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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 study, in a longitudinal prospective, the demographic, psychological and neurobiological factors associated with inter-individual differences in resilience to mental health pandemic impact.

**METHODS:** We included 2,023 healthy participants (age: 54.32±7.18 years, 65.69% females) from the Barcelona Brain Health Initiative cohort. A linear mixed model was used to characterize the change in anxiety and depression symptoms based on the collected pre- and during-COVID-19 data. During pandemic, psychological variables assessing individual differences in perceived stress and coping strategies were obtained. Additionally, in a subsample (N=433, age:53.02 ± 7.04 years, 46.88% females) with pre-pandemic resting-state functional magnetic resonance imaging available, networks’ system segregation (SyS) was calculated. Multivariate linear models were fitted to test associations between COVID-19-related changes in mental health and demographics, psychological features and brain networks 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. SyS of fronto-parietal control and default mode networks were found to modulate the impact of perceived stress on mental health.

**CONCLUSIONS:** Preventive strategies destined for the promotion of mental health at an individual’s level during future similar adverse events should consider intervening on sociodemographic and psychological factors, as well as their interplay with neurobiological substrates.
INTRODUCTION

The Coronavirus Disease 2019 (COVID-19) pandemic has resulted in an unprecedented impact, leading to over 400 M people affected and 6 M 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 due 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, rates of overall 30% in anxiety and depressive symptoms, which are higher than the usual incidence observed in the general population (e.g., 2,3).

Nonetheless, many of the initial studies investigating mental health effects of COVID-19 pandemic have been cross-sectional and have lacked comparable pre-pandemic baseline data. These methodological constraints limit the interpretation of findings and 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 in anxiety and depressive symptoms (e.g., 4,5). There remains also inconsistency among studies with pre-outbreak data, as some report significant increases in psychological distress (6,7) whereas others highlighted general null effects (4). Other research highlighted the high prevalence of individuals showing resilient outcomes, and in general, the need to consider different, even opposite, trajectories across groups of individuals (e.g., 8,9).

Resilience is a broad term, which generally refers to the inter-individual differences as regards the ability of resisting the impact of illness or stress (10). Hence, in the context of the present 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 (see 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 studies in humans (e.g., 16) 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 (e.g., 17). Specifically, numerous studies point out anatomical and functional implications of different frontal (e.g., dorsolateral, orbitofrontal) and limbic areas (e.g., amygdala, insula or striatum), midline structures integrated within the default-mode network (DMN; 14) and of the cingulate cortex, on resilience (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 summarize 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 (e.g., 23), and resilience to neurodegenerative disease (24), but remains poorly explored in the context of mental health resilience.

Altogether, the lines of evidence above suggest that the interaction of psychological individual’s resources (e.g., coping strategies) with brain functional characteristics should predict individual differences in resilience vs 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 two years pre-pandemic and during the first year of pandemic on several occasions, we first aimed to investigate if a general change in anxiety and depression symptoms could be observed in our sample of middle-aged healthy 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 brain networks’ connectivity status were able to predict, in an independent manner or by the interaction with the studied psychological factors, the change in psychological distress associated with the pandemic. In this vein, we hypothesized that we would be able to identify a significant psychological distress change related to the pandemic and that both sociodemographic and psychological factors would influence this change in anxiety and depression symptoms. In particular, 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 Barcelona Brain Health Initiative (BBHI; 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 TV interviews and social media advertisements) took place to draw participants into joining the study. 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 (see 26,27). The present work refers to a BBHI sub-study aiming to investigate mental health during the COVID-19 pandemic (see 10,28).

