Archival Report

Functional Brain Connectivity Prior to the COVID-19 Outbreak Moderates the Effects of Coping and Perceived Stress on Mental Health Changes: A First Year of COVID-19 Pandemic Follow-up Study

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ABSTRACT

BACKGROUND: The COVID-19 pandemic provides a unique opportunity to investigate the psychological impact of a global major adverse situation. Our aim was to examine, in a longitudinal prospective study, the demographic, psychological, and neurobiological factors associated with interindividual differences in resilience to the mental health impact of the pandemic.

METHODS: We included 2023 healthy participants (age: 54.32 ± 7.18 years, 65.69% female) from the Barcelona Brain Health Initiative cohort. A linear mixed model was used to characterize the change in anxiety and depression symptoms based on data collected both pre-pandemic and during the pandemic. During the pandemic, psychological variables assessing individual differences in perceived stress and coping strategies were obtained. In addition, in a subsample (n = 433, age 53.02 ± 7.04 years, 46.88% female) with pre-pandemic resting-state functional magnetic resonance imaging available, the system segregation of networks was calculated. Multivariate linear models were fitted to test associations between COVID-19–related changes in mental health and demographics, psychological features, and brain network status.

RESULTS: The whole sample showed a general increase in anxiety and depressive symptoms after the pandemic onset, and both age and sex were independent predictors. Coping strategies attenuated the impact of perceived stress on mental health. The system segregation of the frontoparietal control and default mode networks were found to modulate the impact of perceived stress on mental health.

CONCLUSIONS: Preventive strategies targeting the promotion of mental health at the individual level during similar adverse events in the future should consider intervening on sociodemographic and psychological factors as well as their interplay with neurobiological substrates.

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The COVID-19 pandemic has resulted in an unprecedented impact, with more than 400 million people affected and 6 million deaths worldwide by mid-March 2022 (https://www.worldometers.info/coronavirus/?utm_campaign=homeAdvegas1). From its inception, this pandemic has been highlighted as a health and societal threat, not only owing to the direct negative effects of SARS-CoV-2 infection but also because of the long-term restrictions imposed by governments and authorities attempting to prevent or limit the spread of the virus. General confinements and quarantines, along with other protective measures, closure of businesses, and limitation of social interactions, can be expected to result in multiple psychological sequelae (1). Accordingly, overall rates of around 30% in anxiety and depressive symptoms have been observed, which are higher than the usual incidence rate observed in the general population [e.g., (2,3)]. Nonetheless, many of the initial studies investigating mental health effects of the COVID-19 pandemic have been cross-sectional and have lacked comparable pre-pandemic baseline data. These methodological constraints limit the interpretation of findings; in fact, other studies challenge the assumption that the effect of the pandemic on mental health can be described as a significant overall negative impact on anxiety and depressive symptoms (4,5). There also remains inconsistency among studies with preoutbreak data, with some studies reporting significant increases in psychological distress (6,7) and others highlighting

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general null effects (4). Other research has highlighted the high prevalence of individuals showing resilient outcomes, and in general, the need to consider different, even opposite, trajectories across groups of individuals (8,9).

Resilience is a broad term that generally refers to the interindividual differences with regard to the ability to resist the impact of an illness or stress (10). Hence, in the context of this study, resilience can be defined as the lack of anxiety or depression during the COVID-19 pandemic. Psychological variables, such as coping abilities, are defined as behaviors to protect oneself by avoiding psychological harm from bad experiences (11) and have been shown to be strongly associated with resilience to life traumas (12). Moreover, the role of distinct neurobiological substrates of resilience have been highlighted (13). Both neuroimaging (14,15) and neurophysiological (16) studies in humans have revealed that the integrity/functionality of specific brain networks are associated with different response adaptations to major threatening life events or during experimental investigations (17). Specifically, numerous studies point out anatomical and functional implications on resilience of different frontal (e.g., dorsolateral, orbitofrontal) and limbic (e.g., amygdala, insula, or striatum) areas, midline structures integrated within the default mode network (DMN) (14), and the cingulate cortex (18–20). Concurrently, graph theory approaches for the study of brain connectivity enable the description of the dynamics of brain organization (21). More specifically, the effective functioning of the network seems to be supported by maintaining the separation of subnetworks while enabling integration between them. This harmony can be quantified by metrics such as system segregation (SyS), which summarizes the balance between integration within and between networks in a single value (22). SyS variability has been studied specifically in the context of aging, cognition (23), and resilience to neurodegenerative disease (24), but it remains poorly explored in the context of mental health resilience.

