Brain mechanisms and psychological determinants of mental health resilience. Learning from the COVID-19 pandemic

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Doctoral Thesis

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Brain mechanisms and psychological determinants of mental health resilience. Learning from the COVID-19 pandemic.

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Els núvols són més blancs, el cel més pur.

Ara és temps de morir, que la vida es reforça.

El món, altra vegada despert davant l'atzur,

present càlidament que ha de tenir un futur

-sempre el somni que precedeix la força!-

Febrer (Màrius Torres, 1937)

A Pedro y Teresa.

This Thesis has been undertaken in the Medical Psychology Unit, Department of Medicine, Faculty of Medicine and Health Sciences, University of Barcelona. The group is part of the Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) and the Institute of Neurosciences of the University of Barcelona.

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INDEX

GLOSSARY OF ABBREVIATIONS

ACC Anterior Cingulate Cortex

BOLD Blood Oxygen Level-Dependent

CD-RISC Connor-Davidson Resilience Scale

CEN Central Executive Network

COVID-19 CoronaVirus Disease 2019

DMN Default Mode Network

FC Functional Connectivity

FPN Fronto-Parietal Network

fMRI Functional Magnetic Resonance Imaging

GMM Growth Mixture Models

HPA Hypothalamic-pituitary-adrenal

ICU Intensive Care Unit

MERS-CoV Middle East Respiratory Syndrome-CoronaVirus

MRI Magnetic Resonance Imaging

PFC Prefrontal Cortex

PTSD Post Traumatic Stress Disorder

ROI Region of interest

Rs-fMRI Resting State Functional Magnetic Resonance Imaging

RSN Resting State Network

SARS-CoV Severe Acute Respiratory Syndrome-CoronaVirus

SARS-CoV-2 Severe Acute Respiratory Syndrome-CoronaVirus 2

SN Salience Network

SyS System Segregation

VAN Ventral Attention Network

VN Visual Network

VS Ventral Striatum

WHO World Health Organization

FOREWORD

This Thesis, presented to obtain the degree of Doctor by the University of Barcelona, is the result of different studies carried out over a three-year period at the Medical Psychology Unit, Department of Medicine, Faculty of Medicine and Health Sciences, University of Barcelona.

This Thesis follows the compendium of publications format, and it includes two published peer-reviewed articles, in which the candidate was first author or second author with equal contribution (indicated by *), and one manuscript submitted for publication as first author. The three studies are presented in the following order:

1. Bayes-Marin I*, **Cabello-Toscano M***, Cattaneo G, Solana-Sánchez J, Fernández D, Portellano-Ortiz C, Tormos JM, Pascual-Leone A, Bartrés-Faz D. COVID-19 after two years: trajectories of different components of mental health in the Spanish population. Epidemiol Psychiatr Sci. 2023 Apr 17;32:e19. [Impact Factor (IF): 7.818 - Q1]

2. **Cabello-Toscano M**, Vaqué-Alcázar L, Bayes-Marin I, Cattaneo G, Solana-Sánchez J, Mulet-Pons L, Bargalló N, Tormos JM, Pascual-Leone A, Bartrés-Faz D. Functional brain connectivity prior to the COVID-19 outbreak predicts mental health trajectories during two years of pandemic. *Submitted.*

3. **Cabello-Toscano M***, Vaqué-Alcázar L*, Cattaneo G, Solana-Sánchez J, Bayes-Marin I, Abellaneda-Pérez K, Macià-Bros D, Mulet-Pons L, Portellano-Ortiz C, Fullana MA, Oleaga L, González S, Bargalló N, Tormos JM, Pascual-Leone A, Bartrés-Faz D. 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. Biol Psychiatry Cogn Neurosci Neuroimaging. 2023 Feb; 8(2):200-209. [IF: 6.050 - Q1]

RELATED ACADEMIC WORK

List of additional publications of the candidate that are not included in the Thesis. These papers are the result of collaborative work with other projects during the time of the Thesis:

- España-Irla G, Morris T, Albu S, **Cabello-Toscano M**, Redondo-Camós M, Delgado-Gallén S, Mulet-Pons L, Roca-Ventura A, Bargalló N, Cattaneo G, Solana-Sanchéz J, Tormos JM, Bartrés-Faz D, Pascual-Leone A. Functional connectivity mediates the relationship between cardiorespiratory fitness and stress in midlife. Ment Health Phys Act. 2023. [IF: 4.700 – Q2]

- Mulet-Pons L, Solé-Padullés C, **Cabello-Toscano M**, Abellaneda-Pérez K, Perellón-Alfonso R, Cattaneo G, Solana Sánchez J, Alviarez-Schulze V, Bargalló N, Tormos-Muñoz JM, Pascual-Leone A, Bartrés-Faz D, Vaqué-Alcázar L. Brain connectivity correlates of cognitive dispersion in a healthy middle-aged population: influence of subjective cognitive complaints. J Gerontol B Psychol Sci Soc Sci. 2023 Aug 17:gbad114. [IF: 6.200 - Q1]

- Abellaneda-Pérez K, Cattaneo G, **Cabello-Toscano M**, Solana-Sánchez J, Mulet-Pons L, Vaqué-Alcázar L, Perellón-Alfonso R, Solé-Padullés C, Bargalló N, Tormos JM, Pascual-Leone A, Bartrés-Faz D. Purpose in life promotes resilience to age-related brain burden in middle-aged adults. Alzheimers Res Ther. 2023 Mar 13;15(1):49. [IF: 8.823 - Q1]

- Delgado-Gallén S, Soler MD, **Cabello-Toscano M**, Abellaneda-Pérez K, Solana-Sánchez J, España-Irla G, Roca-Ventura A, Bartrés-Faz D, Tormos JM, Pascual-Leone A, Cattaneo G. Brain system segregation and pain catastrophizing in chronic pain progression. Front Neurosci. 2023 Mar 16;17:1148176. [IF: 4.300 – Q2]

- Solé-Padullés C, Cattaneo G, Marchant NL, **Cabello-Toscano M**, Mulet-Pons L, Solana J, Bargalló N, Tormos JM, Pascual-Leone Á, Bartrés-Faz D. Associations between repetitive negative thinking and resting-state network segregation among healthy middle-aged adults. Front Aging Neurosci. 2022 Dec 15;14:1062887. [IF: 5.702 - Q1]

ABSTRACT

When confronted with a stressful situation, our reactions can vary greatly. In general, the population comes across to be resilient, being able to resist or adapt to disturbances. However, this is not the case for everyone or every situation, and therefore understanding what lies behind a resilient response becomes very valuable knowledge when promoting emotional, social, and psychological well-being. The study of these phenomena shows that resilience is the result of numerous and complex interactions, among biological, psychological, and environmental factors that evolve throughout life. From the appraisal of the stressful event to coping with it, processes involving the activity of multiple body systems (for example, the hormonal response promoted by the hypothalamic-pituitary-adrenal axis) and mental processes come into play. During these processes, the central nervous system plays a major role, in triggering and modulating this response. Areas such as the hippocampus, the amygdala, and the anterior insula, anterior cingulate, and prefrontal cortices, as well as brain networks partially coinciding with them (Default Mode Network, Salience Network, and Frontoparietal Network), are involved. Much of these findings have been derived from the study of magnetic resonance imaging. However, these studies have serious limitations at various levels, such as the use of small populations or the lack of data prior to exposure to stressful or traumatic events. Within this gap in the literature, the COVID-19 pandemic presents a unique opportunity to study the stress response in large populations, in some cases with data available before the pandemic outbreak. This is possible since the COVID-19 pandemic has been widely regarded as a threat to mental health due to the many stressful situations it has led to.

Particularly, in this doctoral thesis, it was hypothesized that, despite this level of threat, the general population would remain resilient, and if affected, it would do so differently for

different dimensions of mental health (emotional, social, and psychological). Furthermore, associations were expected to be found between this response to the pandemic and basal brain characteristics in terms of functional connectivity balance in certain brain networks, as well as psychological factors, and interactions between them. As a result, the present doctoral thesis aimed to study the emotional, social, and psychological changes in a healthy middle-aged population, with a special focus on understanding the characteristics of the most resilient individuals compared to the most vulnerable ones.

