups and cognitive evaluation systems.

In addition, we also analyzed the relationship between some of those indicators with the scores obtained in neuropsychological tests for the assessment of executive functions and IQ in the DS group only. Statistically significant results were found in the prediction of the FAB test scores and the vocabulary and matrices subtests of the KBIT test. The significant parameters indicate a positive effect of mental age derived from the KBIT (vocabulary) scores and the negative effect of some complexity indicators.

Regarding the complexity indicators as predictors of some cognitive performance and IQ tests, our results, in general, showed little effect. Moreover, the high variability in the indicators hinders identification of possible effects. In our sample, there were a limited number of indicators that showed a statistically significant impact on the prediction of FAB or KBIT scores. Regarding the effects associated with the mental age variable, they must be interpreted within the logic of the expected effects and consistent with the methodology used for their estimation, which was described above. This supports some previous proposals that can be consulted in (Carbó-Carreté et al., 2020) in the sense of controlling age (chronological and mental) across groups and the definition of ID in the context of group designs (paired or not).

Another important effect was the appearance of the number of communities in some networks as a significant effect in the prediction of KBIT matrix scores. First, the signs of the parameters allow us to verify our expectation that increase in complexity are related toa low cognitive level of performance. That is, a higher number of communities implies a greater network disaggregation, which would indicate greater complexity and, therefore, is associated with a low psychometric score.

In the FAB and vocabulary scores (KBIT) predictions, this effect was also enhanced. The negative-weighted mean path length in the sensorimotor network, the visual network small-world network, and the complexity value of ventral DMN indicated the same trend and interpretation. Despite the high variance in the data and the peculiar behaviour of the variables, clipped distributions of some statistically significant effects were observed, which allows us to conclude that the complexity structure, specifically to vocabulary an executive functioning.

These results can be congruent with some others in different populations with psychological, psychiatric and neurobiological disorders: not in the sense of estimating the complexity of nondirected networks, but in the sense of studying abnormalities in the definition

of directed networks (Bassett et al., 2008; Leistedt et al., 2009; Ponten et al., 2009; Stam et al., 2007; Stam et al., 2009; Wang et al., 2009).

Conclusions

To summarize the main conclusions, in our opinion, we can highlight that the current paper is the first study that has been conducted to determine the behaviour of DMN sub-networks through nondirected networks in people with DS.

Our results indicated that the complexity in the structure of the DMN and the analyzed subnetworks was higher in the DS group than in the control group.

There was enormous variability between participants regarding the network's behavior.

Some indicators of complexity for DS group (i.e., path length, complexity and small-worldness) had statistically significant and negative impacts on the prediction of performance for some neuropsychological tests – in this case, the FAB and KBIT.

These results are congruent with the behavior of other segregation or integration measures studied in other populations in which inverse relationships have also been evidenced with other types of psychometric indicators of cognitive performance.

Capítulo 6.

Studio 3: Structural equation models to estimate dynamic effective connectivity networks in resting fMRI. A comparison between individuals Down syndrome and controls.

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Studio 3:

Structural equation models to estimate dynamic effective connectivity networks in resting fMRI. A comparison between individuals with Down syndrome and controls.

Introduction

There are several options in regard to estimating connectivity networks from brain signal data. These options are available not only because there are different types of signals with varied information and behaviors, but also because there are numerous techniques that allow, with more or fewer limitations, to identification of connectivity networks, whether they are functional or effective or whether they are static or dynamic. The study of brain function from the perspective of connectivity networks is a relatively recent approach and is an interesting option for investigating the concept of the brain as a complex system in which different parts of the brain interact under a certain pattern that must be identified. This type of connectivity pattern can be associated with different health states or cognitive characteristics that allow us to establish much more sensitive and precise brain complexity indicators than those used habitually in observational or psychometric records.

In relation to the different brain signals, the one that has been of most interest in the last ten years in the functional magnetic resonance imaging (fMRI) register. The reason for this preference may be because the fMRI signal allows for the generation of representational and mathematical models of brain function; also, although it a somewhat cumbersome record, it is not as invasive to acquire fMRI data as it is to record other signals (Mak et al. 2017).

It seems clear and indisputable is that since Biswall et al. (1995) proposed the first works in a resting situation and estimated functional connectivity networks, we now have many options for application in this field. Lv et al. (2018) offered a list of choices that adequately summarize the state-of-the-art options. A likely important point that the previous work likely

highlights is, on one hand, the incorporation of dynamic connectivity network estimation in a resting situation and, on the other hand, the more current expert vision of systems estimation. In fact, the assumption that a static network obtained from BOLD signal behavior during an established period of time from *k* brain volumes is stable and unique is an assumption that is too banal and simple (Cribben & Yu, 2017). The idea of the existence of spatial property modifications of the network connection between brain areas (regions of interest, ROIs) is much closer to a structural and topological brain functioning concept. The effective or functional connectivity network presents a temporal evolution of its topological properties throughout the period of volumes registration. This assumption, which brings us much closer to the conception of complex system models, must be taken into account to estimate much more realistic connectivity networks.

Certain aspects of dynamic connectivity have been studied in different populations, both in their functional and effective versions. It is true that most of the works have been proposed from the functional connectivity perspective and very few have been conducted involving effective dynamic connectivity. Some examples related to this are the work of Diez-Cirarda et al. (2018), which showed differences in connectivity patterns between Parkinson's patients and a control group. Lin et al. (2016) used the dual signal pathway fMRI and EEG to study dynamic and static connectivity and to determine connectivity patterns in healthy control people. Chen et al. (2018) went a step further and establish the possibility that dynamic connectivity patterns could be considered a biomarker for discrimination between different levels of cognitive competence. Similar results were shown in the work of Threlked et al. (2018), suggesting that consciousness recovery in patients with acute and severe traumatic brain injury (TBI), is associated with partial preservation of DMN correlations. Moreover, Ramani (2015), showed that in patients with a genetic predisposition to Alzheimer's Disease (AD), there is a

connectivity alteration in DMN from very early ages and before the appearance of any cognitive alteration.

There are a variety of options for solving this issue. The best-known is the so-called dynamic causal models (DCM) described by Friston (2011) and described by Park et al. (2018) in a resting state situation. An excellent example of this approach can be found in Sharaev et al. (2016) or Ye et al. (2020). The second option is the dynamic graphical model (DGM) defined by Schwab et al. (2018) that proposes an algorithm for detecting a directed functional connectivity relationship between ROIs, using the mobile window technique to identify parent-child ROIs (according to the authors' terminology).

Nonetheless, an aspect that previous studies do not mention is the one linked to the one linked to use of structural equation models (SEMs) for the estimation of effective dynamic connectivity networks. There are multiple examples of the use of SEMs for effective static estimation that have been employed to establish the directionality of the relationships in the selected ROI's. Most of these contributions have been made, leaving aside the dynamic connectivity vision. For example, Guàrdia et al. (2018a) show effective connectivity networks in diabetic patients, and in the first meta-analysis Guàrdia et al. (2018b) showed the parameters estimated by an SEM in connectivity networks without dynamic components.

However, the idea of effective dynamic connectivity has still not been diligently explored, with even less work having been conducted in the field of SEMs. The recent appearance of the Group Iterative Multiple Model Estimation library (GIMME, 2020)) opens an interesting option in the use of SEMs in effective dynamic connectivity (Gates & Molenaar, 2012; Gates et al., 2017). The initial background on this issue can be identified as the one proposed by Zhang et al. (2020) in the field of dynamic networks and language based on a previous mapping by Beltz & Gates (2017). However, the R library authors propose to understand dynamic

networks components from the estimable impact study of the number of shorts effects that are available to identify.

However, the concepts proposed by the authors of that library consist of understanding the dynamic component of the network from the study of the estimable impact of identifying the number of short effects, deemed lag 1 in the conception of the models. With this, it is possible to estimate the impact of an ROI at moment *t* on the other ROIs at moment *t+1*, which incorporates the dynamic effect in the estimation of the model. The effect of this concept is very limited, and the computational difficulties that SEM models have in this type of work must be taken into account. Inman et al. (2012) argued these difficulties when highlighting the advantages of the GIMME option. The limitations of the GIMME option are also evident and focus on the impossibility of using a high number of ROIs as well as, a short number of lag effects. Even so, the improvements are, in our opinion, evident.

From an applied point of view, there are some works in dynamic connectivity that are important to mention. Pertinently, Chen et al. (2018) with mild cognitive impairment (MCI) patients; Threlkeld et al. (2018) with traumatic brain injury (TR) patients; Park et al. (2018) showing a procedure for baseline estimation in dynamic connectivity studies; Sharaev et al. (2016) with control subjects and study of small networks; Xu et al. (2016) by studying the effect of methylphenidate in healthy subjects; Tang et al. (2016) studying the effect of tobacco use in healthy subjects; Li et al. (2017) with depressed patients; and finally, Xu et al. (2017) studying dynamic connectivity in twins.