Altogether, these lines of evidence suggest that the interaction of an individual's psychological resources (e.g., coping strategies) with brain functional characteristics should predict individual differences in resilience versus vulnerability to mental health outcomes in the face of a sustained stressful situation (e.g., perceived stress during the COVID-19 pandemic). Therefore, taking advantage of longitudinal data collected starting 2 years pre-pandemic and during the first year of the pandemic on several occasions, we first aimed to investigate whether a general change in anxiety and depression symptoms could be observed in our sample of healthy middle-aged individuals as well as to validate previous findings regarding the influence of principal sociodemographic factors (i.e., age, sex, and education) (6,25). Second, we aimed to determine whether psychological factors (perceived stress and coping strategies) explained the change in anxiety and depressive symptoms. Finally, as our main goal, we were interested in elucidating whether the connectivity status of brain networks was able to predict, either in an independent manner or by the interaction with the studied psychological factors, the change in psychological distress associated with the pandemic. We hypothesized that we would be able to identify a significant change in psychological distress related to the pandemic and that both sociodemographic and psychological factors would influence this change in anxiety and depression symptoms. We also predicted that basal connectivity status of particular resilience-related networks, such as those involving frontal, limbic, cingulate, or DMN areas, would influence the degree of pandemic-related change in psychological distress experienced by our cohort.

METHODS AND MATERIALS

Study Design and Participants

Study participants were part of the BBHI (Barcelona Brain Health Initiative; https://bbhi.cat/en/), an ongoing longitudinal cohort study investigating the determinants of brain and mental health in healthy middle-aged and older adults. Recruitment started in 2017, when multiple initiatives (including conferences, radio and television interviews, and social media advertisements) took place to encourage participants to join the study. The BBHI's main inclusion criteria are the absence of neurological, psychiatric, or unstable medical diagnoses and no cognitive impairment. The BBHI includes periodic cognitive, medical, brain imaging, and biological assessments (26,27). This study refers to a BBHI substudy aimed at investigating mental health during the COVID-19 pandemic (10,28).

Data acquisition included a longitudinal design with measures of anxiety and depression symptoms collected 2 times before the pandemic outbreak (i.e., pre-pandemic) between 2018 and 2020 (average interval, 12.73 $\pm$ 2.18 months) and 5 assessments separated on average by 3.04 $\pm$ 2.29 months and covering the first year of the COVID-19 pandemic (i.e., from March 2020 to March-April 2021) (Figure 1). The primary outcome measure for this study was symptoms of anxiety and depression as assessed with the Patient Health Questionnaire-4 (PHQ-4) (see Questionnaires). Only participants who had valid PHQ-4 measures obtained at least once pre-pandemic and once during the pandemic were included (see Questionnaires). Furthermore, because our focus was on studying the impact of the COVID-19 pandemic on the healthy population, we excluded all individuals who had scores suggesting a possible meaningful clinical status at any of the pre-pandemic assessments (i.e., PHQ-4 scores equal to or above 6) according to recommended cutoffs (29) (see BBHI vs whole sample in the Supplement for more information on sample differences). For our main objective, only those participants who had available baseline magnetic resonance imaging (MRI) acquisitions before the outbreak that met the quality check inspection requirements and had normative neuroradiological reports (e.g., no brain tumor suspicions, stroke, or moderate to severe white matter damage) were included. In addition, data from 7 participants were discarded because of outlier values in the functional connectivity (FC) measures (see FC Measures). This led to a study sample of 2023 participants and 10,367 observations and a subsample of 433 MRI-available individuals and 2358 observations (Figure S1). The study was approved by the Unió Catalana d'Hospitals ethics committee (approval references: CEIC 17/06 and CEI 18/07). Written informed consent was obtained from all participants in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

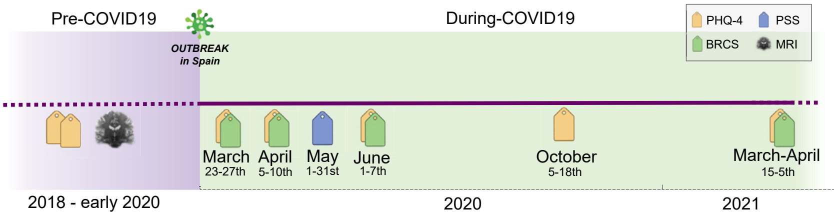

Figure 1. Timeline study design showing baseline (i.e., pre-pandemic) and during-pandemic points of acquisition for the main outcome (i.e., Patient Health Questionnaire-4 [PHQ-4]), magnetic resonance imaging (MRI), and psychological factors (perceived stress measured by the Perceived Stress Scale [PSS] and coping strategies measured by the Brief Resilient Coping Scale [BRCS]). On the left and colored in purple are pre-pandemic data including 1 MRI acquisition and 2 online PHQ-4 measures obtained between 2018 and 2020 (average follow-up: 12.73 ± 2.18 months). The beginning of the pandemic outbreak was defined according to the Spanish Government's State of Emergency declaration on March 14, 2020. On the right and colored in green, 6 online questionnaires were administered during the first year of the COVID-19 pandemic (until March–April 2021). Each questionnaire was available for answering during the specified data periods shown.