Three research studies were conducted to answer the questions posed. All three studies included longitudinal data before and throughout the pandemic, with a total follow-up of up to four years (two of them belonging to the basal pre-pandemic period), for approximately two thousand participants among which up to around seven hundred had magnetic resonance imaging available. The first study identified longitudinal trajectories in which the studied population mainly experienced resilient responses, although vulnerable ones were also observed. In light of the results of this study, together with those of the second study, these trajectories were associated with various protective and risk factors at the sociodemographic, psychological, lifestyle, and functional status of brain network levels. Since each dimension of mental health was affected differently and characterized by distinct factors, these results emphasize the importance of studying mental health as a set of semi-independent components. The third study focused on the emotional response at the individual level, confirming that, despite the predominantly resilient effect of the studied population, a subtle but consistent worsening of anxious-depressive symptoms could be found, which was associated with the levels of stress perceived during the pandemic. It also identified brain and psychological mechanisms that modulated the resilient or vulnerable nature of this emotional change, in line with what was described in the previous two studies. Overall, the present doctoral thesis has identified at-risk populations (individuals living alone, women, or young adults) and factors to promote to protect them (coping strategies or healthy lifestyle habits that foster general and cognitive health). Essentially, this thesis has identified for the first time the role that the balance of connectivity (i.e., the integration-segregation balance) between networks at the level of the complete brain system plays in the resilient response to stressful situations. Specifically, it highlights the role that the Default Mode Network, the Salience Network, and the Frontoparietal Network have in psychological resilience, encouraging the development of future preventive strategies.

As a general conclusion, the work carried out reveals the imperative need to consider psychological, lifestyle, and sociodemographic factors along with brain mechanisms, with a particular emphasis on their interactions, to fully understand the phenomena of resilience and vulnerability and, thus, promote more effective interventions.

RESUM EN CATALÀ

Quan ens enfrontem a una situació estressant, les nostres reaccions poden ser molt variables. En general, la població es mostra resilient, sent capaç de resistir o adaptar-se davant de pertorbacions. Tanmateix, això no és igual per tothom ni en totes les situacions, i per tant, comprendre què hi ha darrere d'una resposta resilient esdevé un coneixement molt valuós per promoure el benestar a nivell emocional, social i psicològic. L'estudi d'aquests fenòmens mostra que la resiliència és el resultat de nombroses i complexes interaccions, entre allò biològic, allò psicològic i allò ambiental, que evolucionen al llarg de la vida. Des de l'avaluació de l'esdeveniment estressant fins a l'enfrontament del mateix, entren en joc processos que involucren l'activitat de múltiples sistemes a nivell corporal (per exemple, la resposta hormonal promoguda per l'eix hipotàlem-hipòfisi-suprarenal) i mental. Durant aquests processos, el sistema nerviós central juga un paper fonamental, desencadenant i modulant aquesta resposta. Àrees com l'hipocamp, l'amígdala i el còrtex insulat anterior, cingulat anterior i prefrontal, així com les xarxes cerebrals que coincideixen parcialment amb aquestes regions (xarxa del Mode per Defecte, xarxa de Saliència i xarxa Frontoparietal). Una gran part d'aquests descobriments s'han derivat de l'estudi d'imatges per ressonància magnètica. Tanmateix, aquests estudis presenten greus limitacions a diferents nivells, com l'ús de mostres petites o la manca de dades prèvies a l'exposició a l'esdeveniment estressant o traumàtic. En aquest buit a la literatura, la pandèmia de la COVID-19 suposa una oportunitat única per estudiar la resposta a l'estrès en grans poblacions, en alguns casos, amb disponibilitat de dades prèvies a l'esclat pandèmic.

Particularment, en aquesta tesi doctoral es va hipotetitzar que, malgrat aquest nivell de risc, la població general es mantindria resilient i que, en cas de veure's afectada, ho faria de manera diferent per a les diferents dimensions de la salut mental (emocional, social i psicològica). A més, es va esperar trobar associacions entre aquesta resposta a la pandèmia i característiques cerebrals bàsiques a nivell del balanç en connectivitat funcional de determinades xarxes cerebrals i factors psicològics, així com les seves interaccions. Com a conseqüència, aquesta tesi doctoral va tenir com a objectius l'estudi dels canvis emocionals, socials i psicològics d'una població sana de mitjana edat, amb un enfocament especial en comprendre els factors que caracteritzen els individus més resilients davant dels més vulnerables.

Es van desenvolupar tres estudis de recerca per respondre a les preguntes plantejades. Tots tres estudis van incloure dades longitudinals prèvies i al llarg de la pandèmia, amb un abast de fins a quatre anys de seguiment en total (dos d'ells pertanyents al període previ). Amb el primer estudi es van identificar trajectòries longitudinals segons les quals la població estudiada va experimentar principalment respostes resilients, tot i que també vulnerables, a la pandèmia. A la vista dels resultats d'aquest estudi, juntament amb els del segon, aquestes trajectòries es van associar amb diversos factors de protecció i risc, a nivell sociodemogràfic, psicològic, d'estils de vida i d'estat funcional de les xarxes cerebrals. Donat que cada dimensió de la salut mental es va veure afectada de manera diferent i caracteritzada per diversos factors, aquesta tesi doctoral posa èmfasi en la importància d'estudiar la salut mental com un conjunt de components semi-independents. El tercer estudi es va centrar en la resposta emocional a nivell de cada individu, confirmant que, malgrat la majoritària resposta resilient de la població estudiada, es podia trobar un subtil però consistent empitjorament dels símptomes ansiosos-depressius associat a l'estrès percebut durant la pandèmia. A més, també es van identificar mecanismes cerebrals i psicològics que modulaven el caire resilient o vulnerable d'aquest canvi emocional, en línia amb el que es descriu en els dos estudis anteriors. En termes generals, aquesta tesi doctoral ha identificat poblacions de risc (individus que viuen sols, dones o adults joves) i factors a promoure per protegir-los (estratègies d'enfrontament o hàbits de vida saludables que fomentin la salut general i cognitiva). De manera essencial, aquesta tesi ha identificat per primera vegada el paper que té l'equilibri de la connectivitat entre xarxes (específicament, l'equilibri entre integració i segregació) a nivell del sistema cerebral complet en la resposta resilient a situacions estressants. De forma concreta, els resultats en neuroimatge destaquen el paper que la xarxa del Mode per Defecte, la xarxa de Saliència i la xarxa Frontoparietal tenen en la resiliència psicològica, incentivant el desenvolupament d'estratègies preventives futures.

Com a conclusió general, la feina realitzada revela la necessitat de tenir en compte factors psicològics, d'estil de vida i sociodemogràfics, juntament amb els mecanismes cerebrals, amb un èmfasi particular en les seves interaccions, per comprendre plenament els fenòmens de resiliència i vulnerabilitat i, així, potenciar intervencions de major efectivitat.

RESUMEN EN CASTELLANO

Cuando nos enfrentamos a una situación estresante, nuestras reacciones pueden ser muy variables. En general, la población se muestra resiliente, siendo capaces de resistir o adaptarse frente a perturbaciones. Sin embargo, no es el caso de todo el mundo ni de todas las situaciones y por tanto entender qué hay detrás de una respuesta resiliente se convierte en un conocimiento muy valioso a la hora de promover bienestar a nivel emocional, social y psicológico. El estudio de dichos fenómenos muestra que la resiliencia es el resultado de numerosas y complejas interacciones, entre lo biológico, lo psicológico y lo ambiental, que evolucionan a lo largo de la vida. Desde la evaluación del suceso estresante, al afrontamiento del mismo, entran en juego procesos que involucran la actividad de múltiples sistemas a nivel corporal (por ejemplo, la respuesta hormonal promovida por el eje hipotálamo-hipófisis-suprarrenal), y mental. Durante los mismos, el sistema nervioso central juega un papel principal, desencadenando y modulando dicha respuesta. Áreas como el hipocampo, la amígdala y las cortezas insultar anterior, cingular anterior y prefrontal, así como redes cerebrales que coinciden parcialmente con las mismas (red de Modo por Defecto, red de Saliencia y red Fronto-parietal). Gran parte de estos hallazgos se han derivado del estudio de imágenes por resonancia magnética. Sin embargo, estos estudios presentan graves limitaciones a distintos niveles, como el uso de poblaciones pequeñas o la falta de datos previos a la exposición al evento estresante o traumático. Dentro de esta brecha en la literatura, la pandemia del COVID-19 supone una oportunidad única para estudiar la respuesta al estrés en grandes poblaciones, en algunos casos, con disponibilidad de datos previos al brote pandémico. Esto es posible dado que la pandemia del COVID-19 ha sido ampliamente considerada como una amenaza para la salud mental por la gran cantidad de situaciones estresantes en la que ha derivado.