All the studies mentioned above and the knowledge about functional connectivity has become the basis of our work and can be summarized as follows: (a) there is evidence of a relationship between the topological properties of complex, basically functional brain networks and certain measures of cognitive performance (Bassett et al., 2009; Crossley et al., 2013; Dosenbach et al., 2007; Hagmann et al., 2010; Lin et al., 2014; van den Heuvel et al., 2009)

(b) functional connectivity of default mode network (DMN) is associated with the cognitive brain function (Bonnelle et al., 2012; Buckner et al., 2008; Kucyi & Davis, 2014); (c) functional brain network connectivity is not a static process over time (Allen et al., 2014; Cocchi et al., 2011; Chang & Glover, 2010; Chen et al, 2013; Handwerker et al., 2012; Hutchison et al., 2013a; Hutchison et al., 2013b; Kucyi et al., 2013; Lee et al., 2013; Leonardi et al., 2013; Tagliazucchi et al., 2012; Tagliazucchi & Laufs, 2014; Thompson et al., 2013) (d) emerging evidence suggests that dynamic functional brain connectivity may indicate changes in the neuronal activity patterns that underlie critical aspects of cognition or clinically relevant information (Allen et al., 2014; Calhoun et al., 2014; Hutchison et al., 2013a; Kucyi & Davis, 2015; Park & Friston, 2013; Tagliazucchi et al., 2012; Tagliazucchi & Laufs 2014) (e) dynamic connectivity is associated with the internal mental state both at rest and during the execution of a task (Fornito et al., 2012); and f) there is evidence of the variability of dynamic functional connectivity networks. The variability is associated with the undirected tracking strategies that people often perform at rest (Kucyi & Davis, 2014). Subregions of the DMN show decreasing variability activity when there is better resolution of cognitive tasks (Garrett et al., 2011; Liang et al., 2013). Thus, an increase in such undirected tracking would be linked to poorer task performance when responding to task stimuli, and it would be expected that this would translate into greater connectivity network complexity, whether dynamic or static.

The simplest comparison in cognitive terms lies in the analysis of the dynamic functional connectivity networks of healthy subjects in comparison with people with compromised cognitive functioning; for example, the Down syndrome (DS) population. These studies must strictly control the selection of the participants' age to avoid the presence of Alzheimer's disease (AD) or other cognitive diseases. The use of fMRI in individuals with DS has provided notable data that justify more in-depth studies of brain functioning in this population. Basically, previous works show that in people with DS, there is an increased internetwork connectivity

(i.e., hyper-connectivity) characterized by positive connectivity even in regions that are negative in control groups; as consequence, there is a clear decreasing anti-correlation (Anderson et al., 2013; Vega et al., 2015; Wilson et al., 2019).

Taking the cited studies, into consideration, the current work aimed to establish the dynamic effective connectivity networks of a DS group and another control, paired by age and sex, using SEMs. This was studied in a resting-state paradigm and only in a part of the DMN (6 ROIs). It also aimed to determine if there is a different pattern between both groups and, finally, to assess the possibility of using those patterns to discriminate between groups.

Because of the results and the evidence of the abovementioned works, we hypothesize that: a) people with DS would show connectivity patterns at rest in the DMN network that would be much more complex than those that characterize in the control group and b) The SEM models for each group would show these effects, and it would be confirmed as a possible biomarker.

Material and method

Participants:

The initial sample was composed of a total of 35 persons with DS (all participants had trisomy 21) between 16 and 35 years of age (M=24.7 and SD=5.49), and 26.5% were women (n_w = 9). Accidental sampling was used, and recruitment took place through contact with different associations dedicated to DS in the state of Jalisco (México) (54.3% of participants) and in Spain (45.7%). The following inclusion and exclusion criteria were applied: a) age between 16 and 35 years and b) formal diagnosis of DS. The exclusion criteria were a) evidence of other comorbid diagnoses implying cognitive dysfunction (for example, the presence of dementia symptoms), b) inability to obtain consent from legal tutors, and c) the presence of medication affecting cognitive functions (specifically, for example, medication for mood regulation).

The intellectual disability diagnostic (out of 29 participants; the rest could not be accredited) revealed that 3.4% had limited intellectual disability, 55.2% had mild intellectual disability, 37.9% had moderate intellectual disability and 3.4% had profound intellectual disability. This classification appeared in the official report that each DS person presented at the time of incorporation into the study; limited intellectual disability is connected with the borderline zone, so this category doesn't appear in the ICD-10 categories (Codes F70-F79). A total 84.4% of the participants were right-handed, and 6.3% of the participants were ambidextrous (n = 32). Laterality was directly assessed by a simple Praxis test during registration and confirmed with information from caregivers.

After recording the fMRI signal, data from ten of the 35 subjects were eliminated due to excessive movement during the recording, and some of them were even removed for the same reason after having repeated the recordings. Records with movement greater than ±2 degrees (or greater than half voxel size) were eliminated. Thus, the final sample for which fMRI was analysed was composed of a total of 22 persons with DS, with the following observed age distribution: M = 25.55 and SD = 5.119. The distribution of the sample by sex indicated 22.7% women. Whether any of the previous variables could be associated with failure to complete the fMRI record was analyzed. The relationship of the variables age, sex, and severity with whether the fMRI registry was completed was evaluated, and no statistically significant relationship was found.

A control group (n=22) was included for comparison with the DS population. These subjects were obtained from the Human Connectome Project (http://www.humanconnectomeproject.org/), specifically from the open access dataset Autism Brain Imaging Data Exchange I (ABIDE I). ABIDE I is an image repository comprised of 17 international sites and collect structural and rest fMRI scans from people with autism spectrum disorder and healthy control groups. All data, including the phenotypic datasets and the

protocol of acquisition parameters, are available in http://fcon_1000.projects.nitrc.org/indi/abide/abide_I. Only the control group of the ABIDE I dataset was used, and the subjects were selected to be matched with DS sample by chronological age (M=24,68; SD=4.90; maximum 2-year of difference in some subjects) and sex (22.7% were women). No significant differences were found in relation to age (t=0.568; df=42; p=.573). To avoid any distortion in the image registry only those registered in the control group with exactly the same technical characteristics as the registries used in the DS group were selected.

Instruments:

The data from this work are part of a larger protocol in which the relationship between the brain signal (fMRI) and various variables connected with cognitive performance, quality of life and physical activity are being studied. In this case, only *ad hoc* questionnaires were used to assess the clinical and educational history, and the following variables were collected: age, sex, place of residence and degree of intellectual disability.

Procedure:

Informed consent was obtained from each participant prior to the first neuropsychological screening session in accordance with the Declaration of Helsinki. Each of the three different protocols was approved by the Ethics Committee of the Bioethics Committee of the University of Barcelona. In accordance with this document, informed consent was obtained from the legal guardians of each person with DS and from themselves. In addition, a medical report was obtained for each participant to rule out incompatibilities with the image acquisition.

MRI image acquisition and preprocessing:

After the administration of the scales, the participants underwent the fMRI recording sequence in the following order: T1-weighted, T2-weighted, FLAIR and 6-minute resting-state. Data were collected from March 2018 to July 2019. Two system models 3 T Philips Ingenia scanners (Phillips Healthcare) were used (one located at the Clinical Laboratory, Integral Medical Diagnostic Center of Guadalajara's RIO Group Center in Jalisco and the other at the Pasqual Maragall Foundation in Barcelona). A T1-weighted turbo field echo (TFE) structural image was obtained for each subject with a 3-dimensional protocol (repetition time [TR] = 2300 ms, echo time [TE] = 2980 ms, 240 slices, and field of view [FOV] = 240 x 240 x 170). Image acquisition was performed in the sagittal plane. For the functional images, a T2*-weighted (BOLD) image was obtained (TR = 2000 ms, TE = 30 ms, FOV = 230 x 230 x 160, voxel size = 3 x 3 x 3 mm, 29 slices). Image acquisition was performed in the transverse plane. As previously mentioned, these technical characteristics correspond exactly to the records used in the control group.

During scanning, the participants were instructed to relax, remain awake, and keep their eyes open and fixed on a cross symbol on the screen.

To avoid excessive movements, the necessary time was allocated for each person to get used to the registration situation. For this, the people who accompanied the members of the DS group were always visible, and during the habituation part of the session, they were able to be in the registration room. Obviously, at the beginning, there was no one in the registration room.

The structural imaging data were analyzed using an FSL (http://www.fmrib.ox.ac.uk/fsl/, RRID:SCR_002823) preprocessing pipeline adapted under authorization from Diez et al. (2015), with its parameters adjusted to fit our experimental data, including a motion correction procedure to resolve the undesired head movements in the fMRI sessions.

In relation to fMRI data the first 10 volumes were discarded for correction of the magnetic saturation effect, and the remaining volumes were slice-time corrected for temporal alignment. All voxels were spatially smoothed with a 6 mm FWHM isotropic Gaussian kernel and after intensity normalization, a band pass filter was applied between 0.01 and 0.08 Hz (Cordes et al., 2001) which was followed by the removal of linear and quadratic trends. Finally, the functional data were spatially normalized to the MNI152 brain template.

T1-weighted images were reoriented to match the same axes as the templates, and a resampled AC-PC aligned image with six degrees of freedom (df) was created. All nonbrain tissue was removed to obtain an anatomical brain mask that would be used to parcel and segment the T1-weighted image data. The use of DARTEL templates was ruled out since some previous analyses did not identify significant differences when using general templates. The final step involved registering our structural imaging data to normalized space using the Montreal Neurological Institute reference brain based on the Talairach and Tournoux coordinate system (Ashburner & Friston, 1999). Finally, during the sessions, a caregiver of the person evaluated focused on helping the participants avoid unnecessary that could lead to exclusion.