Questionnaires

The main outcome was anxiety and depression symptoms assessed with the PHQ-4, a valid ultra-brief tool consisting of 4 Likert-type scale items for detecting both anxiety and depressive disorders (29). Perceived stress was assessed with the Perceived Stress Scale, a 14-item, 5-point Likert-type scale including questions about feelings and thoughts during the past month (30). The Brief Resilient Coping Scale is a 4-item, 5-point Likert-type scale used to estimate the tendency to effectively use coping strategies in flexible, committed ways to actively solve problems despite stressful circumstances (31). For further details regarding the questionnaires, see the Supplement.

FC Measures

MRI data were acquired using a 3T Siemens scanner (Magnetom Prisma; Siemens Healthineers) with a 32-channel head coil at the Unitat d'Imatge per Ressonància Magnètica Institut d'Investigacions Biomèdiques August Pi i Sunyer at Hospital Clínic de Barcelona, Barcelona, Spain. Resting-state functional MRI scans were preprocessed, and then we quantified individual resting-state FC within and between resting-state networks as defined in the Schaefer-Yeo atlas of 100 nodes and 7 networks (32,33) (available at: https://github.com/ThomasYeoLab/CBIG/tree/master/stable_projects/brain_parcellation/Schaefer2018_LocalGlobal for the calculation of the SyS metric (22). Here, SyS values were considered as outliers when they were 3 standard deviations over or under the average (i.e., $|z \text{ score}| < 3$, where z score = [x − mean]/SD). As a result, 7 participants were excluded from the final sample.

See the Supplement for further details regarding the acquisition parameters, preprocessing, and SyS.

Statistical Analyses

All statistical analyses were written in R language (version 3.6.2) (34) and run in RStudio (version 1.3.1093) (35).

To investigate the change in anxiety and depression symptoms (i.e., PHQ-4 scores) along all the time points, a linear mixed-effect model was first fitted for the whole sample using the lmer function from the lme4 R package (36). In this model, fixed and random effect coefficients were estimated for a binary variable indicating whether each observation belonged to pre-pandemic assessments or to assessments made during the pandemic (i.e., COVID-19 period) to quantify pandemic-related PHQ-4 general and individual changes, respectively. The individual effect coefficients were extracted to generate a new variable termed PHQ-4 change (i.e., change in anxiety and depression symptoms) where positive values meant PHQ-4 increases during compared with pre-pandemic observations (i.e., anxiety and depression symptoms worsening). To analyze the associations between sociodemographic variables and PHQ-4 change, a linear regression model was fitted in which PHQ-4 change was the outcome and sex, age, and education were the predictor variables of interest. In addition, an analogous linear mixed-effect model was fitted by including only pre-pandemic observations. Then we fitted 3 linear regression models in which PHQ-4 change was the outcome and the predictors were coping strategies, perceived stress, and their interaction. Finally, we fitted a set of linear regression models to predict PHQ-4 change, in which SyS values from the 7 studied resting-state networks were included as independent variables. In this way, we tested whether there was a direct association between any network SyS and PHQ-4 change and whether SyS measures modulated the effects of the psychological factors (i.e., perceived stress and coping strategies) on the outcome. In addition, 2 analogous models were fitted to test for any association between SyS values and coping strategies or perceived stress, respectively. All these models were adjusted for age, sex, socioeconomic status, employment situation during the pandemic, average pre-pandemic levels of anxiety and depression symptoms, and number of months between the last questionnaire administered before the pandemic and the first questionnaire administered during the pandemic.

RESULTS

Sample Demographics and Psychological Characteristics

This study included a total sample of 2023 participants (age: 54.32 ± 7.18 years, 65.69% female) and a subsample of 433 individuals with available MRI data (age: 53.02 ± 7.04 years, 46.88% female) from the BBHI cohort (26,27). At baseline and as per inclusion criteria, all the subjects presented normal to mild symptomatology (i.e., PHQ-4 > 6 within a range of 0–12) before the pandemic outbreak. Regarding psychological factors of vulnerability (i.e., perceived stress) and those associated with mechanisms of resilience (i.e., coping strategies), both samples mostly presented medium to high coping and low to moderate stress profiles (Table 1).