Particularmente, en esta tesis doctoral se hipotetizó que, pese a dicho nivel de amenaza, la población general se mantendría resiliente y que, en caso de verse afectada, lo haría de manera diferente para las distintas dimensiones de la salud mental (emocional, social y psicológica). Además, se esperó encontrar asociaciones entre dicha respuesta a la pandemia y características cerebrales basales a nivel del balance en conectividad funcional de determinadas redes cerebrales, y factores psicológicos, así como interacciones entre los mismos. Como consecuencia, la presente tesis doctoral tuvo como objetivos el estudio de los cambios emocionales, sociales y psicológicos de una población sana de mediana edad, con especial enfoque en comprender los factores que caracterizan a los individuos más resilientes frente a los más vulnerables.

Tres estudios de investigación se desarrollaron para responder a las preguntas planteadas. Los tres estudios incluyeron datos longitudinales previos y a lo largo de la pandemia, con un alcance de hasta cuatro años de seguimiento en total (dos de los mismos pertenecientes al periodo previo). Con el primer estudio se identificaron trayectorias longitudinales según las cuales la población estudiada cursó principalmente respuestas resilientes, aunque también vulnerables, a la pandemia. A la vista de los resultados de este estudio, junto con los del segundo, dichas trayectorias se asociaron con diversos factores de protección y riesgo, a nivel sociodemográfico, psicológico, de estilos de vida y de estado funcional de las redes cerebrales. Dado que cada dimensión de la salud mental se vio afectado de manera diferente y caracterizada por distintos factores, esta tesis doctoral enfatiza en la importancia de estudiar la salud mental como un compendio de componentes semindependientes. El tercer estudio se centró en la respuesta emocional a nivel de cada individuo, confirmando que, pese a la mayoritaria respuesta resiliente de la población estudiada, se podía encontrar un sutil pero consistente empeoramiento de los síntomas ansioso-depresivos asociado al estrés percibido durante la pandemia. Además, también identificó mecanismos cerebrales y psicológicos que modulaban el cariz resiliente o vulnerable de dicho cambio emocional, en línea con lo descrito en los dos estudios anteriores. En términos generales, la presente tesis doctoral ha identificado poblaciones de riesgo (individuos que viven solos, mujeres o adultos jóvenes) y factores a promover para protegerlos (estrategias de afrontamiento o hábitos de vida saludable que incentiven la salud general y cognitiva). De manera esencial, la presente tesis ha identificado por primera vez el papel que tiene el balance de la conectividad (es decir, el balance integración-segregación) entre redes a nivel del sistema cerebral completo, en la respuesta resiliente a situaciones estresantes. En concreto, hace destacar el papel que la red de Modo por Defecto, la red de Saliencia y la red Fronto-parietal tienen en cuanto a la resiliencia psicológica, incentivando el desarrollo de estrategias preventivas futuras.

Como conclusión general, el trabajo realizado revela la imperatividad a la hora considerar factores psicológicos, de estilo de vida y sociodemográficos junto con los mecanismos cerebrales, con un énfasis particular en sus interacciones, para comprender plenamente los fenómenos de resiliencia y vulnerabilidad y, así, potenciar intervenciones de mayor efectividad.

CHAPTER 1

General Introduction

1. Resilience in the face of psychological stress

Resilience is a broad term that is present in many fields, as varied as going from psychology to engineering. In its more fundamental conceptualization, it refers to a phenomenon by which a subject (i.e., person, object, or system) is able to resist, adapt, or recover in front of a perturbation (e.g., either a human that is living with a disease, or the bumper of a car designed to absorb impacts).

In the context of psychology, Sisto et al. (2021) highlight the complexity of resilience and the heterogeneity in the literature regarding its conceptualization, and conclude with the following definition:

> "Resilience is the ability to adapt positively to life conditions. It is a dynamic process evolving over time that implies a type of adaptative functioning that specifically allows us to face difficulties by recovering an initial balance or bouncing back as an opportunity for growth." (Sisto et al., 2021).

Historically, research has primarily focused on acute grief, chronic grief, and PTSD as typical responses to adversity in adults. However, it is well-documented that most individuals exposed to loss or life-threatening events do not develop chronic symptoms; instead, many exhibit healthy, resilient functioning (Bonanno, 2004). This pattern holds true for the general population in the context of pandemics or other natural disasters (Chen & Bonanno, 2020), as discussed in section 3. Nevertheless, the intricate mechanisms underlying the differences between more resilient and vulnerable outcomes are still being established.

1.1. Resilience: a static trait or a dynamic process?

The definition given by Sisto et al. (2021) remarks the dynamic evolving nature of resilience, disapproving with those that consider it a non-modifiable trait along the lifespan (Miller, 1988). In this line, the American Psychological Association defines resilience as a "process of adapting well in the face of adversity, trauma, tragedy, threats or significant sources of stress" (APA, 2023).

However, while resilience is considered a dynamic process that can change over a lifetime, numerous studies highlight the impact of unavoidable factors on one's propensity for resilience or vulnerability, such as genetic predisposition or past experiences, such as dysfunctional childhood contexts or traumatic events at any stage of life. Much of the literature on this topic focuses on studying early childhood experiences and their strong influence on responses to stress, among other health outcomes during adulthood. For example, individuals with at least four adverse childhood experiences were found to be at increased risk for various health conditions, including substance use, sexual health issues, mental health problems, weight and physical exercise issues, violence, and physical health conditions (Hughes et al., 2017). Indeed, the development and functioning of biological systems is believed to be influenced by these events, which in turn would underlie the subsequent increased vulnerability. Adverse childhood experiences significantly affect the developing brain, particularly areas related to emotional regulation, stress response, and cognitive function (Hanson et al., 2015; McLaughlin et al., 2014; Mukherjee et al., 2008). Additionally, these can affect the stress response system, including the hypothalamic-pituitary-adrenal (HPA) axis, potentially causing cortisol dysregulation, further impacting brain development and function (Danese et al., 2012; Heim & Nemeroff, 2001). Nevertheless, while adverse childhood experiences promote vulnerability, the absence of these and, oppositely, the presence of healthy supportive environments, facilitate resilience. Childhood has been proven to be a crucial period in life in regard to conditioning the development of future psychopathology. In a review, Holz et al. (2020) contextualized how psychosocial aspects shape the brain in structure and function, enhancing or restraining psychological resilience. Particularly, they conclude that both perigenual Anterior Cingulate Cortex (ACC) activity and gray matter volume are conditioned by social early life exposures such as urbanicity (Haddad et al., 2015) and have a role in self-referential social comparisons (Gianaros et al., 2007). They also emphasized the critical importance of prefrontal regulation of regions implicated in social-stress signaling. Altogether, social aspects may have a strong effect on resilience by shaping the brain structure and function. Thus, only considering these facts to understand the resilient phenomenon may incorrectly lead to the idea that it is a constitutional factor of the individual, acquired during development and then relatively immutable.

Although highly constrained by biology and the environment, many other modifiable factors need to be contemplated to comprehend the complexity of resilience. As shown in figure 1 (adapted from Feder et al., 2019), resilience may be interpreted as the final result of neural circuitry and stress response systems (see section 2) and psychological factors (see 'Psychological factors – 'Stress, appraisal and coping' model', section 1.2), along with the interactions between them. These are simultaneously conditioned by both our natural predisposition (i.e., genes) and the environment, which have direct and indirect effects through the regulation of gene expression (i.e., epigenetics). Finally, preventive, and therapeutic interventions aimed at enhancing resilience may do so through three of the mentioned pathways: environment, psychological factors, and brain-body mechanisms (Feder et al., 2019). The following sections focus on psychological factors and neurobiological mechanisms on psychological resilience.