ROI's:

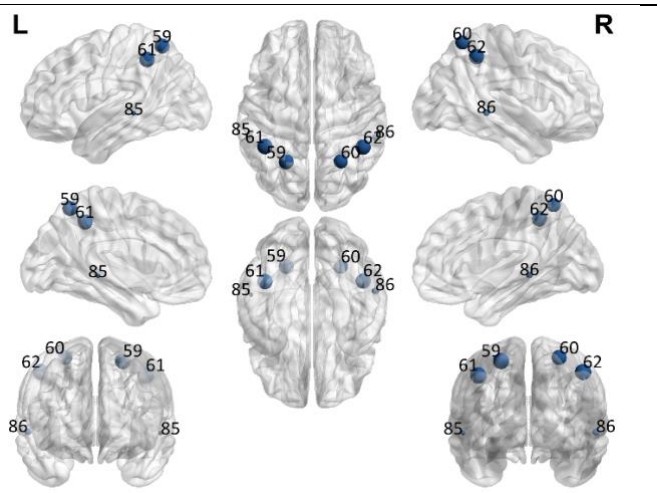
The automated anatomical labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) was used to define ROIs. This atlas contains 45 cortical and subcortical areas in each hemisphere (90 areas in total), which are alternatively interspersed (available by request). To acquire the full signal of a given ROI, it was necessary to compute an average over the entire time series of all the voxels of a given brain area following the AAL atlas. In relation to the objective of the present study regarding the brain connectivity patterns in people with DS, we identified only the DMN. The posterior DMN subnetwork included the lateral parietal and middle temporal

gyrus (Farras-Permanyer et al., 2019) as indicated in table 14. This selection was justified on two criteria. The first criterion is that this network represents the most basic functioning of the DMN; therefore, it should be the most sensitive structure of tall the subareas that comprise the most extensive DMN network (Farras-Permanyer et al., 2019). The second criterion refers to the computational difficulties derived from estimating such a large number of possible structural models, which imposes a series of restrictions regarding the number of ROIs and networks to consider.

Table 14

Relationship of ROIs for the construction of the DMN according to the AAL90 atlas and their spatial localization.

DMN		
ROI	Roi AAL90	Region name
1	59	Parietal_Superior_Left
2	60	Parietal_Superior_Right
3	61	Parietal_Inferior_Left
4	62	Parietal_Inferior_Right
5	85	Temporal_Middle_Left
6	86	Temporal_Middle_Right



Statistical Analysis:

Once the images were preprocessed, correlation matrices were obtained between the 6 ROIs mentioned in table 13 for each subject evaluated. To avoid the aberrant effect of values in some especially high or low ROIs (outliers), the jackknife correlation was estimated. There are other simulation possibilities for estimating statistical significance, but for small samples, jackknife correlation is still recommended. This technique consists of calculating all the correlation coefficients between all the possible ROI pairs, and one of the observations is

excluded on each occasion. The average of all the correlations for each ROI pair attenuates the effects of the outliers. Each jackknife correlation coefficient was estimated using the following expression:

$$\theta_{(ROIi,ROIj)} = Jackknife\ Correlation\ Mean\ (ROIi, ROIj) = \frac{1}{n}\sum_{k=1}^{n} r_i$$

where r_i is Pearson's correlation between each pair of ROIs and n is the sample number in which the correlations in each pair have been estimated by extracting the record (volume) *i*. The SE of each average was also estimated from the expression:

$$SE = \sqrt{\frac{n-1}{n}\sum_{i=1}^{n}(r_i - \theta)^2}$$

This allowed confidence interval estimation for each correlation coefficient. Selecting either the correlation coefficient obtained with the whole sample or the one obtained through jackknife estimation depended on the bias value obtained. Bias was defined by the following expression:

$$Bias = (n-1) * (\theta - \hat{r})$$

For each correlation between ROIs, the bias value was obtained, and when this was close to 0, the average jackknife value was used. In cases in which bias was different from 0, the lower limit value of the confidence interval was used to avoid the probability of a type I error. To perform these analyses, the dist R library (3.6.3) was used. The different correlation matrices were used used as input for the estimation of each SEM for each subject in both groups.

In essence, the adjustment of all structural models was performed by minimizing the matrix $(R - \Sigma)$. This expression, involves the reproduction (Σ) of the initial matrix of correlations (R) between ROI's observed distributions. In other words, the result shows the best possible model for each subject, taking into account the incorporation of the recursive and nonrecursive effects between ROIs and incorporation the lang effects already described. A much broader description of SEMs applied to this context can be found in Guàrdia et al. (2018b), and thus, under certain conditions, the SEM is exactly the same as the DCM. The difference in the current case, as already mentioned, is the incorporation of the dynamic effect.

Results:

Table number 15 shows the result of the adjustment models for each of the subjects analyzed according to the previously defined groups. It is important to highlight that this targeted classification offered a modularity value of 0.0139 which would indicate the non-existence of other communities that were different from the two proposals, a group of DS persons and another group of control persons.

Table 15

Fit indexes of each SEM model.

SUBJ	χ^2	df	Ratio χ^2/df	Parameters estimated	p value	RMSEA	SRMR	NNFI	CFI	BIC	AIC	Log L	Group
1	191.8731	27	7.11	63	<.001	0.167	0.023	.910	.963	3414.03	3200.52	-1537.26	PWDS
2	218.4414	27	8.09	63	<.001	0.179	0.018	.899	.959	3274.80	3061.29	-1467.64	PWDS
3	241.6815	25	9.67	65	<.001	0.198	0.022	.897	.961	2376.82	2156.53	-1013.26	PWDS
4	168.9308	26	6.50	64	<.001	0.158	0.033	.919	.968	3377.41	3160.51	-1516.25	PWDS
5	225.2993	27	8.34	63	<.001	0.183	0.027	.884	.952	3763.02	3549.51	-1711.75	PWDS
6	227.5189	29	7.85	61	<.001	0.176	0.027	.922	.965	2058.62	1851.88	-864.94	PWDS
7	302.5942	28	10.81	62	<.001	0.211	0.036	.888	.952	2171.63	1961.51	-918.75	PWDS
8	218.4397	29	7.53	61	<.001	0.172	0.021	.922	.966	2365.59	2158.85	-1018.42	PWDS
9	231.1276	26	8.89	64	<.001	0.189	0.021	.889	.956	3263.38	3046.48	-1459.24	PWDS
10	338.1405	32	10.57	58	<.001	0.209	0.025	.873	.938	3036.03	2839.47	-1361.73	PWDS
11	174.5769	22	7.94	68	<.001	0.178	0.033	.909	.969	2857.04	2626.58	-1245.29	PWDS
12	340.9745	33	10.33	57	<.001	0.206	0.023	.903	.951	1651.15	1457.97	-671.98	PWDS
13	193.8546	31	6.25	59	<.001	0.154	0.030	.922	.963	3453.65	3253.70	-1567.85	PWDS
14	280.8342	31	9.06	59	<.001	0.191	0.019	.894	.950	2922.68	2722.73	-1302.36	PWDS
15	271.0832	30	9.04	60	<.001	0.191	0.034	.913	.960	1827.89	1624.55	-752.27	PWDS
16	299.5114	26	11.52	64	<.001	0.219	0.022	.892	.957	1589.88	1372.98	-622.49	PWDS
17	276.2692	32	8.63	58	<.001	0.186	0.016	.905	.954	2555.82	2359.26	-1121.63	PWDS
18	263.6547	28	9.42	62	<.001	0.196	0.021	.894	.955	2727.12	2517	-1196.5	PWDS
19	291.7739	25	11.67	65	<.001	0.220	0.017	.876	.953	2336.86	2116.57	-993.28	PWDS
20	275.042	35	0.79	55	<.001	0.177	0.036	.914	.954	2634.48	2448.08	-1169.04	PWDS
21	319.3598	37	8.63	53	<.001	0.186	0.024	.911	.950	2261.42	2081.80	-987.90	PWDS
22	417.0518	34	12.27	66	<.001	0.273	0.017	.796	.925	2847.41	2623.73	-1245.86	PWDS
23	197.524	28	0.71	62	<.001	0.166	0.044	.913	.963	3275.26	3065.14	-1470.57	Control
24	202.0626	32	6.31	58	<.001	0.155	0.024	.932	.967	2725.41	2528.84	-1206.42	Control
25	348.7178	36	9.69	54	<.001	0.199	0.024	.909	.950	1668.12	1485.11	-688.55	Control
26	209.3197	31	6.75	59	<.001	0.162	0.022	.905	.955	3883.22	3683.27	-1782.63	Control
27	334.9779	35	9.57	55	<.001	0.197	0.018	.906	.950	1986.09	1799.69	-844.84	Control