Table 1. Sample Characteristics

Characteristic	Whole Sample, N = 2023	MRI Subsample, n = 433
Age, Years	54.32 ± 7.18	53.02 ± 7.04
Sex		
Female	1329 (65.69%)	203 (46.88%)
Male	694 (34.31%)	230 (53.12%)
Educational Level[a]		
Primary	67 (3.31%)	12 (2.77%)
Secondary	436 (21.55%)	104 (24.02%)
Higher	1520 (75.14%)	317 (73.21%)
Socioeconomic Status[b,c]		
Low	51 (2.53%)	10 (2.31%)
Low−middle	374 (18.54%)	83 (19.17%)
Middle−high	1198 (59.40%)	234 (54.04%)
High	394 (19.53%)	106 (24.48%)
Employment During the Pandemic[d]		
Employed	1123 (55.51%)	266 (61.43%)
Unemployed	900 (44.49%)	167 (38.57%)
Anxiety and Depression[e]		
Pre-pandemic		
Normal−mild, 0–5	2023 (100%)	433 (100%)
Moderate−severe, 6–12	0 (0.00%)	0 (0.00%)
During the pandemic		
Normal−mild, 0–5	1818 (89.87%)	400 (92.38%)
Moderate−severe, 6–12	205 (10.13%)	33 (7.62%)
Coping Strategies[c,e]		
Low, 4–13	371 (18.70%)	60 (13.92%)
Medium, 14–16	1106 (55.75%)	226 (52.44%)
High, 17–20	507 (25.55%)	145 (33.64%)
Perceived Stress[c,e]		
Low, 0–13	465 (30.80%)	128 (38.65%)
Moderate, 14–26	928 (61.46%)	188 (55.29%)
High, 27–40	117 (7.75%)	24 (7.06%)

Continuous variables are described by mean ± SD values, while categorical variables are described by the absolute number of individuals and its corresponding percentage (%) within the sample.

BRCS, Brief Resilient Coping Scale; MRI, magnetic resonance imaging; PHQ-4, Patient Health Questionnaire-4; PSS, Perceived Stress Scale.

[a]Primary educational level corresponds to general basic education or equivalent (8 years approximately), secondary corresponds to baccalaureate or equivalent (up to approximately 12 years), and higher corresponds to university degrees such as diploma, degree, Master, or Ph.D. (over 12 years).

[b]Socioeconomic status corresponds to the approximate range of the individuals' monthly family income (low: <1000; low-middle: 1000–2000; middle-high: 2000–5000; high: >5000; all amounts in euros).

[c]Missing data are due to noncompletion of the questionnaires by participants.

[d]An individual was considered as employed when answered so at all time points.

[e]Psychological variables are described here as categories created according to available cutoffs regarding severity of anxiety and depressive symptomatology (i.e., PHQ-4), level of coping strategies (i.e., BRCS), and perceived stress (i.e., PSS). Note that this categorization was done under descriptive purposes, but these variables were used as continuous in this study. In addition, as anxiety and depression were assessed on multiple occasions in both periods (pre-pandemic and during the pandemic), a subject was considered to present moderate to severe symptomatology when scoring within this range at least once.

Changes in Anxiety and Depressive Symptoms: Age and Sex Effects

A linear mixed-effect model on the total sample showed that PHQ-4 scores increased during the pandemic compared with pre-pandemic (during the pandemic > pre-pandemic: β = 0.229, t = 7.428, $p < .001$) (Figure 2). The random effect coefficients estimated for each individual were used to compute the PHQ-4 change variable (Figure S2). PHQ-4 change was negatively associated with age (β = −0.006, t = −4.084, $p <$ .001) (see Figure S3A) but not with educational level (β = 0.034, t = 1.683, p = .092). This model (adjusted R^2 [a-R^2] = 0.278) also revealed that female individuals had higher PHQ-4 change values than males (β = 0.141, t = 6.622, $p < .001$) (Figure S3B). In addition, we did not find any interaction between age and sex associated with our outcome (a-R^2 = 0.278; age × sex interaction; β = −0.004, t = −1.225, p = .221). Finally, considering only baseline data, we found that female (females > males; β = 0.261, t = 4.299, $p < .001$) and younger individuals (age: β= −0.158, t = −4.338, $p < .001$) had higher pre-pandemic PHQ-4 values.

The results of repeating these analyses for the MRI subsample (n = 433) can be found in the Supplement.

Changes in Effects of Perceived Stress and Coping Strategies on Anxiety and Depressive Symptoms

In the total sample, we fitted 3 different linear models. The first model (a-R^2 = 0.337) showed a negative association between coping strategies and PHQ-4 change (β = −0.069, t = −14.147, $p < .001$), and the second model (a-R^2 = 0.421) showed a positive association between perceived stress and PHQ-4 change (β = 0.036, t = 19.241, $p < .001$). Finally, the third model (a-R^2 = 0.447) revealed that the change was significantly described by an interaction between perceived stress and coping strategies (β = −0.003, t = −4.370, $p < .001$) (Figure 3A). In the latter analysis, the direct effect of perceived stress on PHQ-4 was reduced but maintained (β = 0.075, t = 7.085, $p < .001$), while the direct effect of coping strategies on anxiety and depressive symptoms change disappeared (β = 0.001, t = 0.801, p = .423) (Figure 3B).