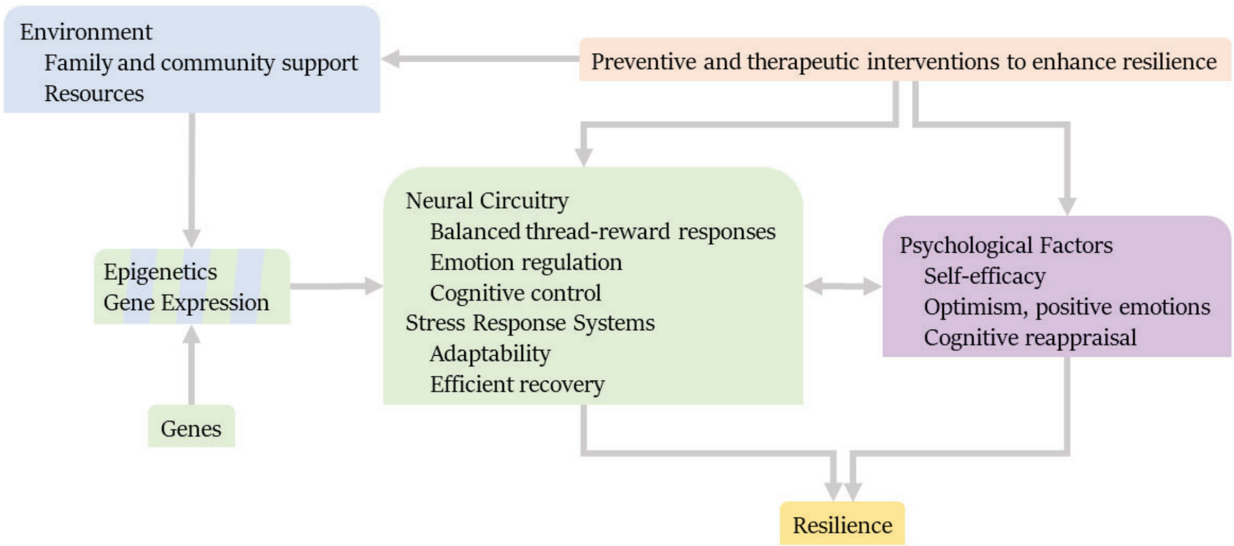

Figure 1. Biopsychosocial model of resilience as adapted from Feder et al., (2019). Resilience (in yellow) is the direct result of the interaction between biological mechanisms (in green), such as the brain and the hypothalamus-pituitary-adrenal axis, and psychological factors (in purple). Genes and environment (in blue) indirectly affect resilience through the effects of epigenetics and gene expression. Finally, preventive interventions may act via environmental influences and all intermediate paths.

1.2. Psychological factors – 'Stress, appraisal and coping' model

Regarding psychological factors, the model proposed by Lazarus & Folkman almost 40 years ago (Lazarus & Folkman, 1991) still serves as the foundational basis for research on psychological stress and coping (e.g., Cooper & Quick, 2017). Their theory is based on the interplay between three elements: stress, appraisal, and coping. They emphasize that stress is strictly conditioned by the relationship between the person encountering the potential stressor and their environment. In this line, a stressful situation may, or not, exceed one's resources endangering their well-being. Whether this happens or not depends greatly on their appraisal of stress. According to them, there are two levels of stress appraisal. Primary appraisal consists of evaluating the threatening nature of the potential stressor ("Am I at risk?"), while secondary appraisal focuses on the evaluation of coping resources or abilities to deal with it ("What can I do?").

Importantly, primary cognitive appraisal processes are not necessarily conscious. For example, studies on appraisal processes have demonstrated that individuals can quickly and automatically evaluate stimuli as threatening or non-threatening (e.g., images of snakes and spiders) without conscious deliberation (i.e., involuntarily, e.g., Phelps et al., 2006; Öhman et al., 2001). Furthermore, cognitive appraisal processes are expected to be affected by the person's commitment and beliefs (i.e., person factors), along with other situational factors such as the novelty of the event, its predictability, imminence, duration, and temporal uncertainty (i.e., situational factors). These personal and situational factors are interdependent, and their results depend on them and their interaction.

In the second level of appraisal, the strategies to cope with an event that has been already perceived as stressful come into play. As regards coping strategies, these were categorized by Lazarus & Folkman (1991) into two broad types: problem-focused and emotion-focused. The first implies a direct implication of the individual in addressing and mitigating the effect of the stressor. In the second, on the contrary, the individual intends to regulate their emotional response and does not actively aim to lessen the source of stress. Additional to these two main categories, more recent studies distinguish among other coping styles such as positive coping, avoidance, and social support (e.g., Poulus et al., 2020; Eisenberg et al., 2012; Dias et al., 2012). In addition, different facets of coping are proposed and classified into different categories: self-distraction, denial, substance use, behavioral disengagement, emotional support, venting, humor, acceptance, self-blame, religion, active coping, use of instrumental support, positive reframing, and planning (e.g., as assessed by items within the 'COPE Inventory' by Carver et al., 1989; Poulus et al., 2020; Eisenberg et al., 2021; Dias et al., 2012).

In general, coping strategies can be defined as cognitive and behavioral processes learnt along experiences. Despite their association with specific profiles of personality or resilience traits, these are understood as more dynamic factors that are modifiable by exposition to stressful events during life. Particularly, self-reflection practices mediate the relationship between the initial stress response and future resilient capacities (Crane et al., 2019).

2. Brain mechanisms of mental health resilience

2.1. The biology of stress

According to the Oxford English Dictionary, resilience is defined as "the quality or fact of being able to recover quickly or easily from, or resist being affected by, a misfortune, shock, illness, etc." (OED, 2023). In life sciences, this concept is proposed to be conceptualized as a homeostatic mechanism (Pascual-Leone & Bartrés-Faz, 2021). Homeostasis is the essential state of internal equilibrium of an organism, which is unfolded by a set of well-coordinated physiological processes, ensuring its preservation and development (Cannon, 1932). A stressor should be understood as any stimulus or experience potentially able to interrupt homeostasis. When an organism faces a stressor, which may have either internal or external origins, homeostasis can be momentarily lost. In response, very specific biological systems are engaged as a form of allostatic processes (both anticipatory and reactive) to recover homeostasis.

Such allostatic processes (i.e., those that maintain homeostasis) may depend on a hierarchy of feedback loops by which the outcomes of the different organism responses would regulate the mechanisms to appraise the potential stressors or to give place to a more adaptive or maladaptive outcomes. In the proposed scenario, these loops constitute the processes that aim to optimize the outcome to ensure equilibrium (see Figure 2B).

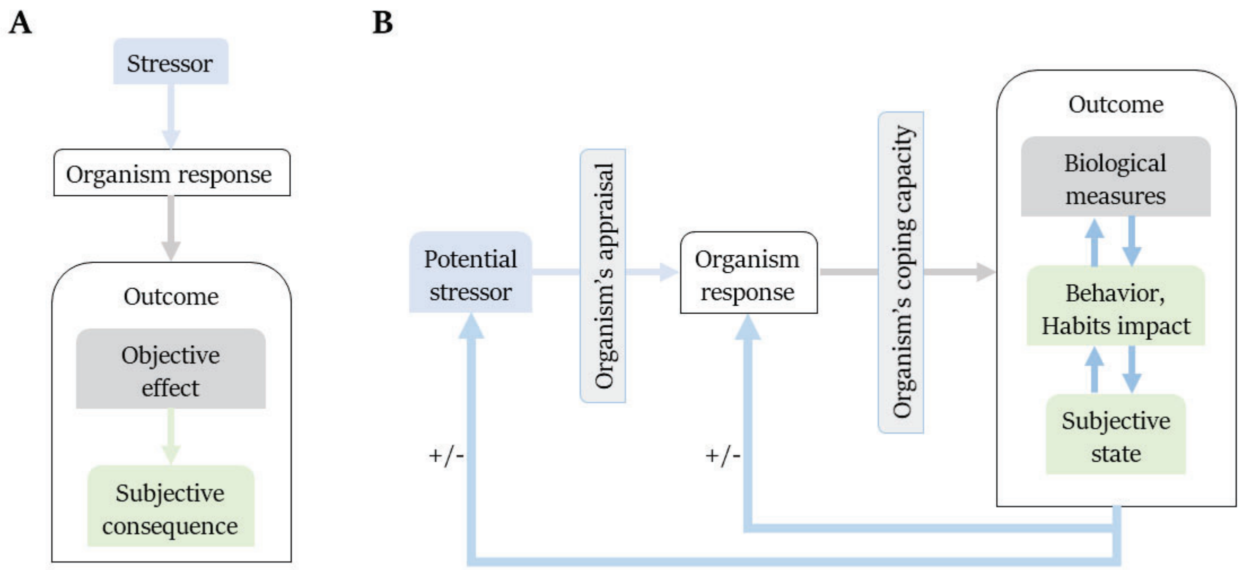

Figure 2. Schematic representation of stress-response paradigm (A) and its modification to reflect resilience as an evolving, active process (B). Adapted from Pascual-Leone & Bartrés-Faz (2021).

From a physiological perspective, allostatic processes encompass the HPA axis, the autonomic nervous system, metabolic mechanisms, and the immune system, all of them interacting with each other. The HPA axis is particularly responsible for the coordinate cascade of endocrine signals in response to neuronal transmissions when facing a stressor (Kinlein & Karatsoreos et al., 2020). Very briefly, when the stressor is perceived via sensory input in the brain, neurons in the hypothalamus synthesize and secrete corticotrophin-resealing hormones, which reaches cells in the anterior lobe of the pituitary. This activates the secretion of adrenocorticotrophic hormones by the pituitary into the circulating blood, which reach the adrenal glands located on top of both kidneys. Here, glucocorticoids such as cortisol are secreted in response to stress (see Figure 3). Glucocorticoids mediate the negative feedback loop by which the HPA axis functions. This negative feedback happens both directly through the action of glucocorticoids in the hypothalamus and indirectly in the medial prefrontal cortex (PFC), hippocampus, and amygdala (Kinlein & Karatsoreos et al., 2020). The implication of these areas in stress processing has been also analyzed in neuroimaging studies (see the following section for further details).