Data acquisition included a longitudinal design with measures of anxiety and depression symptoms collected two times before the pandemic outbreak (i.e., pre-pandemic) between 2018 and 2020 (average interval: 12.73 ± 2.18 months), and five assessments separated on average 3.04 ± 2.29 months, and covering the first year of COVID-19 pandemic (i.e., from
March 2020 to March-April 2021; Figure 1). The primary outcome measure for the present study was symptoms of anxiety and depression as assessed with the Patient Health Questionnaire-4 (PHQ-4, see below). Only those subjects who had valid PHQ-4 measures obtained at least once pre-pandemic and once during-pandemic were included (see the following section). Further, since our focus was on the study of the COVID-19 pandemic impact on the healthy population, we excluded all individuals exhibiting scores suggesting a possible meaningful clinical status at any of the pre-pandemic assessments (i.e., PHQ-4 scores equal or above 6), according to recommended cut-offs (29; see section 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, had normative neuroradiological reports (e.g., no brain tumor suspicions, stroke or moderate to severe white matter damage) were included. Additionally, data from seven participants were discarded due to outlier values in the FC measures (see ‘Functional Connectivity measures’). This led to a study sample of 2,023 participants and 10,367 observations, and a sub-sample of 433 MRI-available individuals and, 2358 observations (see Figure S1 in Supplement). 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).

*** Insert Figure 1 here ***

Questionnaires

The main outcome was anxiety and depression symptoms assessed with the PHQ-4, a valid ultra-brief tool (i.e., based on 4 items Likert-type scale) for detecting both anxiety and depressive disorder (29). Perceived stress was assessed with the Perceived Stress Scale (PSS), 14 items 5 Likert-type scale including questions about feelings and thoughts during the last month (30). The Brief Resilient Coping Scale (BRCS) is a 5 Likert-type scale with 4 items
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.

**Functional Connectivity measures**

MRI data were acquired in a 3T Siemens scanner (MAGNETOM Prisma) with 32-channel head coil, at the *Unitat d’Imatge per Ressonància Magnètica IDIBAPS (Institut d’Investigacions Biomèdiques August Pi i Sunyer)* at Hospital Clínic de Barcelona, Barcelona, Spain. Resting state functional MRI (rs-fMRI) scans were preprocessed, and then we quantified individual resting state functional connectivity (rs-FC) within and between resting state networks (RSNs) as defined in the Schaefer-Yeo atlas of 100 nodes and 7 networks (32,33; https://github.com/ThomasYeoLab/CBIG/tree/master/stable_projects/brain_parcellation/Schaefer2018_LocalGlobal) for the calculation of the system segregation (SyS) metric (22). Here, SyS values were considered as outliers when three standard deviations over or under the average (i.e., |z-score|<3, where z-score=(x-mean)/standard-deviation). In consequence, seven participants were discarded 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).

In order to investigate the change in anxiety and depression symptoms (i.e., PHQ-4) along all the time points, a linear mixed-effects model was first fitted for the whole sample using ‘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- or during-pandemic assessments (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., anxiety and depression symptoms change) where positive values meant PHQ-4 increases during vs pre 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. Additionally, an analogous linear mixed effects model was fitted by only including pre-pandemic observations. Then, we fitted three linear regression models in which PHQ-4 change was the outcome and the predictors were (i) coping strategies, (ii) perceived stress, and (iii) their interaction. Finally, we fitted a set of linear regression models to predict PHQ-4 change, in which SyS values from the seven studied RSNs 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. Additionally, two analogous models were fitted to test any association between SyS values and coping strategies or perceived stress, respectively. All these models were adjusted by age, sex, socioeconomic status, employment situation during pandemic, pre-pandemic average levels of anxiety and depression symptoms, and months between last pre-pandemic and first during-pandemic questionnaires.

RESULTS

Sample demographics and psychological characteristics

The present study included a whole sample of 2,023 participants (age: 54.32 ± 7.18 years, 65.69% females) and a sub-sample of 433 individuals with available MRI (age: 53.02 ± 7.04 years, 46.88% females) from the BBHI cohort (see 26,27). At baseline and as per inclusion criteria, all the subjects presented normal-mild symptomatology (i.e., PHQ-4<6 within a range of 0 to 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-high coping and low-moderate stress profiles (Table 1).