The results of repeating these analyses for the MRI subsample (n = 433) were in accordance with those in the total sample (see the Supplement).

Changes in Anxiety and Depression Symptoms as a Function of Brain Network Status and Psychological Factors

Nonsignificant direct associations between mental health change, coping strategies, and perceived stress and any of the SyS values were found (all p values > .05). However, we aimed to test whether SyS variables were able to modulate the perceived stress effect on PHQ-4 change or the modulatory effect of coping strategies (i.e., PHQ-4 change ∼ coping strategies × perceived stress interaction). The first model (a-R^2 = 0.536) showed a significant interaction between the frontoparietal control network SyS (FPCN-SyS) (Figure 4A) and perceived stress (β = 0.108, t = 2.446, p = .009) (Figure 4C) and between the DMN-SyS (DMN-SyS) (Figure 4B) and perceived stress (β = −0.096, t = −2.626, p = .015) (Figure 4D) to the described PHQ-4 change. These interactions show that higher

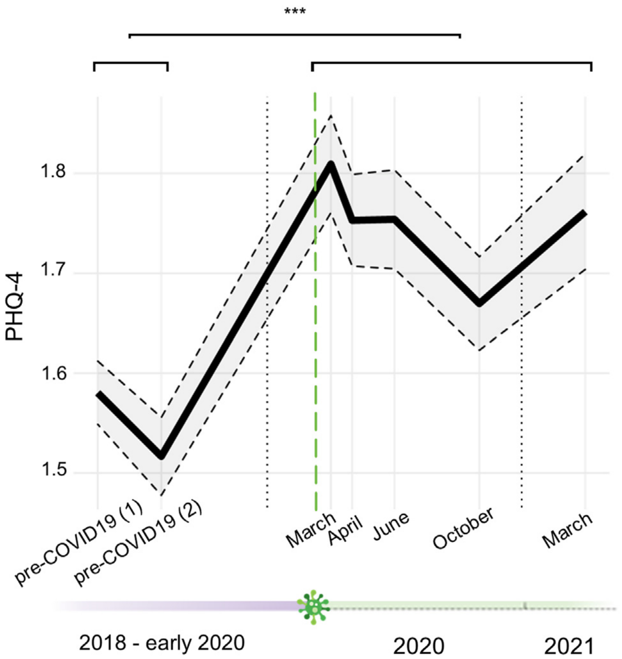

Figure 2. Average values of the Patient Health Questionnaire-4 (PHQ-4) along time point measurements for the whole sample (N = 2023) showing ratings increases. Shadow areas above and below the average PHQ-4 line (i.e., thick line) represent standard errors. Abscissa axes indicate the timeline of observations in the study, which are grouped within pre-pandemic (i.e., from 2018 to early 2020) and during-pandemic observations (i.e., those from March 2020 to March–April 2021). The green line indicates the beginning of the lock-down (March 14, 2020 in Spain) and separates pre-pandemic and during-pandemic observations. Black vertical dashed lines delimit 2020 and 2021. Finally, in the upper part of the figure, the increase in PHQ-4 values at points during the pandemic compared with pre-pandemic is indicated.

FPCN-SyS levels enhanced the positive association between perceived stress and PHQ-4 change. Conversely, higher levels of DMN-SyS attenuated the association between perceived stress and PHQ-4 change (Figure 4E) similar to the modulation by coping strategies, which remained significant in this model ($\beta = -0.003$, $t = -2.136$, $p = .033$). Because these 2 neural mechanisms (i.e., FPCN-SyS and DMN-SyS) were significant even after accounting for the effects of coping strategies, it appears that these could be independent of each other. Finally, the second model (a-R^2 = 0.539) showed a trend toward significance between the limbic network SyS variable and the coping strategies' effect on the association between perceived stress and PHQ-4 ($\beta = -0.024$, $t = -1.727$, $p = .085$) in the sense that a higher limbic network SyS could be related to an increased effect of coping strategies as a psychological regulatory mechanism (Figure S4).

DISCUSSION

This study found a general increase in anxiety and depressive symptoms during the COVID-19 pandemic in a healthy middle-aged population where age and sex were found as independent predictors. We identified that coping strategies attenuated the impact of perceived stress on mental health. Finally, to our knowledge, this is the first study to identify the modulation of the impact of perceived stress on anxious-depressive responses through baseline FPCN and DMN network connectivity balance.