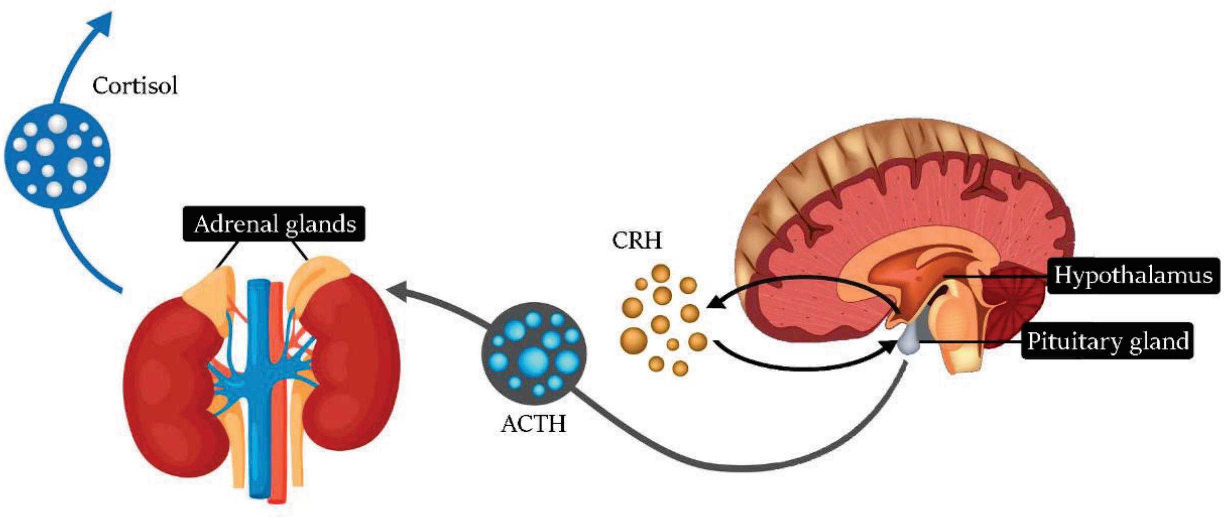

Figure 3. Schematic representation of the hypothalamus-pituitary-adrenal (HPA) axis and its functioning. Abbreviations: Corticotrophin releasing hormone, CRH; Adrenocorticotropic hormone, ACTH.

The interactions between brain areas implicated in the processing of stress by the HPA axis (i.e., amygdala, medial PFC and hippocampus), and the hormonal cascade promoted by the latter, are suggested to be responsible for emotional behavior such as increased vigilance and associated with anxiety and depressive symptomatology (Gray et al., 2015; McEwen, 1998). Although useful during specific instances of survival, using these systems too often, for too long, or inadequately can result in gradual damage to tissues and organs. This negative impact is known as allostatic load, which is reflected by the cumulative dysregulation of neuroendocrine, immunological, metabolic, and cardiovascular systems (McEwen & Stellar, 1993) and can lead to physical and psychological pathologies (Engel et al., 2022). In fact, recent studies have found associations between allostatic load and dementia risk (AD and non-AD dementias; Adedeji et al., 2023; Twait et al., 2023). However, not all individuals exposed to stress will be affected negatively. In this context, it has been proved that HPA axis activity is strongly related to coping style, mediating the difference between more resilient vs. vulnerable profiles (Höhne et al., 2014).

2.2. Magnetic resonance imaging to assess resilience

As discussed in the previous section, resilience is a very complex phenomenon that is strongly conditioned and mediated by brain mechanisms and their interactions with other factors (e.g., environmental, genetic, or psychological features). The use of Magnetic Resonance Imaging (MRI) techniques has been especially useful for the study of these brain mechanisms, but there are still many questions arising to be assessed about them. At the end of this section, a review of the state of the art concerning brain mechanisms of mental health resilience is given. However, the following subsections are devoted to contextualizing MRI in neuroimaging; its principles, modalities, and main techniques of analysis with a special emphasis on resting-state functional (fMRI), Resting State Networks (RSNs), and Functional Connectivity (FC), to allow a better understanding of the findings in the field.

2.2.1. Magnetic resonance imaging

One of the most widely applied neuroimaging techniques is MRI. MRI is a non-invasive technique with highly competitive characteristics concerning the quality and resolution of the resulting images. Very briefly, its functioning is based on the application of a strong magnetic field (nowadays commonly ranging from 1.5 to 7 Tesla) on the subject to be studied. Under this field, hydrogen atoms within the body of the subject (in large quantities due to the amount of water in the body and its molecular composition) become aligned and then excited by radio waves or pulses that perturb the alignment. The energy emitted by the protons after this perturbation, during the process of relaxation, reflects the composition of the tissues and is captured to build three-dimensional images (Huettel, Song & McCarthy, 2004).

Different properties of the tissue can be measured by different contrasts, giving place to several MRI modalities or sequences (Huettel, Song & McCarthy, 2004). Within the field of neuroimaging, these can be grouped as structural and functional modalities. As these terms indicate, structural MRI is devoted to studying the structures in the brain and its biophysical and physiological properties, and fMRI describes its activation and patterns of functioning. Structural MRI, besides being a powerful diagnostic tool for many medical conditions, enables us to quantitatively assess focal differences in brain anatomy, which are essential to neuroscience. Specifically, the quantification of grey matter and white matter characteristics, such as cortical thickness, subcortical volumes, white matter hypo/hyper-intensities (e.g., as quantified by algorithms of FreeSurfer https://surfer.nmr.mgh.harvard.edu), represents some of the most widely used metrics of structural MRI in neuroscience. The most common structural modality is T1-weighted imaging (see Figure 4), which not only facilitates the quantification of the before-mentioned characteristics but also aids in preprocessing other modalities, as is the case with fMRI. On the other hand, fMRI goes beyond the static view of the brain and aims to study it on the basis of its activity. To do so, fMRI captures Blood Oxygen Level-Dependent (BOLD) signal along time (see Huettel, Song & McCarthy [2004] for further reading).

2.1.1. Functional MRI

BOLD contrast, as its name indicates, measures the degree of blood oxygenation in the tissues. This is possible since hemoglobin oxygen-carrying and deoxygenated hemoglobin have different magnetic properties that distort the magnetic field and affect the relaxation times to be captured (Matthews & Jezzard, 2004). Controversial discussions have challenged the interpretability of this signal as an indirect measure of brain activity. Nevertheless, there are numerous studies supporting the existence of a relationship between BOLD signal and brain activity (Drew, 2019; Gauthier & Fan, 2019; see Khader et al., 2008 for a review). Importantly, some have found that, when removing the abundant physiological noise, there are correlations between the BOLD signal and the electroencephalography signal (Birn, 2012). The idea of interpreting increases in BOLD signal as increases in neural activity derives from neurons' necessity for blood supply in obtaining oxygen to optimally operate (Huettel, Song & McCarthy, 2003). At the neuronal level, increased blood flow facilitates substrate delivery for energy metabolism. However, it is not the increase in energy used by the neurons, but the neurotransmitters' action in local signaling which promotes blood flow increases (Matheus & Jezzard, 2004). Even so, when interpreting BOLD, or any other MRI signal, it must be kept in mind that spatial resolution is at the scale of millimeters, where a thousand neurons fit easily. This should not be considered a limitation since aiming to understand the complexity