*** Insert Table 1 here ***

**Anxiety and depressive symptoms change: age and sex effects**

A linear mixed effects model on the whole sample showed that PHQ-4 scores increased during-pandemic compared to pre-pandemic (during- > pre-pandemic: β=-0.229, t=7.428, p<0.001; Figure 2). The random effect coefficients estimated for each individual were used to compute the ‘PHQ-4 change’ variable (Figure S2 in Supplement). PHQ-4 change was negatively associated with age (β=-0.006, t=-4.084, p<0.001; see Figure S3A in Supplement), but not with educational level (β=0.034, t=1.683, p=0.092). This model (adjusted R² (a-R²)=0.278) also revealed that females had higher PHQ-4 change values than males (β=0.141, t=6.622, p<0.001; Figure S3B in Supplement). Additionally, we did not find any interaction between age and sex associated to our outcome (a-R²=0.278; age * sex interaction; β=-0.004, t=-1.225, p=0.221). Finally, only considering baseline data, we found that females (females > males; β=0.261, t=4.299, p<0.001) and younger individuals (age; β=-0.158, t=-4.338, p<0.001) were those with higher pre-pandemic PHQ-4 values.

The results of repeating these analyses for the MRI sub-sample (N=433) can be found in the Supplement.

*** Insert Figure 2 here ***

**Effects of perceived stress and coping strategies on anxiety and depressive symptoms change**

In the whole sample, we fitted three different linear models. The first model (a-R²=0.337) showed a negative association between coping strategies and PHQ-4 change (β=-0.069, t=-
14.147, p<0.001), and the second model (a-R²=0.421) showed a positive association between perceived stress and PHQ-4 change (β=0.036, t=19.241, p<0.001). Finally, the third model (a-R²=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<0.001; Figure 3A). In this latter analysis, the direct effect of perceived stress on PHQ-4 was reduced but maintained (β=0.075, t=7.085, p<0.001), while the direct effect of coping strategies on anxiety and depressive symptoms change disappeared (β=0.001, t=0.801, p=0.423; Figure 3B).

The results of repeating these analyses for the MRI sub-sample (N=433) were in accordance with those in the entire cohort (see Supplement).

*** Insert Figure 3 here ***

**Anxiety and depression symptoms change as a function of brain networks’ status and psychological factors**

Non-significant direct associations between mental health change, coping strategies, and perceived stress, and any of the SyS values were found (all p-values>0.05). However, we aimed to test whether SyS variables were able to modulate (i) the perceived stress effect on PHQ-4 change or (ii) the modulatory effect of coping strategies (i.e., PHQ-4 change ~ coping strategies * perceived stress). The first model (a-R²=0.536) showed a significant interaction between fronto-parietal control network SyS (FPCN-SyS; Figure 4A) and perceived stress (β=0.108, t=2.446, p=0.009; Figure 4C), and between DMN SyS (DMN-SyS; Figure 4B) and perceived stress (β=-0.096, t=-2.626, p=0.015; Figure 4D) to described PHQ-4 change. These interactions showed that higher FPCN-SyS levels enhance the positive association between perceived stress and PHQ-4 change. Conversely, higher levels of DMN-SyS attenuate this association between perceived stress and PHQ-4 change (Figure 4E), similarly to the modulation by coping strategies, which remained significant in this model (β=-0.003, t=-2.136, p=0.033). As these two 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 (\(R^2=0.539\)) showed a trend towards significance between the limbic network SyS (LN-SyS) variable and the coping strategies effect on the association between perceived stress and PHQ-4 (\(\beta=-0.024, t=-1.727, p=0.085\)), in the sense that a higher LN-SyS could be related to an increased effect of coping strategies as a psychological regulatory mechanism (see Figure S4 in Supplement).