Our findings revealed a measurable COVID-19 impact on mental health among healthy middle-aged individuals, arguing against a complete lack of a general effects (4). However, only approximately 10% of individuals were found to surpass the suggested clinical cutoff scores at any time point during the pandemic. This finding reflects lower estimates, consistent with recent reviews (36) ranging from 20% to >30% (2,3) and also suggests the presence of an overall high proportion of resilient outcomes (8,37,38). In addition, our results provide confirmatory evidence that female individuals experienced the psychological impact of COVID-19 to a greater extent than males, in accordance with a previous large population probability study (6) and with former meta-analytical evidence (2). Furthermore, our study is in accordance with many previous reports indicating higher rates of psychological distress during the pandemic among younger individuals (5,37). However, it should be noted that a recent review studying the impact of age on mental health changes during the pandemic (39) highlighted heterogeneous findings in the literature. In fact, there are also reports indicating that rates of relevant mental health aspects such as loneliness increased progressively during successive pandemic months among older adults (40).

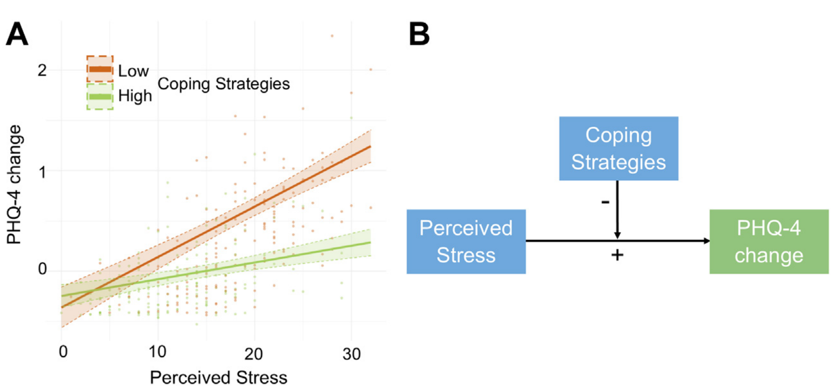

Figure 3. Plots illustrating the associations found between the studied psychological factors (i.e., coping strategies and perceived stress) and psychological distress worsening (i.e., Patient Health Questionnaire-4 [PHQ-4] change). **(A)** Scatter and lines plot showing the association between PHQ-4 change (vertical axis) and perceived stress (horizontal axis) as modulated by coping strategies. Dots show individual observations of PHQ-4 change and perceived stress for 2 groups with low (in brown; i.e., below median) and high (in green; i.e., above median) coping strategies. Thick lines illustrate estimated slopes for the association between PHQ-4 change and perceived stress for extreme minimum and maximum levels of low (in brown) and high (in green) coping strategies. This difference between slopes was found to be significant as an interaction between coping strategies and perceived stress to predict PHQ-4 change. Shadow areas above and below the slope lines represent standard errors. **(B)** Schema of the associations between variables of psychological factors and psychological distress worsening.