28	264.1082	36	7.34	54	<.001	0.170	0.014	.938	.966	1075.90	892.89	-392.44	Control
29	273.0015	35	7.80	55	<.001	0.176	0.036	.921	.958	2250.01	2063.61	-976.80	Control
30	232.3735	33	7.04	57	<.001	0.166	0.022	.922	.961	2763.95	2570.77	-1228.38	Control
31	192.4308	37	5.20	53	<.001	0.138	0.017	.940	.966	3204.28	3024.66	-1459.33	Control
32	254.8419	33	7.72	57	<.001	0.175	0.035	.928	.964	1754.87	1561.69	-723.84	Control
33	295.6647	35	8.45	55	<.001	0.184	0.018	.909	.952	2548.80	2362.41	-1126.20	Control
34	253.6002	35	7.25	55	<.001	0.168	0.022	.928	.962	2154.40	1968.00	-929.00	Control
35	263.7589	31	8.51	59	<.001	0.185	0.033	.921	.963	1679.04	1479.09	-680.54	Control
36	244.5833	39	6.27	51	<.001	0.155	0.014	.946	.968	1411.35	1238.51	-568.25	Control
37	322.3649	39	8.27	51	<.001	0.182	0.014	.916	.950	2215.97	2043.12	-970.56	Control
38	275.5027	35	7.87	55	<.001	0.177	0.017	.910	.952	2875.64	2689.24	-1289.62	Control
39	193.1305	31	6.23	59	<.001	0.154	0.028	.931	.968	2827.17	2627.21	-1254.60	Control
40	291.5398	39	7.48	51	<.001	0.172	0.027	.926	.956	2122.56	1949.71	-923.85	Control
41	307.095	31	0.99	59	<.001	0.201	0.028	.898	.952	2200.34	2000.38	-941.19	Control
42	291.1519	29	10.04	61	<.001	0.203	0.025	.889	.951	2597.86	2391.12	-1134.56	Control
43	334.1892	34	9.83	56	<.001	0.200	0.018	.905	.951	1843.28	1653.50	-770.75	Control
44	260.0007	39	6.67	51	<.001	0.160	0.049	.926	.956	2827.91	2655.07	-1276.53	Control

Note: χ^2 = chi square estimation; df = degree of freedom; a ratio $\chi^2/df > 3$ indicates good fit; RMSEA= root mean square error adjusted (RMSEA ≈ 0 indicates a better fit); SRMR = standardized root mean residual (SRMR ≈ 0 indicates a better fit); NNFI = non normed fit index (NNFI > .90 indicates a better fit); CFI = comparative fit index (CIF > .90 indicates a better fit) ; BIC = Bayesian information criteria (smaller indicates a better fit) ; AIC = Akaike information criteria (smaller indicates a better fit); Log L = logarithm of maximum likelihood (ML) function (smaller indicates a better fit); PWDS = person with DS.

Tables 16a and 16b show the number of parameters with statistically significant effects in each of the six ROIs considered and differentiated for each group -persons with DS and controls. Figure 12 summarizes these results and presents the total number statistically significant parameters.

Table 16a

The number of statistically significant parameters in the group number 1 of control persons with DS.

	GROUP NUMBER 1											
	ROI1 Lag	ROI2 Lag	ROI3 Lag	ROI4 Lag	ROI5 Lag	ROI6 Lag	ROI1	ROI2	ROI3	ROI4	ROI5	ROI6
ROI1	22	0	22	3	2	5	0	0	22	3	2	6
ROI2	22	22	5	22	1	3	22	0	5	22	2	4
ROI3	2	3	22	22	7	1	2	2	0	22	7	2
ROI4	2	0	1	22	1	0	1	0	1	0	1	0
ROI5	1	6	6	1	22	22	4	5	6	2	0	22
ROI6	1	0	2	22	4	22	1	0	4	22	2	0

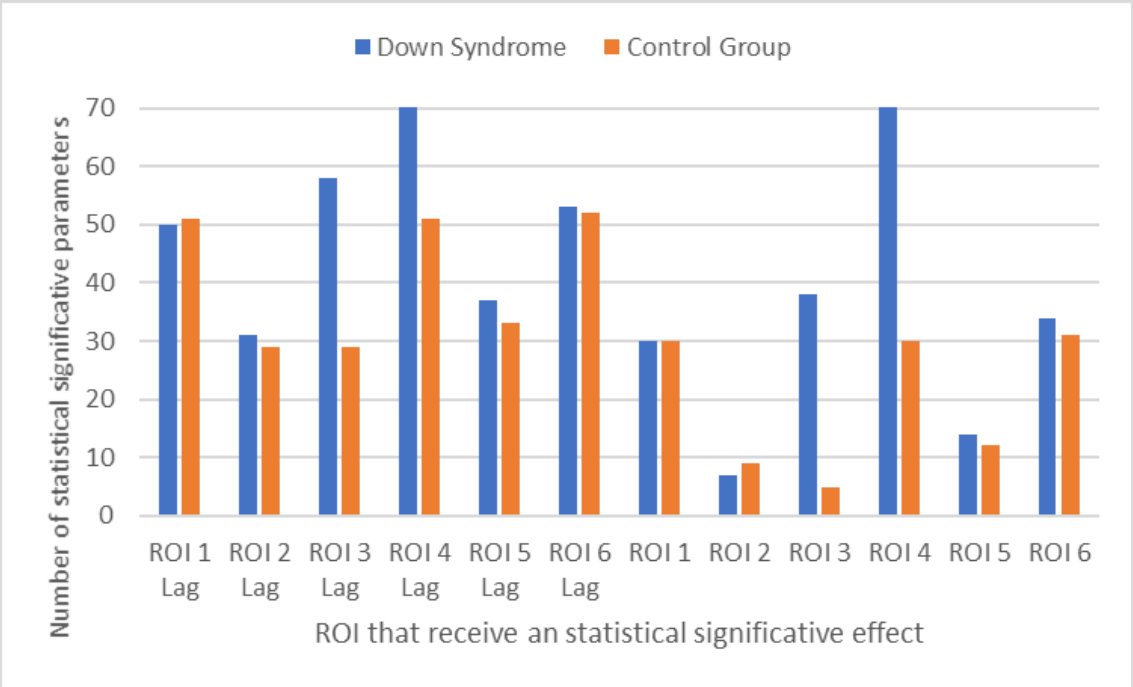
Table 16b

The number of statistically significant parameters in the group of control persons.

	GROUP NUMBER 2											
	ROI1 Lag	ROI2 Lag	ROI3 Lag	ROI4 Lag	ROI5 Lag	ROI6 Lag	ROI1	ROI2	ROI3	ROI4	ROI5	ROI6
ROI1	22	2	2	1	2	2	0	1	2	1	3	2
ROI2	22	22	1	3	1	1	22	0	0	3	1	1
ROI3	2	1	22	22	3	2	3	3	0	22	4	2
ROI4	1	2	1	22	5	3	1	3	2	0	4	4
ROI5	0	1	2	1	22	22	0	1	1	2	0	22
ROI6	4	1	1	2	0	22	4	1	0	2	0	0

Figure 12

The total number of statistically significant parameters detected in each of the two groups.



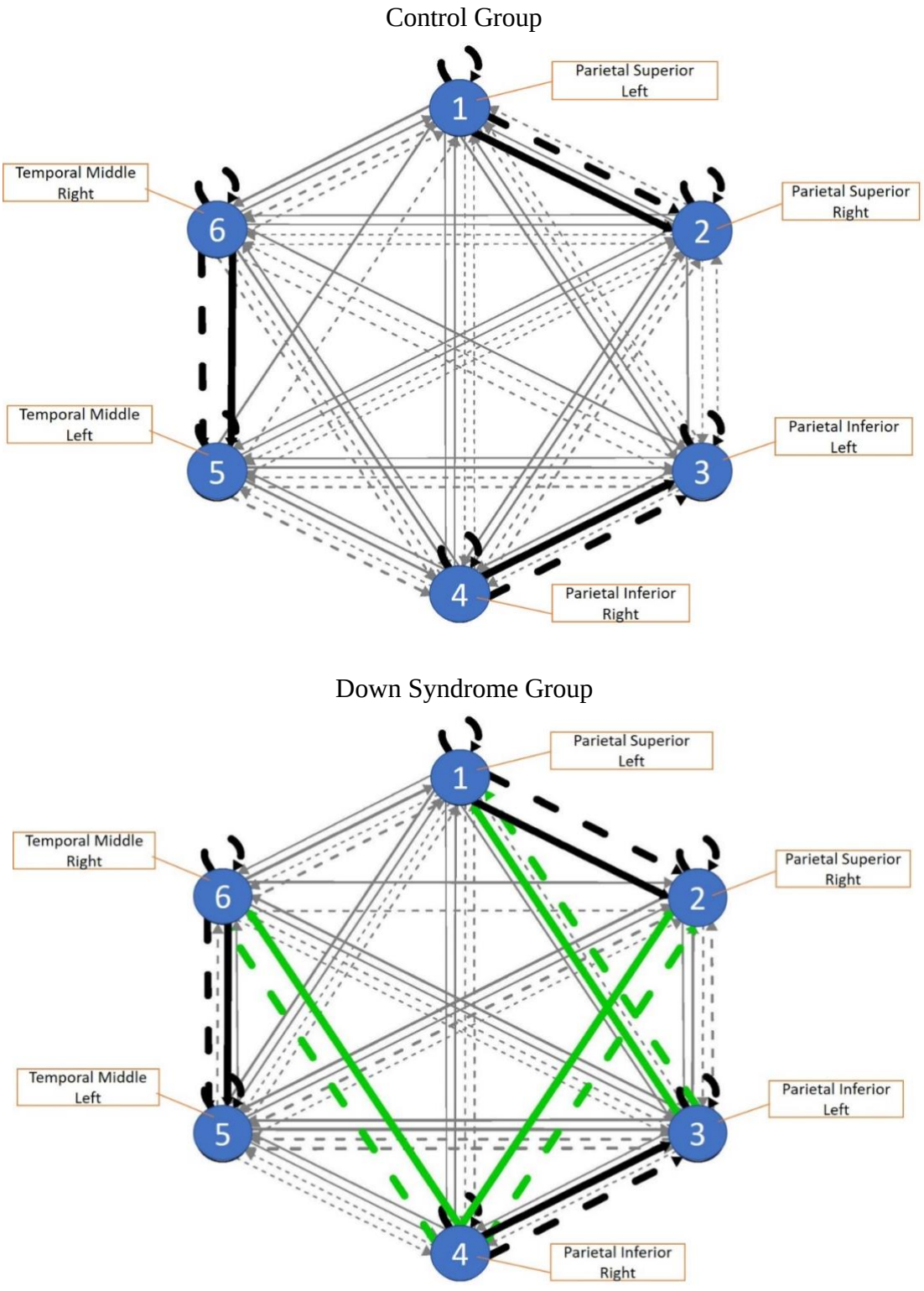
Note: Each column assumes the number of effects that each ROI receives, regardless of the original ROI, in a synchronous situation or lag 1.