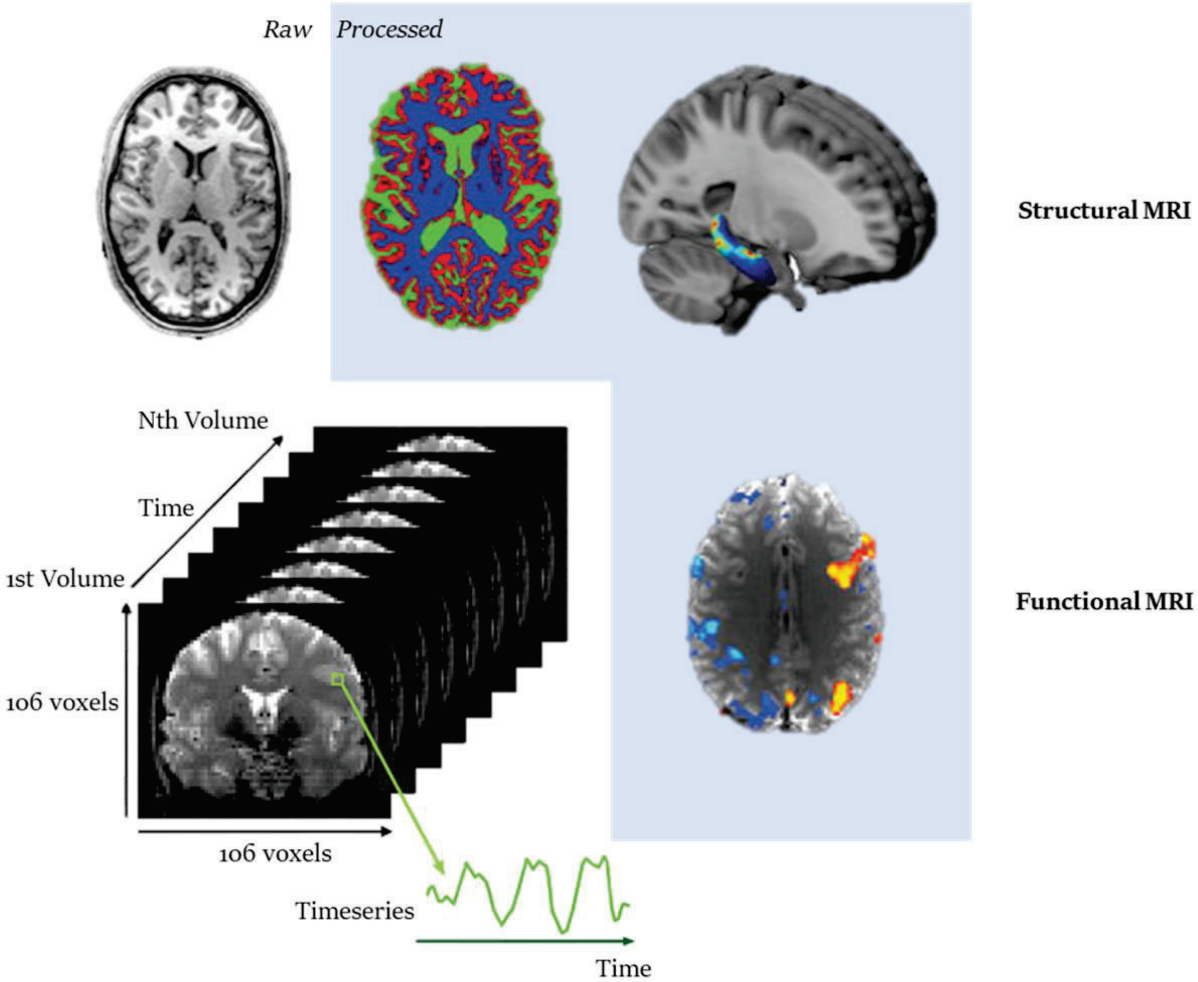

Figure 4. Structural and functional MRI modalities. Within structural MRI, T1-weighted acquisitions lead to images such as the first in the left. Processing of this image derive into segmentation of brain tissues (first row, middle) and structures (e.g., hippocampus; first row right). Regarding functional MRI, raw BOLD images are four-dimensional. This is, as illustrated in the bottom left schema, a number of volumes (i.e., three-dimensional MRI images comprise a single BOLD acquisition. Within these images, timeseries represent the temporal change on the signal within a voxel (or spatial unit). The analysis of timeseries and BOLD images lead to many different results such as functional activation maps (bottom row, right). This figure has been adapted from Jenkinson & Chappel (2018).

of brain functioning by the study of single cells is likely to be a great underestimation of its complexity (Yuste, 2015).

One of the most characteristic aspects of fMRI is that results in four-dimensional data. The fMRI acquisition is constituted by sets of consecutive MRI scans along the time from which BOLD changes are assessed (as displayed in Figure 4 - bottom row, left). These temporal changes in blood oxygenation can be studied as associated with particular conditions or tasks. This modality of fMRI (i.e., task-based fMRI) has been widely exploited and is responsible for many important discoveries and advances in neuroscience. However, during the last two decades, task-free fMRI acquisition has become increasingly important for the study of brain function. This task-free modality, commonly known as resting-sate fMRI, consists of recording BOLD signal during a priori non-particular task. The participant is frequently requested not to do anything in particular (nor fall asleep) and sometimes it varies on whether they are allowed to close their eyes or to fix their eyes on a particular point of the space. The simplicity of the setup is a very powerful strength when it comes to the reproducibility of the experiment in any research study, particularly in conditions where behavioral responses collected within the MRI scanner are complicated by the subjects' characteristics (i.e., populations with communicative difficulties or inability to understand or resolve the tasks due to cognitive dysfunction). Some authors have pointed out the resting paradigm being more appropriate and adequate to study brain function, with results comparable enough to those from task-based fMRI (Smith et al., 2009).

2.1.2. Brain Connectivity

Apart from the study of activation-deactivation patterns associated with task conditions in the brain, analyzing temporal and/or spatial patterns of connectivity provides very meaningful knowledge about the dynamics by which this organ works. Connectivity can be studied at two main levels: neuroanatomical and functional, among which FC has been the one capturing the most attention in the field (Bressler & Menon, 2010; Fingelkurts et al., 2005). Neuroanatomical connectivity provides a static view of the physical means by which grey matter structures are interconnected through white matter tracts (mainly studied with diffusion MRI acquisitions; Bressler & Menon, 2010; Mukherjee et al., 2008; Basser et al., 1994). However, FC aims to analyze the relationship between the activation of brain regions that very often occurs between non-adjacent areas (Bressler & Menon, 2010). In this case, FC quantifies whether activation of different areas occurs simultaneously (i.e., are correlated; Jenkinson & Chappel, 2018). Other emerging metrics focus on relationships implying temporal lags and often regards interpretation through causality (i.e., effective connectivity), meaning that activation of an area can be identified as a measurable consequence of the activation of another area (e.g., Deco et al., 2021).

There are multiple methodological approaches to assessing FC (see Shahhosseini & Miranda, 2022). Hypothesis-driven studies normally focus on the quantification of FC between particular pre-specified areas. In these studies, it is very common to use seed-based approaches, where a "seed" or Region of Interest (ROI) of variable size is pre-defined. Then, the coupling between the signal within this seed and the rest of the brain, or other ROIs, is quantified (Shahhosseini & Miranda, 2022). On the contrary, other studies, predominantly data-driven ones, aim to describe FC at the level of the whole brain. Then, the brain is frequently parceled into units that can vary from voxels to bigger ROIs delimited by pre-characterized atlases, and FC is quantified between each pair of these units (see Figure 5 for an example of pipeline to obtain FC measures at the level of RSNs). Here it is relevant to mention that when the units decrease in size, the number of FC calculations increases exponentially, which is very likely to lead to computational problems. Apart from using bigger ROIs to reduce the number of pair-wise FC calculations, there are other dimension reduction approaches to study FC. These are based on the decomposition of the three-dimensional sets of BOLD signals