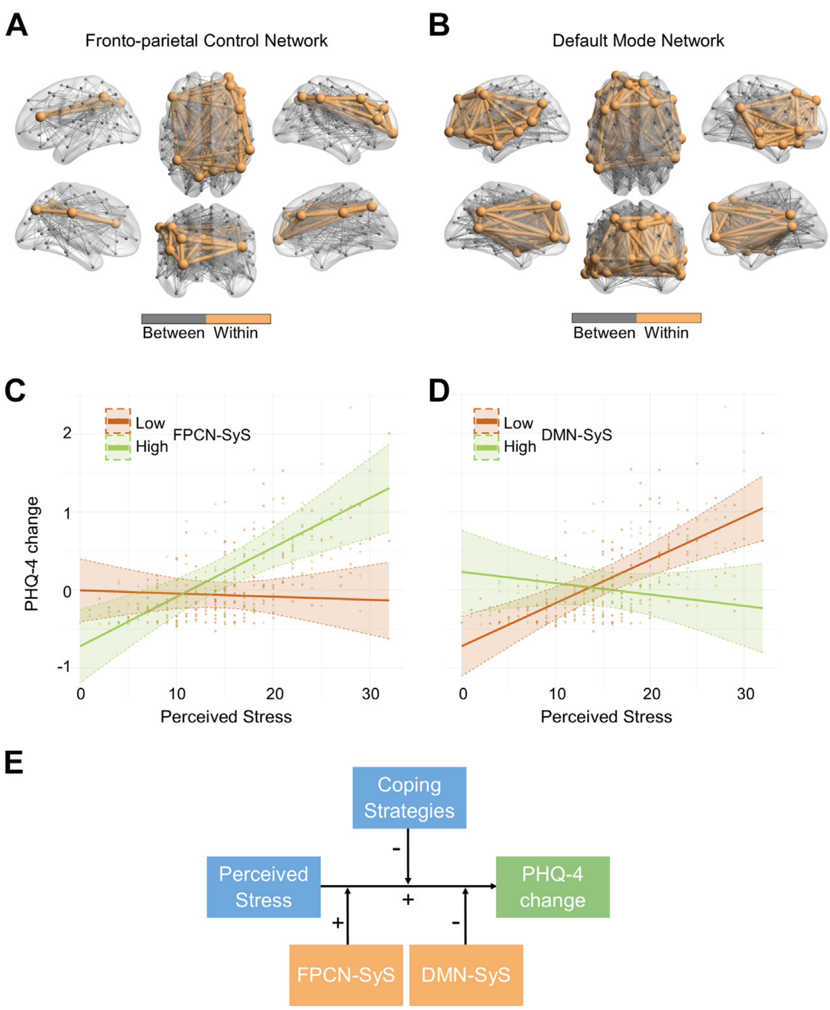

Figure 4. Representation of the modulatory effect of frontoparietal control network (FPCN) and default mode network (DMN) system segregation (SyS) values on the association between perceived stress and Patient Health Questionnaire-4 (PHQ-4) change. **(A, B)** Graphs representing within- and between-network connectivity taking part in the computation of FPCN and DMN-SyS values, respectively. Nodes in the graph represent studied regions of interest (ROIs) as defined by the Schaefer-Yeo atlas of 100 nodes and 7 networks. The nodes and edges in light orange illustrate ROIs and within-network connectivity of the studied network (i.e., FPCN or DMN), while those in gray refer to outside network ROIs and the connectivity between them and the studied network. These graphs were created with the BrainNet Viewer (http://www.nitrc.org/projects/bnv/). **(C, D)** Scatter and lines plot showing the association between PHQ-4 change (vertical axis) and perceived stress (horizontal axis), as modulated by values of SyS, from the FPCN in panel **(C)** and the DMN in panel **(D)**. Dots show individual observations of PHQ-4 change and perceived stress for 2 groups with low (in brown; i.e., below median) and high (in green; i.e., over median) SyS values. Thick lines illustrate estimated slopes for the association between PHQ-4 change and perceived stress for extreme minimum and maximum levels of low (in brown) and high (in green) SyS. This difference between slopes was found significant as an interaction between each particular SyS variable and perceived stress to predict PHQ-4 change. Shadow areas above and below the slope lines represent standard errors. **(E)** Schema of the associations between perceived stress and psychological distress worsening, as regulated by FPCN-SyS, DMN-SyS, and coping strategies.

In addition, it should be noted that our findings may not apply to particular aged populations, i.e., those with medical diagnosis for risk conditions, those of extreme ages, or those in specific situations (i.e., individuals who are institutionalized). Our observation that people who experienced greater levels of perceived stress exhibited increased levels of anxiety and depressive symptoms pre-pandemic compared with post-pandemic outbreak is aligned with the stress-vulnerability models of psychopathology (41). Negative associations between coping and anxiety and depressive symptoms also fit with the understanding of coping abilities as cognitive and behavioral strategies that individuals use to manage stressful situations (42). Previous research has reported a positive impact of coping behaviors on anxiety and depressive symptoms during the pandemic, both in the general population (5,43) and in specific risk groups (44,45). Hence, our findings confirm the relevance of coping behaviors and highlight the fact that they may benefit mental health status primarily through an attenuation of the negative impact of perceived stress (11,46).

Notwithstanding the impressive amount of research related to the psychological impact of the COVID-19 pandemic, few reports have considered functional brain status characteristics as predictors of associated mental health outcomes (47–52). We observed that areas conforming the FPCN (largely overlapping with the executive control network) should be considered as relevant neurobiological indicators of individual differences in mental health outcomes during the COVID-19 pandemic. This network connecting the prefrontal dorsolateral and the superior parietal cortices supports executive functions, is central to adequate social navigating and achievement of long-term goals (53), and has been identified with resilience processes (14,15,54). Prior research showed that the FPCN and more specifically the dorsolateral prefrontal cortex orchestrate a regulatory role over other cortical and subcortical regions related to cognitive emotion regulation (55–57). Such aspects may therefore help explain the observation of a modulatory role of the FPCN on buffering the negative effects of perceived stress on the expression of anxiety and depressive symptoms.