Given these results, concordances between the two groups were verified, especially regarding the variations in differential functioning of the effects related to ROI numbers 3 and 4 (Parietal_Left and Parietal_Lower_Right). Figure 13 shows the characteristic SEM models of each group, taking into account the 22 subjects in each group with better-fitting SEMs were selected as examples.

Given these results, two subjects from each group with better-fitting SEMs models were selected as examples. These four models are shown in figure 14.

Figure 13

Path diagram representation of each group.



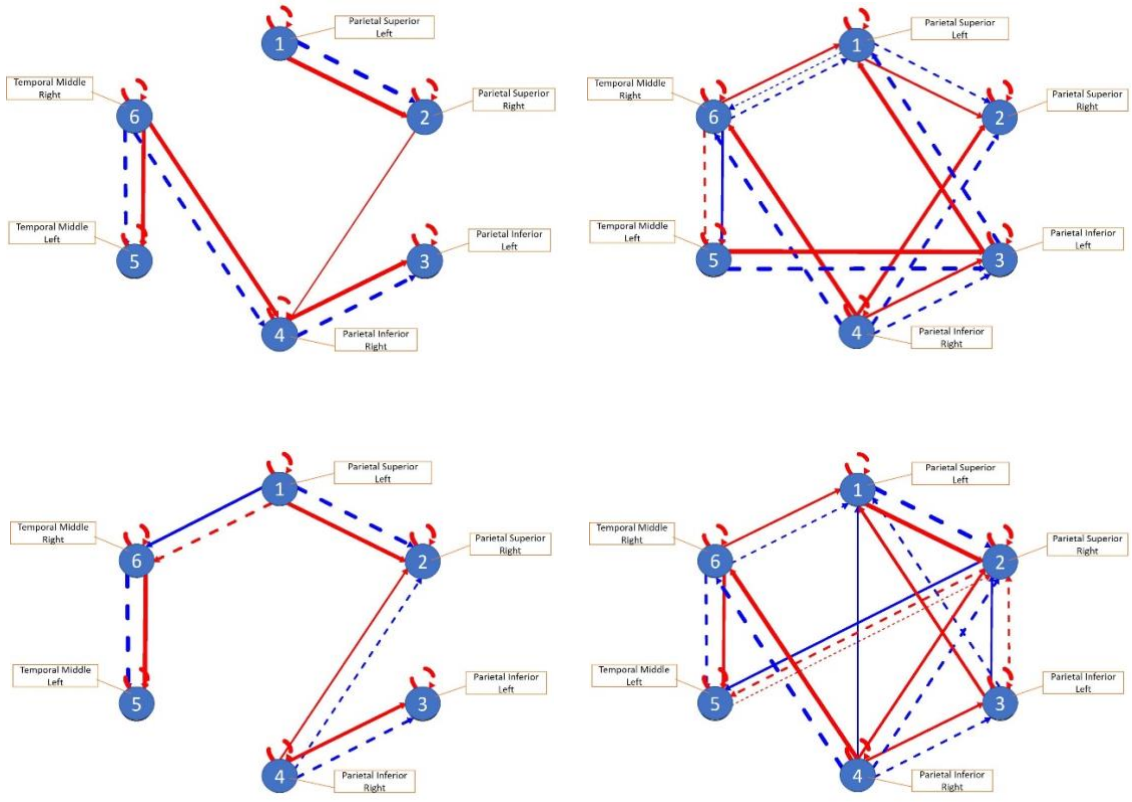
Note: Black paths are group-level, green paths are subgroup-level, and grey paths are individual-level, the thickness of the line represents the count.

Figure 14

Only two models from each group to were selected to show the differences between adjusted SEMs models.

Control Group
Subjects number 25 and 27

Down Syndrome Group
Subjects number 7 and 19



Note: Red paths represent positive weights and blue paths represent negative weights. Dashed lines denote lagged relations (lag 1), and solid lines are contemporaneous (lag 0).

Concerning the second proposed objective, the analysis described above was reproduced, but without any directed classification. That is, we estimated the matrix of similarities among the 44 models to establish the number of detectable communities. The results showed a total of two communities, consistent with the number of groups defined (a

control group and a DS group). Also, the modularity obtained in the nondirected classification was 0.0468, which would again indicate several communities no greater than those found.

These results imply that a total of 36 subjects (81.82%) were correctly classified into two different groups; group number 1 consisting of individuals with DS (17) and group number 2 consisting of controls (19). In this case, the percentages of correct classification for each group were 77.27% for the DS group and 86.36% for the control group. However, 3 subjects in the control group were classified in the DS group, and 5 members in the DS group were classified in the control group. In addition, whether any of the sociodemographic variables could be related to the correct or incorrect classification was investigated. No statistically significant relationship was found that would allow us identify a systematic factor that would explain the correct or incorrect classification.

Furthermore, it seems interesting that the percentage of correct classification was higher in the control group than in the SD group. We believe that the 9.09% difference in correct classification between groups could be attributed to the fact that in the DS group, there is more intersubjective variability that may make it difficult to recognize typical patterns for that group. However, the sample sizes do not allow for stronger explanations.

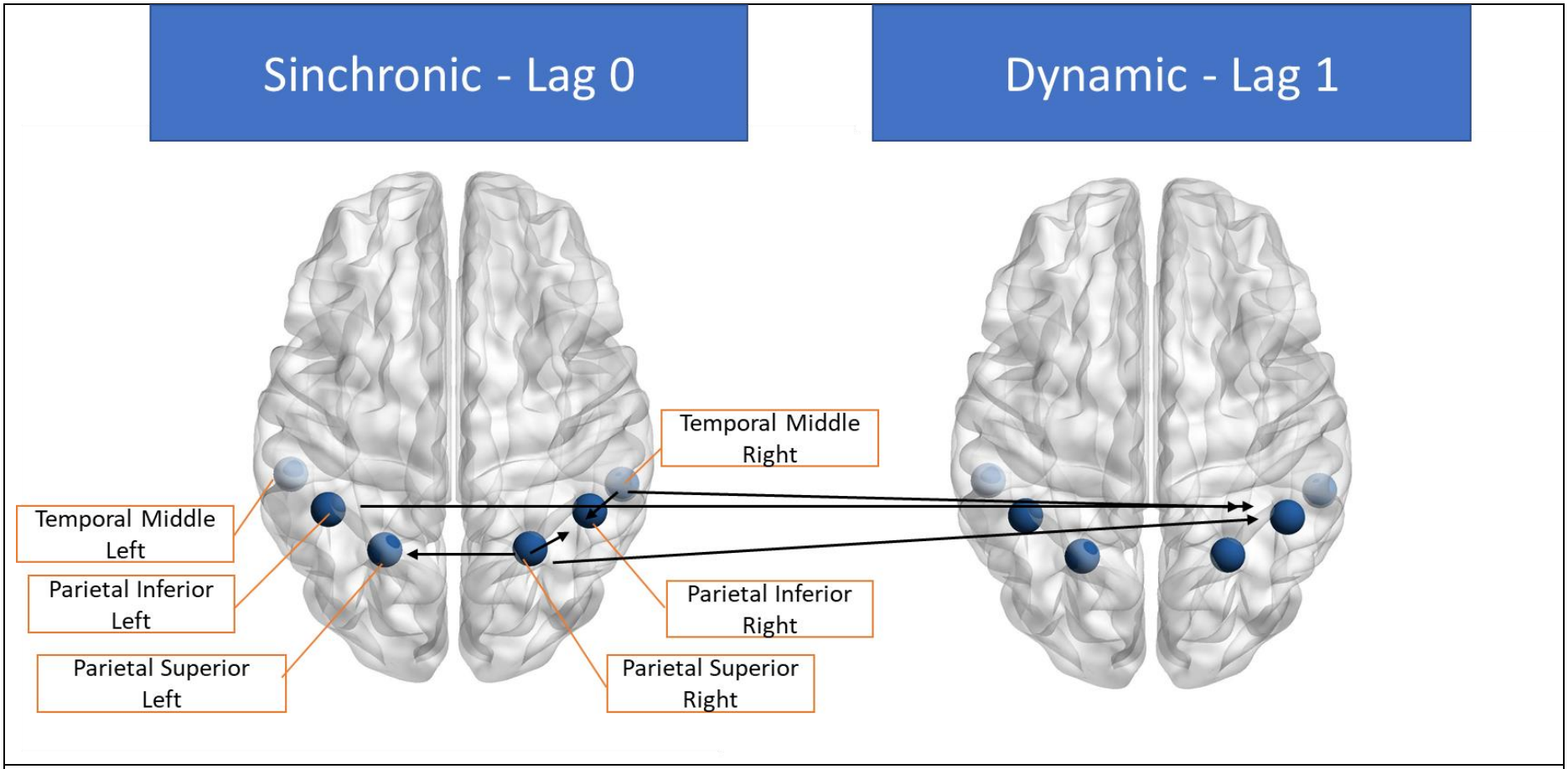
The differences in the SEM models structure for each group can be complemented with the analysis of the statistically significant effects values found in each subject. Each one of the 44 adjusted models was analyzed (Table 14) and the concrete values of the parameters between ROI's were studied; consequently, some evidence on the density of effects in each subject and group was obtained. For this purpose, all the values of the standardized parameters were positive and the following results were obtained. In the group of DS persons, 251 significant effects were obtained whereas in the group of controls persons, only 98 were obtained; which implies a $OR = 2.56$. This clearly indicates a greater number of effects in the DS Group. In