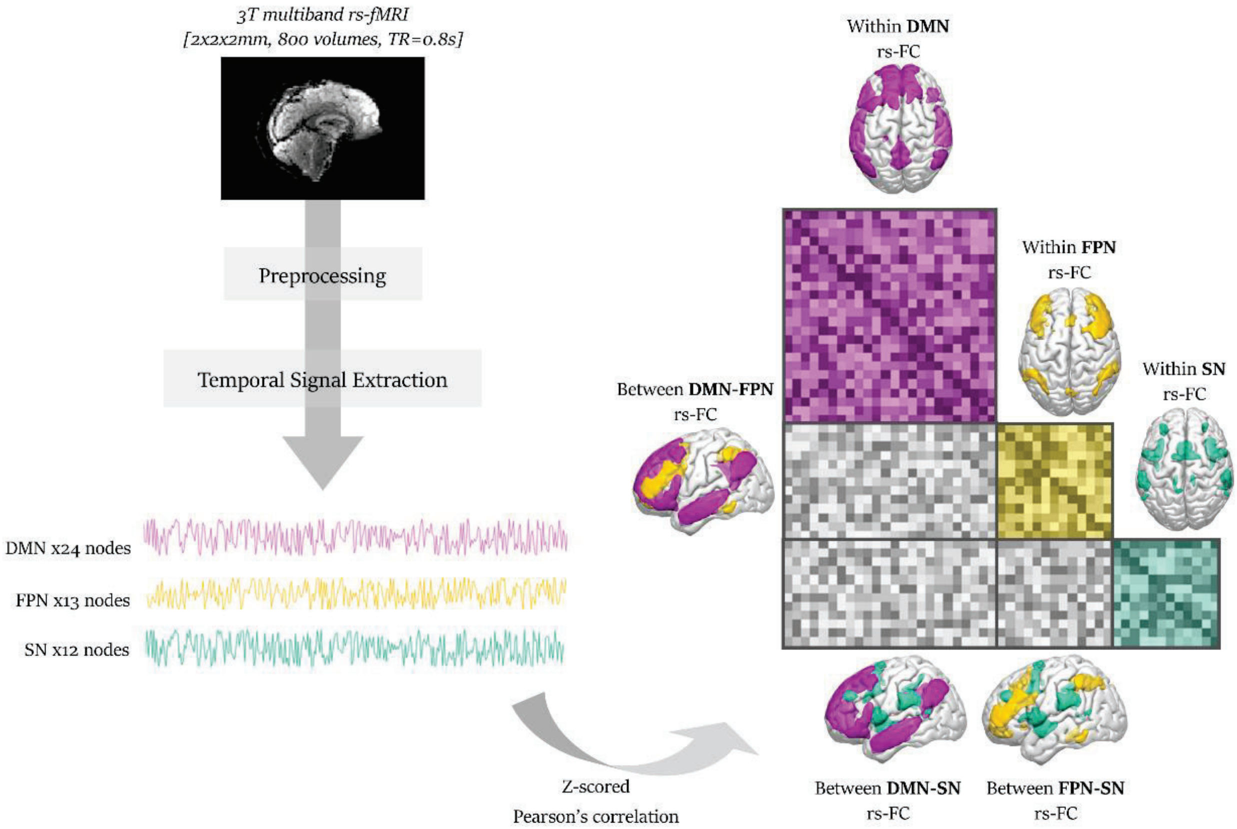

Figure 5. Example of fMRI data analysis pipeline, adapted from España-Irla et al. (2023). Raw fMRI data was preprocessed and extracted as average of the time series belonging to predefined parcels (or nodes). Correlation between each pair of time courses were estimated to obtain the functional connectivity matrices of the studied population. In this particular example, connectivity was only studied for three particular predefined networks, each of them comprising a determined number of nodes. Within rs-FC values were computed by averaging FC values for all pairs of nodes belonging to the same network. Conversely, for the between rs-FC values, only those values describing connectivity degree between two pairs of nodes from different networks were averaged. The balance between these two metrics (i.e., within and between rs-FC) derives into system segregation measures. Abbreviations: Default Mode Network, DMN; Fronto-parietal Network, FPN; resting state functional connectivity, rs-FC; resting state functional Magnetic Resonance Imaging, rs-fMRI; Salience Network, SN.

(i.e., the fMRI data) into a small number of latent components characterizing spatial and/or temporal FC patterns (i.e., maps of regions with similar patterns of synchronized activity;

Nickerson et al., 2017). The most commonly used methods in this line are Principal Component Analysis (Salem et al., 2021) and Independent Component Analysis (Zhao et al., 2021), which importantly contributed to the discovery of the main RSNs, as further described below.

2.1.3. Large-scale (resting state) networks

FC analyses on task-based fMRI studies have helped to understand the mechanistic underlying complex cognitive (e.g., Bressler & Menon, 2010) or emotional processes (e.g., Linhartová et al., 2019). However, during resting conditions, FC analyses have given place to the discovery of the increasingly well-characterized large-scale RSNs (Biswal et al., 1995). These have been compared with those implicated in task conditions. Particularly, RSNs are thought to be equally relevant to understanding the brain dynamics responsible for complex behavior (Smith et al., 2009). RSNs have been consistently identified by the use of dimension reduction approaches across studies (Moussa et al., 2012). These comprise a finite set of specific coherent patterns on the cortex, including the DMN, a visual processing network, and cerebellum, sensorimotor, auditory, executive control, and fronto-parietal networks (FPN; Smith et al., 2009; Damoiseaux et al., 2006). Cortical regions comprising them are highly functionally connected at rest (i.e., high FC between each other; Smitha et al., 2017). In particular, the Default Mode Network (DMN) has attracted much interest for its strength and consistency in being identified when looking for these patterns at rest. Importantly, convergent findings show that connectivity and volume of areas within this RSN are critically vulnerable to aging (Fjell et al., 2014a; Buckner et al., 2008), which also explains the predilection of these areas to be primarily affected in dementia (e.g., by amyloid-β deposition; Buckner et al., 2008). This organization in communities (i.e., systems or networks; Damoiseaux et al., 2006; Smith et al., 2009; Biswal et al., 1995) and their unfolded hierarchies (Deco et al., 2021) allows the efficient functioning of the brain (Wig, 2017). As far as areas within the same network are expected to be more segregated (i.e., high within-network connectivity), the integration

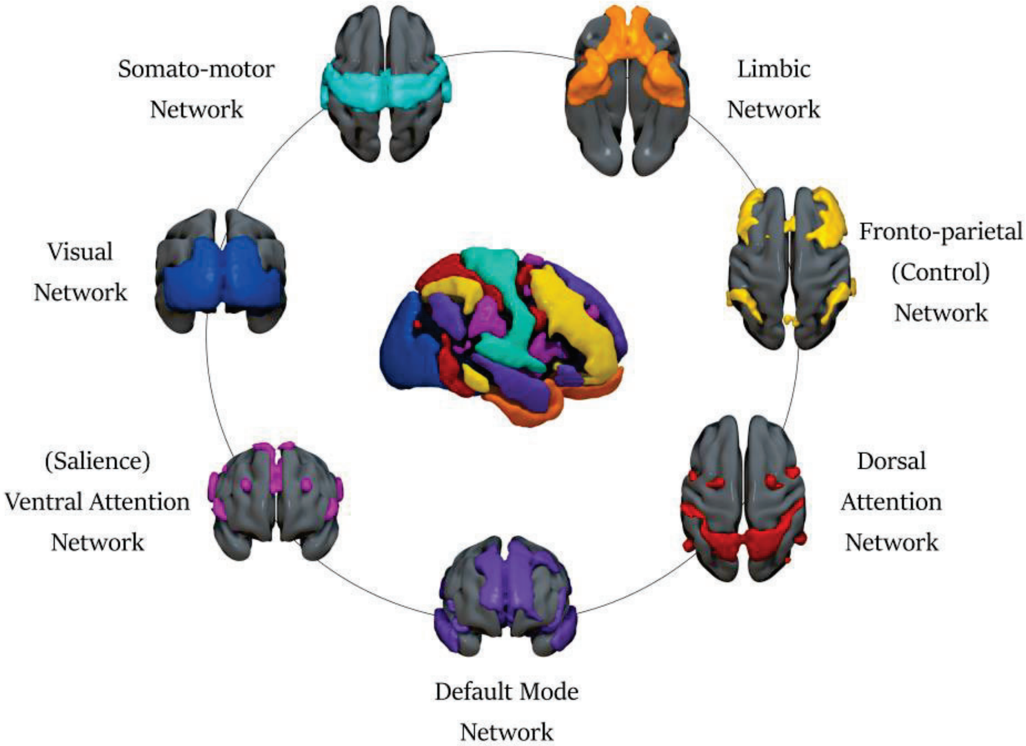

Figure 6. Seven major Resting State Networks as defined by the Yeo atlas (Yeo et al., 2011).

between networks is also crucial and remains the basis of the brain giving place to cognition and behavior. Under different experimental paradigms, employing varying methodological approaches, and obtained in different populations, numerous observations have converged to reveal how this simple property (i.e., system segregation, which quantifies the balance between within and between networks FC) of brain network organization relates to unique and fundamental features of brain function (Wig et al., 2017; Chan et al., 2018; Chan et al., 2014). Although high segregation is associated with many positive outcomes such as better cognition

(Chan et al., 2017; Chan et al., 2014), the correct balance between segregation and integration across systems (Wig et al., 2017; Sporns et al., 2018) has been also discussed to play a critical role in resilience. As a concrete example, when local damage occurs, integration between different brain areas may facilitate recovery or diminish the negative consequences of these lesion and vice versa (e.g., Siegel et al., 2016). Thus, the degree to which different brain regions are strongly connected and can communicate with each other efficiently allows for information to flow across the system (Bertolero et al. 2015). In this regard, the segregation-integration balance, quantified as a metric termed System Segregation (SyS) in previous studies (e.g., Ewers et al., 2021; Chan et al., 2017; Chan et al., 2014), poses a relevant aspect of brain connectivity for investigation. Importantly, SyS varies with age and cognitive differences among individuals (Chan et al., 2017; Chan et al., 2014). Specifically, SyS tends to decrease with age, with variations in its decline across different networks, while the SyS of RSNs involved in sensory processing remains relatively stable. Additionally, global SyS has been suggested as a potential marker of resilience in the context of Alzheimer's Disease (Ewers et al., 2021).