Our results also highlight the role of the DMN in attenuating the impact of perceived stress on change in anxiety and depressive symptoms. Abnormal DMN functionality (along with FPCN and salience network dysfunctions) is characteristic of anxiety and depression disorders (58,59), including the fact that individual anatomic and functional differences within this circuit contribute to individual differences in psychological resilience (14). The DMN is also involved in interindividual variability in stress responsiveness (60) and may contribute to behavioral homeostasis in response to induced stressors (61). In our study, the effects of the DMN operated in an opposite manner than the FPCN (i.e., higher SyS for the DMN and lower SyS for the FPCN attenuated the effect of high perceived stress), which may be related to the inverse FC changes between the 2 networks during exposure to sustained stress (17). Here, beyond exclusively considering the role of brain network intrinsic connectivity as markers of vulnerability versus resilience, our study stresses the need to interpret effects in the context of a given individual's psychological resources. In this regard, we found a trend toward significance, suggesting that higher segregation of orbital (i.e., the ventromedial prefrontal cortex) and temporal pole regions, constituting the limbic network previously associated with cognitive reappraisal and resilience (62), could be related to greater protective effects of an individual's coping capacities on final mental health outcomes. To our knowledge, previous publications in the field testing associations between mental health and brain network characteristics have mainly used metrics of internetwork or intranetwork FC (60). In this light, we based our analyses in a graph theory–based metric able to capture the organizational properties supporting brain function (22), a functional architecture measure that has been used in other contexts to characterize the neurobiological substrates of resilience (63).

Taken together, these findings highlight the need to consider the study of resilience using a person-centered approach wherein relevant contributing factors (psychological, lifestyles, sociocultural, and neurodevelopmental aspects) should ultimately be integrated and where effects of neurobiological markers should be interpreted within this context (10). Our results may have implications for enabling preventive strategies not only for the current COVID-19 pandemic but also in the face of similar future events. First, cognitive behavioral interventions to improve coping strategies combined with stress reduction approaches (e.g., mindfulness-based stress reduction) may be of benefit, particularly for individuals with high levels of perceived stress, female individuals, and younger individuals. Second, the status of functional brain networks was shown to be a valuable predictor of the probability of response to psychological interventions [see (63) for a meta-analysis] and can reveal neural mechanistic effects of successful treatments (64,65). Our observation that such functional features moderate the effect of psychological resources on mental health suggests that a combined approach that uses brain imaging to monitor whether the effects of interventions are targeting such key circuits may be of particular interest. Finally, this approximation could also benefit from the use of approaches that allow a direct modulation of brain network connectivity. Here, noninvasive brain stimulation may directly improve symptoms of anxiety (66) and depressive symptoms (67,68). Notably, the combination of such techniques with electroencephalography and/or functional MRI allows for modulation of the spatiotemporal dynamics of specific brain networks in an individualized manner (69–73). Furthermore, the brain responses evoked by stimulation may hold predictive value regarding clinical and behavioral outcomes (74). Hence, such experimentally controlled approaches could be integrated with other factors to predict an individual's risk of experiencing negative mental health impact in the event of unexpected and sustained stressors (10).

Our study is not without limitations. First, we used the PHQ-4 as the primary outcome measure to maximize the fact that we had assessments across all the time points (pre-pandemic and during the pandemic) for this variable, but we acknowledge that it may entail constraints in terms of the sensitivity and specificity of the mental health symptoms assessed. Second, the included sample exhibits particular characteristics, in part because of the recruitment method used, notably the fact that the sample is composed of individuals with high interest in their own brain health, with an underrepresentation of low mental health rates and with a high educational level. Hence, even though the lack of effects for education in our study aligns with previous reports (11), findings might have differed if the sample had included a greater representation of individuals with no or fewer educational qualifications (25). Third, many other variables including individual dispositional factors, health- and family-related issues, and environmental and cultural aspects possibly affecting the investigated outcome were not considered here [see Discussion in (75)]. In this regard, the availability of pre-pandemic information regarding perceived stress would have been useful to better characterize the COVID-19–related impact on this variable of interest. Particularly, information about ethnicity and race was not included in our analyses because we did not collect information about ethnicity and because our population was homogeneous, mostly considering themselves Caucasian or White (i.e., 94.39%). It should also be noted that owing to our inclusion criteria, our results might not generalize to samples of patients or those individuals exhibiting higher pre-pandemic anxiety and depression scores. Finally, the analytical approach was neither specifically designed to formally test for changes across temporal pandemic stages nor designed to investigate group trajectories potentially contributing to longitudinal individual differences (37,38), which will be the matter of future investigations.

In conclusion, leveraging data from a longitudinal prospective study including a large sample of healthy middle-aged individuals and multiple data points spanning from 2 years prior to the SARS-CoV-2 outbreak until the end of the first year of the pandemic, we have been able to elucidate how basic sociodemographic measures, psychological factors, and neurobiological characteristics relate to a general measure of mental health impact. FPCN and DMN segregation/integration status was found to modulate the influence of psychological factors, acting through distinct pathways, and conferring interindividual differences in vulnerability versus resilience regarding the change in psychological distress associated with the COVID-19 pandemic.

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AP-L is listed as an inventor on several issued and pending patents on the real-time integration of noninvasive brain stimulation with electroencephalography and MRI. He is cofounder of Linus Health and TI Solutions. AG and serves on the scientific advisory boards for Starlab Neuroscience, Magstim Inc., Nexstim, and MedRhythms. All other authors report no biomedical financial interests or potential conflicts of interest.

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