relation to the value of the estimated parameters, in the DS group the mean value was *M* = 3.49 (*SD* = 0.293) and in the control group, the mean value was *M* = 4.21 (*SD* = 0.296).

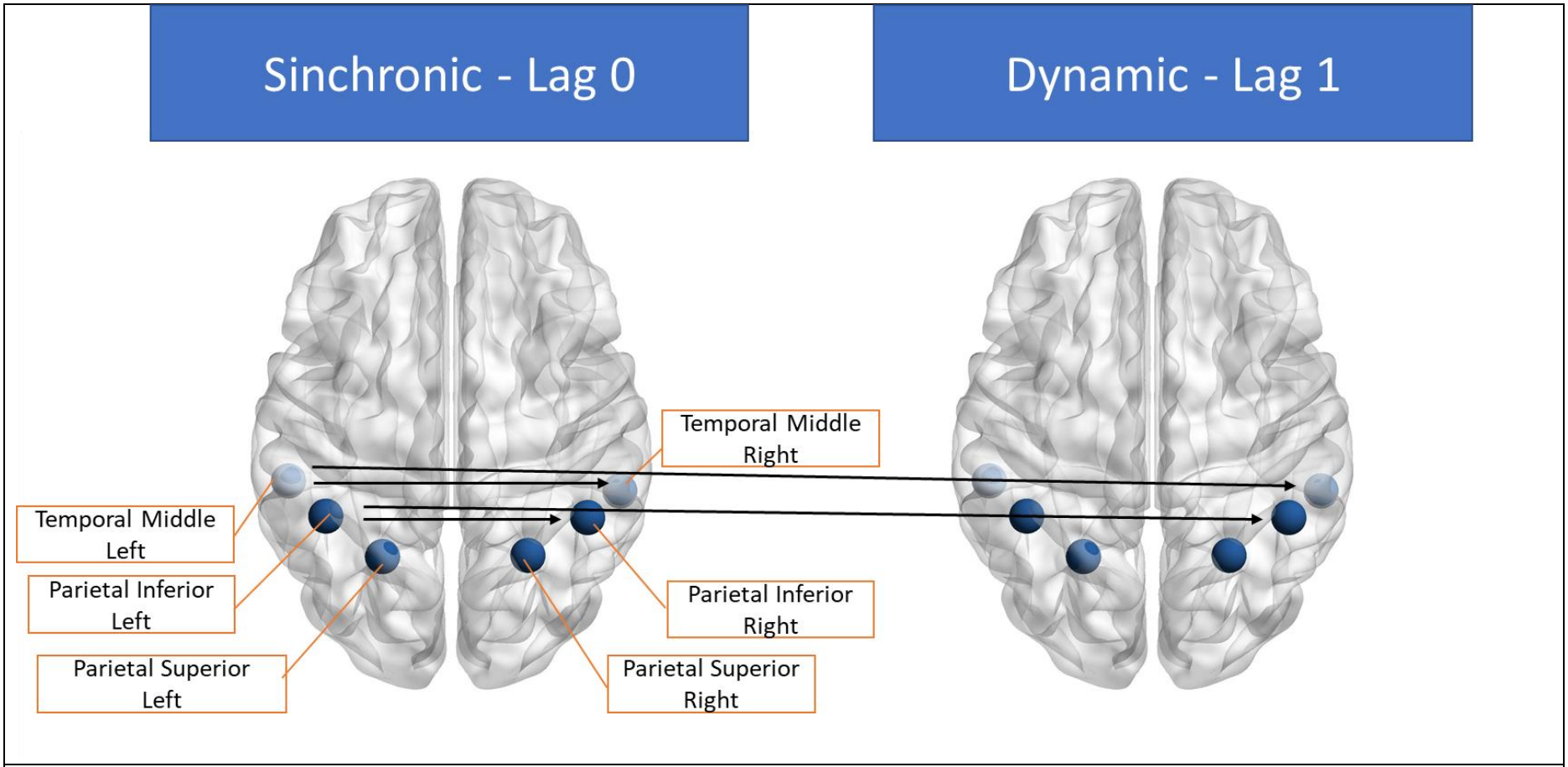
The comparison between both means indicates a statistically significant effect [*t* = 2.054; *df* = 347; p_{uni} = .0205; *95% CI difference* = 1.41-3.05; *r* = .11] although with a smaller effect size. In relation to the characteristics of the effects, the values of the estimates were compared to evaluate synchronous effects and dynamic effects. The results indicated a total of 179 synchronous effects and 170 dynamic effects in lang 1. In this case, no statistically significant differences were found between these two types of effects in terms of parameter values (positivized) [*t* = 0.972; *df* = 347; *p* = .332]. In the case of synchronic effects, the average was *M* = 3.54 (*SD* = 0.28) and in the case of dynamic effects *M* = 3.85 (*SD* = 0.23). Finally, the possible interaction between groups and types of effects was analyzed by simple factorial ANOVA. The results indicate that there was no statistically significant effect on the interaction between groups (*F* = 0.045; *df* = 1, 345; *p* = .832) so we must rule out differential effects between groups and effects. Therefore, between the two groups, differences were shown in the synchronous and dynamic effects associated with ROI's 3 and 4 and in the number of significant effects, which was greater in the case of the DS group, that difference was not related to the synchronous or dynamic effects that were similar between the two groups. Finally, the parameters values in the control group were somewhat higher than those in the DS group, with a much lower number of significant effects, but a somewhat higher value. Figure 15 shows the most distinctive effects of those shown in figure 13 but identifies the brain areas included in the dynamic effects. The effects that are more repeated in each group were selected to facilitate the identification of the best effects. Figure 15 shown the most frequent effects in both groups.

Figure 15

Spatial representation of global structural equation model for each group.



DOWN SYNDROME GROUP



CONTROL GROUP

Conclusions

In this paper, we compared the results obtained in the adjustment of dynamic SEMs models (including effects associated with Lag 1) in two groups of people. One of them focused on DS persons, and the other focused on control persons. Both groups were paired by age and sex. The results were obtained with the GIMME library. Although the DS group showed more statistically significant effects (almost four times more effects ofthe control group), the impact effect was higher in the control group. There were no differences between the two groups concerning the number of synchronous or dynamic effects. Nevertheless, the structural differences between the global models of the two groups were associated with the presence of more effects between ROI numbers 3 and 4 in the DS group rather than the effects in the control group. These two ROIs imply the areas of the upper parts on the left and right, which indicates an asymmetrical effect in the synchronic estimation that is also manifested in the dynamic range defined in lag 1.

Buckner et al. (2008), Bonnelle et al. (2012) and Kucyi & Davis (2014) found that DMN functional connectivity is associated with cognitive brain function. These areas integrate the association cortex related to the processing of all spatially oriented and fine motor stimuli that arrive through visual information. This connection is evident when we see that there are more effects between networks ROIs 3 and 4 in the DS group than in the control group. This is to be expected in task involved studies such as in Garrett et al. (2011) and Liang et al. (2013); these authors inferred that an increase in such undirected tracking would be linked to poorer task performance during task stimuli that a greater complexity network, whether dynamic or static, would be expected.

Through this study we demonstrate that the same outcome is evident in. a resing situation when comparing the DS group with a control group. This finding alludes that the connectivity patterns are different and that DS are more complex than control networks. Both of these

characteristics are due to the existence of more significant effects in the DS group but with a lower value compared to that of the control group; the control group presents fewer effects but with a greater value than that of the DS group. Therefore, there is no difference concerning between the DS group and the control group does not seem to be in the dynamic component; it seems to be more evident in the complexity component.