**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 identifying 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 amongst healthy middle-aged individuals, arguing against a complete lack of a general effects (4). However, only around 10% of individuals were found to surpass the suggested clinical cut-off scores at any time point during the pandemic. This finding reflects lower estimates, consistent with recent reviews (36) ranging from 20 to over 30% (e.g., 2,3), but also suggests the presence of an overall high proportion of resilient outcomes (8,37,38). In addition, the present results provide confirmatory evidence that females suffered to a greater extent than males the psychological impact of the COVID-19, in accordance with a previous large population probability study (6) and with former meta-analytical evidence (e.g., 2). Furthermore, our study is in accordance with many previous reports indicating higher rates of psychological distress during-pandemic at younger ages (e.g., 5,37). However, it should be noted that a recent review regarding 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 (i.e., 40). In addition, it should be noted that present findings may not apply to particular aged populations (i.e., with medical diagnosis for risk conditions), extreme ages, or in specific situations (i.e., individuals being institutionalized). Our observation that people experiencing greater levels of perceived stress exhibited increased levels of anxiety and depressive symptoms pre vs 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 employ to manage stressful situations (42). Previous research reported a positive impact of coping behaviors on anxiety and depressive symptoms during the pandemic, both in the general population (e.g., 5,43) and specific risk groups (e.g., 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 COVID-19 pandemic, only 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 prefrontal dorsolateral and superior parietal cortices) supports executive functions, is central to the adequate social navigating and long-term goal achievements (53) and has been identified with resilience processes (14,15,54). Former research, showed that the FPCN and specifically dorsolateral prefrontal cortex, orchestrate a regulatory role over other cortical and subcortical regions, related to cognitive emotion regulation (e.g., 55–57). Such aspects therefore may help explain the observation of a modulatory role of 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 anxiety and depressive change. Abnormal DMN functionality (along with FPCN and salience network dysfunctions), is characteristic of anxiety and depression disorders (e.g., 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 inter-individual variability in stress responsiveness (60) and may contribute to behavioral homeostasis in response to induced stressors (61). In our study, the effects of DMN operated in an opposite manner than the FPCN (i.e., higher SyS for the DMN and lower SyS for FPCN attenuated the effect of high perceived stress) which may be related to the inverse functional connectivity changes between the two networks during exposure to sustained stress (17).

Here, beyond considering exclusively the role of brains’ intrinsic connectivity as markers of vulnerability vs 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 towards significance, suggesting that higher segregation of orbital (i.e., ventromedial PFC) and temporal pole regions, constituting the LN previously associated with cognitive reappraisal, and resilience (62), could be related to greater protective effects of individual’s coping capacities, on final mental health outcomes. From our knowledge, previous publications in the field testing associations between mental health and brain network characteristics have mainly used metrics of inter or intra network functional connectivity (e.g., 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 employed in other contexts to characterize the neurobiological substrates of resilience (e.g., 63).

Altogether, these findings highlight the need of considering the study of resilience using a person-centered approach, where relevant contributing factors (psychological, lifestyles, sociocultural, neurodevelopmental aspects, etc.) should ultimately be integrated, and where ‘neurobiological markers’ effects should be interpreted within this context (10). Present results
may have implications to enable preventive strategies not only for the current COVID-19 pandemic, but also to face 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 and younger age individuals. Second, the status of functional brain networks were shown to be valuable predictors 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, using brain imaging to monitor if the effects of interventions are targeting such key circuits, may be of particular interest. Finally, this approximation could be also benefited from the use of approaches that allow a direct modulation of brain networks’ connectivity. Here, non-invasive brain stimulation may directly improve symptoms of anxiety (66) and depressive symptoms (67,68). Notably, it should be highlighted that the combination of such techniques with electroencephalography and/or fMRI allows modulating the spatio-temporal dynamics of specific brain networks in an individualized manner (e.g., 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 mental health impact of unexpected and sustained stressors (10).

Our study is not without limitations. First, we used PHQ-4 as the primary outcome measure to maximize the fact that we had assessments across all the time points (pre- and during-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 due to the recruitment used, notably that of being composed by individuals with high interest in their own brain health, with an under-representation of low mental health rates, as well as a high educational level. Hence, even
though the lack of effects for education in our study are aligned with previous reports (11), findings may have differed if the sample had included a higher representation of individuals with no or fewer educational qualifications (25). Third, many other variables including individual dispositional factors, health and family related issues as well as environmental and cultural aspects, possibly affecting the investigated outcome were not considered here (i.e., see discussion in 75). In this line, the availability of pre-pandemic information regarding perceived stress would have been useful in order 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, since we did not collect information about ethnicity, and since our population was homogeneous, mostly considering themselves as “Caucasian or white” (i.e., 94.39%). In addition, it should be noted that due to our inclusion criteria, present results should not generalize to samples of patients or those individuals exhibiting higher pre-pandemic scores in anxiety and depression. Finally, the analytical approach was not specifically designed to formally test the changes across temporal pandemic stages, nor was it designed to investigate group trajectories potentially contributing to longitudinal individual differences (e.g., 37,38), which will be the matter of future investigations.