By taking into account the models of each person with DS and the control group using the SEM technique, we demonstrate that the network pattern could be a biomarker that clarifies and helps to discriminate the different levels of cognitive competence. In this case, the differences were very extreme given the conditions between both comparison groups. It is important to take into account that this study was conducted with two comparison groups with large difference between them. Therefore, it is important to initiate new studies with two groups not as different, mainly at the cognitive level. From our data, the very evident capacity to correctly distinguish between persons with DS and controls should be considered a good first step for the proposal of a biomarker based on the study of the network complexity. The 81.82% of correctly classified individuals found in our data is a good principle, but only that.

Furthermore, there was a sample percentage that was incorrectly classified (18.18%) and we do not know what variables could explain this behavior. We should pay attention to these subjects, in future studies to identify the cognitive properties and any other that could adequately describe the behavior of that blurred area between both groups.

The limitations we encountered were evident from the type of analysis that the SEM technique is based on. On the other hand, it is difficult to compare brain structures between persons with DS and controls, not only for morphological reasons but also for functioning. The sample size was small, and this must be taken into account in excessive generalizations. Moreover, the control group was not a group registered using the same protocol. It was a group extracted from the Connectome project and was a possible source of noise. In this sense, it

seems reasonable to ask whether the use of a control group matched by mental age (not by chronological age) could offer interesting results in relation to be type of dynamic connectivity studied here. Our experience is that the generation of control groups matched by mental age implies, in general such reduced mental ages that the comparison in neurofunctional and structural neural systems becomes difficult and is scarcely clarifying. However, this question a study between persons with DS and a control group matched by mental age that would confirm the results found here, since we understand that the question, in the case of people with DS, connectivity processes may be innately affected.

Similarly, the 6 ROIs evaluated limited connectivity and therefore had a very small scope. We must solve computer-related problems to carry out larger studies with complete brain atlases.

Apart from the above considerations, our data allowed us to identify the first results in the estimation of dynamic connectivity networks in a sample of DS people. Furthermore, there was enough evidence to affirm that there is a differential pattern of dynamic connectivity between a sample of DS people compared to a sample of controls and that this pattern suggests that DS persons show a more complex connectivity network than that of the control group. These results, in addition, suggest that the complexity of a connectivity network could be an efficient biomarker for discrimination between these groups. Obviously, these statements should be reserved for the people evaluated, and studies with a greater number of ROIs are required, with a much more exhaustive analysis of the mediating variable that can occur in a complex population such as in people with DS (attention levels, mood, other comorbid structures, etc.). Finally, although the sample in this study was small, it was in line with other papers published with similar and even lower samples sizes.

Capítulo 7.
Discusión y conclusiones

Discusión

La presente tesis pretende estimar los patrones de conectividad funcional y conectividad efectiva dinámica en un grupo de jóvenes con síndrome de Down y en un grupo control en situación de reposo, a partir de indicadores de complejidad de la amplia red DMN en relación con pruebas neuropsicológicas y del estudio de redes de sistemas complejos.

Para abordar correctamente la temática se realizaron tres estudios que repondieran a este objetivo.

A continuación se discutirán los principales resultados de los estudios, a fin de mostrar una discución general que permita abordar detalles tratados hasta el momento y posteriormente elaborar conclusiones principales, con recomendaciones, limitaciones y futuras líneas de investigación.

- **Aproximaciones en la variabilidad de la densidad de conectividad.**

De acuerdo a los resultados obtenidos en el análisis de la conectividad funcional de la redes de la DMN en personas con DS, se ha demostrado la amplia variabilidad en la densidad de la conectividad que cada participante presenta, así como el resultado promedio de redes que muestran una mayor conectividad, como la red sensoriomotora y la red visual. Las demás conexiones entre las ROIs resultaron ser estadísticamente significativas aunque en menor intensidad.

En relación al grupo control, los resultados indican que estas redes son similares a las de las personas con síndrome de Down, pero están en menor intesidad de conexión entre las ROIS. Este efecto, no es diferente al reportado en similares estudios con otras poblaciones (Smitha et al., 2021), incluyendo estimación de redes en personas sanas (Farras-Permanyer et al., 2019).

- **La red DMN de las personas con síndrome de Down**

A través de los estudios realizados se caracterizó la red DMN en personas con síndrome de Down con mayor conectividad es la red DMNv, relacionada con el procesamiento visuoespacial y la codificación de información, a través de la vía visual y auditiva, así como las áreas sesnsoriomotoras y visuales, que fueron las que reportaron un grado más alto de conectividad dentro de las ROIs, en comparación con la DMNa, caracterizada por el procesamiento emocional, control del estado de ánimo y de la red DMN posterior, relacionada con el reconocimiento de información. Este hallazgo es consistente con el estudio de Pujol et al. (2015) que reportó mayor conectividad en el sistema cerebral ventral en oposición al sistema cerebral anterior. Por lo tanto, nuestros resultados indican un perfil de conectividad en personas con síndrome de Down en relación con los que no tiene síndrome de Down, con mayor conectividad funcional y/o fuerza correlativa dentro de la DMN entre la corteza prefrontal medial, es decir, la DMNv, que disminuye progresivamente a medida que

aumenta la edad, lo cual es congruente con lo reportado por Mak et al. (2017). Sin embargo; falta una explicación razonable para la sobreactivación que se mostró en áreas sensoriomotora y visuales, puesto que parace plausible suponer que las personas con síndrome de Down evaluados tenían anomalías con el seguimiento de los ojos durante la grabación, que podía generar estas difrerencias y movimientos en extremidades inferiores y superiores. Del mismo modo, las características morfológicas de personas con síndrome de Down, como las disminuciones en el cerebelo, en la corteza prefrontal, hipocampo y circonvolución del lóbulo temporal, así como circuitos de redes que presentan menor extensión y una inferior capacidad organizativa (Flòrez et al., 2015), puede complementar la descripción de la excesiva activación detectada en el estudio.

De igual manera, es importante considerar que no se puede establecer de manera clara la intersubjetividad y variabilidad que se mostró en el comportamiento de las redes en términos de densidad en la conectividad. Puesto que pueden estar influyendo el efecto de variables externas (p. Ej., factores cognitivos o de reserva cognitiva, así como aspectos psicológicos como la calidad de vida), para explicar este fenómeno.

- **La complejidad de la red DMN en 48 ROIs en personas con síndrome de Down y grupo control.**

A través de los estudios se constató que a partir de emparejar al grupo de personas con síndrome de Down con el grupo control por edad y sexo, se mostró que el primer grupo tenía redes mucho más complejas en las diferentes subredes, asi como mayor variabilidad que con el grupo control.

De acuerdo a los indicadores de complejidad en las personas con síndrome de Down se reveló que en relación a las medidas de segregación, los valores fueron mayores que los del grupo control, tal cual Lloyd (2001) reportó en un grupo con sindrome de Down en relación al coeficiente de agrupamiento global.

En cuanto a las medidas de integración, las personas con síndrome de Down, tanto la capacidad de transmisión y de conectar la informacion en su totalidad en el cerebro, se encuentra alterada, cómo también lo reportó Xu et al. (2020). El indicador de modularidad por su parte, se incrementa en las personas con rendimiento congitivo inferior, lo que fue perceptible en los estudios, en los indicadores de medidas de coeficientes de agrupamiento global, de complejidad y en el número de triángulos. La densidad fue mayor en las subredes de la red DMNv y en la red DMNa. Sin embargo, por el tamaño de la muestra utilizada, estos resultados no son más que descripciones iniciales. Lo que es notorio son las grandes diferencias en la estimación de las subredes DMN en personas con síndrome de Down.

El valor medio en el número de comunidades en cada subred indicó la imposibilidad de asumir que cada subred estaba configurada con una única red dirigida. Esto muestra una anomalía en la estructura de la DMN global y sus redes en términos de complejidad de la red. Todos estos resultados confirman la apreciación sobre el

comportamiento aberrante de las redes de conectividad en las personas con síndrome de Down. Por lo que se puede inferir que estó este asociado con graves alteraciones cognitivas. Que de acuerdo, a los resultados obtenidos por la aplicación de pruebas neuropsicológicas, con la evaluación específica de funciones efecutivas y del coeficiente intelectual de solo el grupo con síndrome de Down, se encontraron resultados estadísticamente significativos en la predicción de los puntajes de la prueba FAB y las subpruebas de vocabulario y matrices de la prueba KBIT. Lo que indicó un efecto positivo de la edad mental derivado del KBIT (vocabulario) y del efecto negativo de algunos indicadores de complejidad.

Los signos de los parámetros nos permiten verificar nuestra expectativa de que los aumentos de complejidad están relacionados con un peor desempeño en el vocabulario y en el funcionamiento ejecutivo. Esto es importante relacionarlo con el bajo nivel congitivo y de rendimiento de las personas con síndrome de Down. Por lo tanto, mientras mayor sea el número de comunidades, implica que hay una mayor desagregación de la red, por consecuencia, mayor complejidad asociada a un puntaje psicométrico bajo.