In conclusion, leveraging data from a longitudinal prospective study including a large sample of middle-aged healthy individuals and multiple data points spanning from two years prior to the SARS-CoV-2 outbreak until the end of the first year of pandemic, we have been able to elucidate how basic sociodemographic measures, psychological factors as well as neurobiological characteristics relate to a general measure of mental health impact. FPCN, and DMN segregation/integration status was found to modulate the influence of the psychological factors, acting through distinct pathways, and conferring interindividual differences in vulnerability vs resilience regarding the change in psychological distress associated with the COVID-19 pandemic.
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Dr. A. Pascual-Leone is listed as an inventor on several issued and pending patents on the real-time integration of noninvasive brain stimulation with electroencephalography and magnetic resonance imaging. He is co-founder of Linus Health and TI Solutions AG; and serves on the scientific advisory boards for Starlab Neuroscience, Magstim Inc., Nexstim, and MedRhythms. The remaining authors report no biomedical financial interests or potential conflicts of interest.
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TABLE LEGENDS

Table 1. Sample characteristics.
Data for the whole sample (N=2,033) and the MRI sub-sample (N=433). 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 PhD (over 12 years). Socioeconomic status corresponds to the approximate range of the individuals’ monthly family income (Low: <1000; Low-Middle: 1000 to 2000; Middle-High: 2000 to 5000; High: >5000; all amounts in euros). Regarding employment status during-pandemic, an individual was considered as “Employed” when answered so at all time points. Psychological variables are described here as categories created according to available cut-offs regarding severity of anxiety and depressive symptomatology (i.e., Patient Health Questionnaire-4), level of coping strategies (i.e., Brief Resilient Coping Scale) and perceived stress (i.e., Perceived Stress Scale). Note that this categorization was done under descriptive purposes, but these variables were used as continuous in the present study. In addition, as anxiety and depression were assessed on multiple occasions in both periods (pre- and during-pandemic), a subject was considered to present ‘Moderate-Severe’ symptomatology when scoring within this range at least once. Continuous variables are described by mean ± standard deviation values, while categorical variables are described by the absolute number of individuals and its corresponding percentage (%) within the sample.

FIGURE LEGENDS

Figure 1. Timeline study design showing baseline (i.e., pre-pandemic) and during-pandemic points of acquisitions for the main outcome (i.e., PHQ-4), MRI and psychological factors (perceived stress, PSS and coping strategies, BRCS). On the left and purple color, pre-pandemic data including one MRI acquisition and two on-line PHQ-4 measures obtained between 2018 and 2020 (average follow-up: 12.73 ± 2.18 months). The beginning of the pandemic outbreak was considered according to the Spanish Government's State of Emergency declaration, on the 14th of March 2020. On the right and green color, six on-line questionnaires were administered during the first year of COVID-19 pandemic (until March-April 2021). Each questionnaire was available for answering during the specified data periods shown. Abbreviations: PHQ-4, Patient Health Questionnaire-4; MRI, magnetic resonance imaging, BRCS, Brief Resilient Coping Scale; PSS, Perceived Stress Scale.
Figure 2. Average values of PHQ-4 along time-point measurements for the whole sample (N=2023), showing PHQ-4 ratings increases. Shadow areas above and below the average PHQ-4 line (i.e., thick line) represent standard errors. Abscissa axes indicated 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 (14th March 2020 in Spain) and separates pre- and during-pandemic observations. Black vertical dashed lines delimitate 2020 and 2021. Finally, in the upper part of the figure, the increase of PHQ-4 values at during-pandemic compared to pre-pandemic is indicated. Abbreviations: Patient Health Questionnaire-4, PHQ-4.

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., 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 two groups with low (in brown; i.e., below median) and high (in green; i.e., over 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 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. Abbreviations: Patient Health Questionnaire-4, PHQ-4.

Figure 4. Representation of the modulatory effect of FPCN and DMN SyS values on the association between perceived stress and PHQ-4 change. (A) and (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 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) and (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 FPCN in C and DMN in D). Dots show individual observations of PHQ-4 change and perceived stress, for two 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 CN-SyS, DMN-SyS and coping strategies. **Abbreviations:** FPCN, fronto-Parietal Control Network; DMN, default mode network; SyS, system segregation; PHQ-4, Patient Health Questionnaire-4.
<table>
<thead>
<tr>
<th></th>
<th>Whole sample</th>
<th>MRI sub-sample</th>
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<tbody>
<tr>
<td></td>
<td>N = 2,023</td>
<td>N = 433</td>
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<tr>
<td><strong>Age (years)</strong></td>
<td>54.32 ± 7.18</td>
<td>53.02 ± 7.04</td>
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<tr>
<td><strong>Sex</strong></td>
<td></td>
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</tr>
<tr>
<td>Women</td>
<td>1,329 (65.69%)</td>
<td>203 (46.88%)</td>
</tr>
<tr>
<td>Men</td>
<td>694 (34.31%)</td>
<td>230 (53.12%)</td>
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<tr>
<td><strong>Educational level</strong></td>
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<tr>
<td>Primary</td>
<td>67 (3.31%)</td>
<td>12 (2.77%)</td>
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<tr>
<td>Secondary</td>
<td>436 (21.55%)</td>
<td>104 (24.02%)</td>
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<tr>
<td>Higher</td>
<td>1,520 (75.14%)</td>
<td>317 (73.21%)</td>
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<tr>
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<tr>
<td>Low</td>
<td>51 (2.53%)</td>
<td>10 (2.31%)</td>
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<tr>
<td>Low-Middle</td>
<td>374 (18.54%)</td>
<td>83 (19.17%)</td>
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<tr>
<td>Middle-High</td>
<td>1,198 (59.40%)</td>
<td>234 (54.04%)</td>
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<tr>
<td>High</td>
<td>394 (19.53%)</td>
<td>106 (24.48%)</td>
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<td><strong>Employment during pandemic</strong></td>
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<tr>
<td>Employed</td>
<td>1,123 (55.51%)</td>
<td>266 (61.43%)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>900 (44.49%)</td>
<td>167 (38.57%)</td>
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<td><strong>Anxiety and depression</strong></td>
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<tr>
<td>Pre-pandemic Normal-Mild</td>
<td>2,033 (100%)</td>
<td>433 (100%)</td>
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<td>(0-5)</td>
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<tr>
<td>Moderate-Severe</td>
<td>0 (0.00%)</td>
<td>0 (0.00%)</td>
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<tr>
<td>(6-12)</td>
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<tr>
<td>During-pandemic Low</td>
<td>1,818 (89.87%)</td>
<td>400 (92.38%)</td>
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<tr>
<td>Coping Strategies</td>
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<tr>
<td>Low</td>
<td>371 (18.70%)</td>
<td>60 (13.92%)</td>
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<tr>
<td>Medium</td>
<td>1,106 (55.75%)</td>
<td>226 (52.44%)</td>
</tr>
<tr>
<td>High</td>
<td>507 (25.55%)</td>
<td>145 (33.64%)</td>
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<tr>
<td>Perceived Stress</td>
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<tr>
<td>Low</td>
<td>465 (30.80%)</td>
<td>128 (38.65%)</td>
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<tr>
<td>Moderate</td>
<td>928 (61.46%)</td>
<td>188 (55.29%)</td>
</tr>
<tr>
<td>High</td>
<td>117 (7.75%)</td>
<td>24 (7.06%)</td>
</tr>
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</table>
Pre-COVID19

During-COVID19

OUTBREAK in Spain

- March 23-27th
- April 5-10th
- May 1-31st
- June 1-7th

- October 5-18th
- March-April 15-5th

2018 - early 2020

2020

2021

Journal Pre-proof