En las predicciones de las puntuaciones del FAB y de vocabulario (KBIT), este efecto tambien se incremento, lo que permite concluir que la estructura de la complejidad de las redes de conectividad funcional esta inversamente relacionada con el desempeño cognitivo, específicamente con el vocabulario y el funcionamietno ejecutivo.

Estos resultados pueden ser congruentes con algunos otros estudios con diferentes poblaciones con trastornos psicológicos, psiquiátricos y neurobiológicos,

en el sentido de las anomalías que estudian en las redes dirigidas (Bassett et al., 2008; Leistedt et al., 2009; Ponten et al., 2009; Stam et al., 2007; Stam et al., 2009; Wang et al., 2009).

- **Patrones de conectividad efectiva con modelos de ecuaciones estructurales en personas con síndrome de Down y grupo control.**

A través de los resultados del tercer estudio, se hizo evidente que los patrones de conectividad son diferentes que las redes de las personas son síndrome de Down, que son más complejas que las redes del grupo control. Ambas características se deben a la existencia de efectos mas significativos en el grupo de personas con síndrome de Down pero con un valor menor en comparación con el grupo control. A través de la técnica SEMs, se demostró que la red de patrón podría ser un biomarcador que clarifique y ayude a discriminar los diferentes niveles de competencia congitiva. En este caso, las diferencias son extremas dadas las condiciones de ambos grupos, especificamente el nivel cognitivo. Se mostró que el 81.82% de los participantes se clasificaron correctamente, sin embargo el 18.18% no fue así y se desconoce que variables podrían explicar este comportamiento de los datos. También se hizo evidente que es díficil comparar estructuras cerebrales en personas con síndrome de Down y controles, no solo por razones morfológicas sino tambien por su funcionamiento. Aún así los resultados otenidos reflejan la complejidad y variabilidad de conectividad funcionay dinámica en una población con carácterísticas muy heterogeneas.

Conclusiones generales

Teniendo en cuenta los resultados obtenidos en los estudios llevados a cabo, así como los objetivos que enmarcan la presente tesis doctoral, las conclusiones finales a las cuales se ha podido llegar son las siguientes:

1. Este es el primer estudio que se ha realizado para determinar el comportamiento de las subredes de DMN a través de redes no dirigidas en personas con SD.
2. Existe una enorme variabilidad entre los sujetos en cuanto al comportamiento de la red que muestra un comportamiento muy diferente en términos de la densidad de conectividad detectada en los participantes. Este comportamiento no es exclusivo de la muestra utilizada en este estudio, ya que la variabilidad en las poblaciones que no tienen SD es similar.
3. Se observa una importante variación en los indicadores de complejidad estimados en todos los sujetos y en todas las subredes. Estos resultados concuerdan con los anteriores en el sentido de que la DMN es difícil de identificar en su forma teórica en esta muestra.
4. Algunos indicadores de complejidad para el grupo de SD (essentially the path lengh, the complexity and the Small-World) tienen un impacto estadísticamente significativo y negativo en la predicción del rendimiento en algunas pruebas neuropsicológicas, en este caso, FAB y KBIT. Estos resultados son congruentes con el comportamiento de otras medidas de segregación o integración estudiadas en otras poblaciones en las que también se han evidenciado relaciones de orden inverso con otros tipos de indicadores psicométricos de rendimiento cognitivo.
5. La estructura de complejidad de la DMN y las subredes analizadas son mayores en el grupo de SD en comparación con el grupo de control. Esto está de acuerdo con nuestra hipótesis basada en la estructura de complejidad de la conectividad del cerebro como biomarcador

del estado saludable. Los bajos niveles de complejidad se relacionan con una mejor situación de salud.

6. Teniendo en cuenta los modelos del grupo de personas con SD y grupo control con la técnica SEM, podemos demostrar que el patrón de red podría ser un biomarcador que aclara y ayuda a discriminar los diferentes niveles de competencia cognitiva.
    a. En este caso las diferencias son muy extremas dadas las condiciones entre ambos grupos de comparación. Es importante tener en cuenta que este estudio se realiza con dos grupos de comparación con grandes diferencias a nivel cognitivo y físico entre ellos. Por lo tanto, es importante iniciar nuevos estudios con dos grupos no tan diferentes como éste, principalmente en el nivel cognitivo.
    b. A partir de nuestros datos, se hace evidente la clasificación entre personas con SD y controles de un biomarcador basado en el estudio de la complejidad de la red. El 81,82% encontrado en nuestros datos es un buen principio, pero sólo eso. Además, hay un porcentaje de muestra que está mal clasificado (18,18%) y no sabemos qué variables pueden explicar este comportamiento. Aun cuando el porcentaje de clasificación correcto dentro de cada grupo (personas con SD como grupo 1 con 77,27% y controles como grupo 2 con 86,36%) indiquen especificidad y sensibilidad adecuada, deberíamos prestar atención a estos sujetos mal clasificados, en futuros estudios, para identificar las propiedades cognitivas y cualquier otra que pueda describir adecuadamente el comportamiento de esa zona borrosa entre ambos grupos.
7. Aparte de las consideraciones anteriores, nuestros datos nos permiten identificar los primeros resultados en la estimación de las redes de conectividad dinámica en una muestra

de personas con SD. Además, hay suficientes pruebas para afirmar que existe un patrón diferencial de conectividad dinámica entre una muestra de personas con SD en comparación con una muestra de controles y que este patrón sugiere que las personas con SD exponen una red de conectividad más compleja que la del grupo de control. Lo cual sugiere que la complejidad de una red de conectividad podría ser un biomarcador eficiente para la discriminación entre estos grupos, aún cuando sea evidente las diferencias físicas entre los dos grupos, la conectividad funcional dinámica nos puede ofrecer un panorama más específico de la funcionalidad de la red. Por último, a pesar de que la muestra es pequeña, está en línea con otros trabajos publicados con tamaños de muestra similares e incluso más bajos.

- **Recomendaciones y límites de los estudios**

Se puede considerar para futuros estudios:

1. El tamaño de la muestra es limitado, el grupo de control no es un grupo registrado en el mismo protocolo, sino que es extraído del proyecto Connectome y esto puede estar maximizando las diferencias encontradas.
2. No existen trabajos que hayan estudiado las propiedades psicométricas del DSQIID en muestra española y en el presente trabajo no se ha podido realizar puesto que no se dispone de suficiente muestra para poder llevar a cabo un estudio psicométrico riguroso.
3. La inclusión de un grupo control, al ser una contribución relevante, no deja de presentar dificultades en la interpretación de los resultados debido a las diferencias de morfología cerebral entre los grupos. A pesar de ello, se ha incluido dos plantillas diferentes para establecer mejor las propiedades de la red en el grupo de personas con SD.

4. Cabe señalar que esta labor debe complementarse con un análisis exhaustivo de las funciones cognitivas de las personas con SD para evaluar los posibles vínculos de las propiedades de la red de conectividad con las distribuciones de las pruebas de rendimiento cognitivo.
5. Los resultados obtenidos y su interpretación nos llevan a considerar que la red DMN en la población de SD puede verse afectada por la dificultad de registro de los movimientos interferidos (motores y visuales) y una clara asimetría entre las subredes. Obviamente, la ausencia de este tipo de efectos en el grupo de control debe atribuirse a la ausencia de alteraciones en la red, tanto en términos cerebrales como de comportamiento, en personas que no tienen SD.
6. El uso del instrumento KBIT para la evaluación cognitiva de las personas con síndrome de Down, puesto que, aunque tiene el mérito de ser una prueba corta y sencilla para una evaluación compleja de estas características, no permite estimar la edad mental con certeza en personas con discapacidad intelectual, tanto puede puntuar en el límite inferior a cuatro años, o por el contrario sobrestimar la edad mental utilizando el límite superior del intervalo de confianza de la edad.
7. El tipo de análisis en el que se basa la técnica SEM, puesto que es difícil comparar las estructuras cerebrales entre personas con SD y controles. No sólo por razones morfológicas, sino también por el funcionamiento.
8. El estudio de 6 ROI muestra una conectividad limitada y por lo tanto tiene un alcance muy pequeño. Debemos resolver los problemas informáticos para realizar estudios más amplios con atlas cerebrales completos.

- **Futuras investigaciones**.

Los resultados de la presente tesis doctoral contribuyen a investigar en próximos estudios las variables modificadoras de la densidad que pueden explicar parte de la variación observada en las redes de conectividad con personas con DS. Será necesario estudiar si el efecto de más mecanismos neuroestructurales o el efecto de variables externas (por ejemplo, factores cognitivos como el nivel de respuesta cognitiva o posibles efectos de reserva cognitiva o más aspectos psicológicos como la calidad de vida, entre otros) podrían explicar este fenómeno.

Complementariamente, se sugiere investigar la relación que guarda el SD con las condiciones de salud de base orgánica como el hipotiroidismo y las enfermedades cardíacas congénitas, así como con el uso de medicamentos. Del mismo modo, los estudios longitudinales podrían permitir analizar las propiedades de la red DMN desde el seguimiento de sujetos jóvenes a ancianos, y evaluar la posibilidad de que esta red se convierta en un temprano biomarcador de DTA .

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Referencias

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