2.1.4. Brain areas and networks associated with mental health resilience

There is a number of brain regions that have been related to mental health resilience and vulnerability (see Table 1). In brief, these mainly involve PFC and ACC areas, and subcortical structures such as the amygdala, the hippocampus and the insula (see Figure 7; e.g., see Bolsinger et al., 2019 for a review on resilience to traumatic events). Other reviews also include the ventral striatum (VS; Richter et al., 2019; Feder et al., 2019). In addition, large-scale networks related to resilience/vulnerability in this context partly consist of the mentioned anatomical areas. These RSNs are the SN (analogous to Ventral Attention Network [VAN]; including anterior insular areas, dorsal ACC, amygdala, and VS), the DMN (including areas from the medial PFC and the hippocampus; Buckner et al., 2008), and the FPN (analogous to the Central Executive Network [CEN]; including areas from the dorsolateral PFC) (see Figure 7).

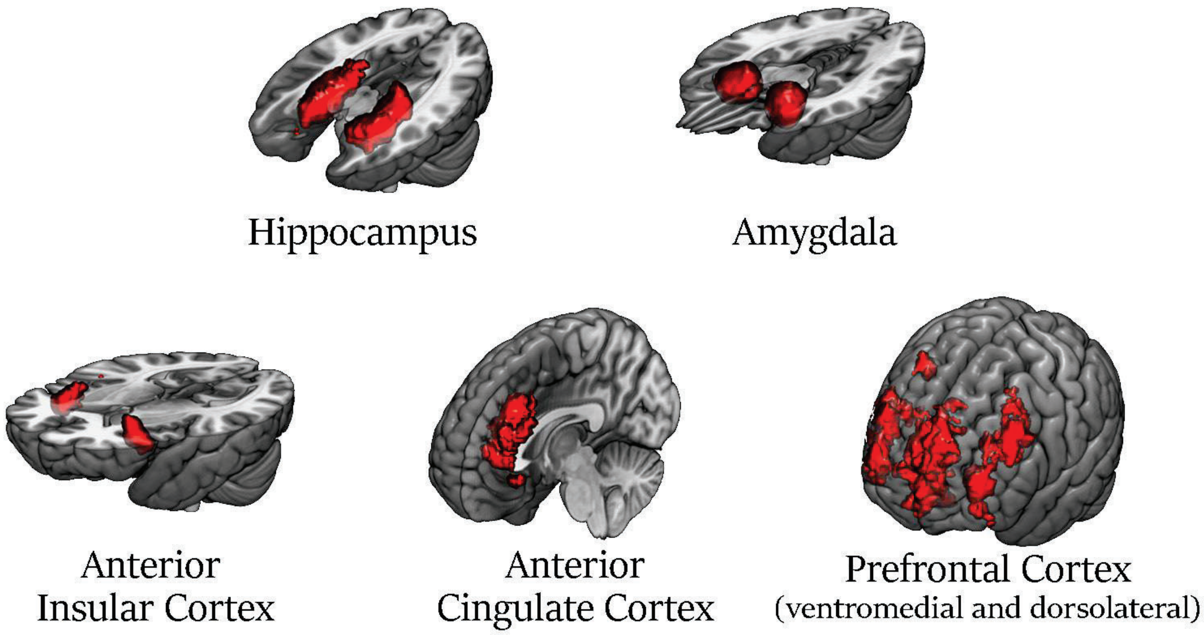

Figure 7. Main brain areas associated to psychological resilience and vulnerability. Adapted from Bolsinger et al., 2018.

Table 1 summarizes the results of a series of MRI studies that aimed to discover the brain mechanisms of resilience. The review was focused on the articles that were most relevant and aligned with the context of this dissertation. In general, the studies were varied not only regarding the modality of MRI or the technique to analyze the MRI data (see the sixth column in Table 1), but also and importantly regarding the definition of resilience that is to be assessed. For the later, as it has been discussed in the previous section, it should be remembered that defining resilience already brings complexity. In this vein, here we differentiate four principal categories to approach resilience in the MRI literature (see the third column in Table 1). (i) Resilience as a trait, has been explored in previous studies (Kong et al., 2015; Gupta et al., 2017; Iadipaolo et al., 2018; Long et al., 2019; Richter et al., 2019). Additionally, analogous characteristics and phenomena that may serve as indicators of resilience include: (ii) psychological factors that could be dynamic such as coping styles (Holz et al., 2016; Santarnecchi et al., 2018) or closer to trait-like characteristics (e.g., optimism; Dolcos et al., 2015); (iii) responses to induced stress (Goldfarb et al., 2020; van Oort et al., 2020; Sinha et al., 2016); and (iv) responses to trauma (van Rooij et al., 2021; van der Werff et al., 2013). In general, approaches (i) and (ii) infer resilience by the use of dedicated scales, while (iii) and (iv) assess actual response to stress. Particularly, it is worth mentioning that studies encompassed within category (ii) can measure both dynamic or static characteristics but the difference with category (i) is that these characteristics enhance resilience but do not directly reflect it.

(i) Understanding resilience as a trait

Although resilience is more appropriately understood as a dynamic process than as a trait (as concluded in section 1.1.), there are numerous studies that consider it as a constitutional factor of the individual. Then, this being closer to a personality trait, relatively immutable and acquired during development. Very often, the studies investigating *resilience as a trait,* quantify the degree to which an individual is considered resilient by using a dedicated scale (e.g., the Connor-Davidson Resilience Scale [CD-RISC]; Connor & Davidson, 2003). Considering structural markers, Gupta et al. (2017) found multiple associations between morphological brain measures and CD-RISC scores in a healthy population of young adults. Particularly, they focused on ROIs of the executive control and the emotional arousal networks and found relationships between resilience and areas within the amygdala, the parietal, and the cingulate cortex, as regards cortical thickness, surface area, and grey matter volume. Parallelly, Kong et al. (2015) found that lower regional homogeneity (i.e., degree of regional coherence of BOLD signal across adjacent brain areas) in the right dorsal and rostral ACC and bilateral insula was a predictor of higher resilience trait, also quantified by CR-RISC. Other studies analyzing resting-state fMRI data have found dynamic brain network measures to be related to CD-RISC scores. Specifically, lower brain network flexibility (i.e., average rate of switching between different modules in the framework of dynamic network model) of the whole brain, but also of the Visual Network (VN) and particular ROIs within this and the DMN, was associated to higher resilience scores (Long et al., 2019). Under a similar approach, Iadipaolo et al. (2018) found neural correlates of trait resilience concerning a dynamic functional state characterized by heightened anterior DMN FC to ventral DMN and right CEN. According to their findings, those children and adolescents exhibiting this dynamic state during shorter fraction of time and with lower state-specific FC between the SN and the right CEN or the anterior DMN. Finally, Richter et al., 2019 found resilient individuals (i.e., scoring higher at WYRS) showing higher activation patterns within hippocampal and ventral tegmental areas, accompanied by deactivation of the VS, during a reward processing task.

(ii) Psychological factors enhancing resilience

In line with the definition given above, resilience is understood as a dynamic process that is subjected to different modifiers that can be trait-like (e.g., personality) or derived from learning (e.g., coping strategies). Accordingly, coping strategies, although can be also associated to static personality traits, are central modifiable factors in resilience. At the structural level, Holz et al., (2016) found a higher volume of the perigenual and subgenual ACC to be associated with higher scores of positive coping strategies. Indeed, they found that those females in the study who exhibited higher ACC volume and accordingly positive coping strategies showed decreased levels of anxiety and depression. These positive –or adaptative- coping strategies are those leading to a reduction of stress and cover a variety of approaches such as those promoting a positive attitude or seeking social support, while other styles such as avoidance are expected to be maladaptive (e.g., Marchlewska et al., 2022). Making these distinctions, different coping styles were associated with particular functional brain properties following a data-driven approach by Santarnecchi et al. (2018). They detected FC correlates of coping styles among areas belonging to the anterior SN and the DMN. Particularly, the avoidance style was predicted by reduced negative FC between SN and DMN nodes.

Apart from coping strategies, *more static psychological factors that are considered as protective (i.e., resilience enhancers)* have been linked to brain characteristics by the use of MRI. Optimism, for instance, was related to higher orbitofrontal cortex volume, which at the same time mediated the association between this brain feature and trait anxiety (Dolcos et al., 2015). It is worth mentioning here that the area utilized in the study to delineate the orbitofrontal cortex, according to the atlas utilized, partially overlaps with the ventromedial PFC.

(iii) Resilience according to the response to induced stress

Moving away from the direct measurement of psychological characteristics, *resilient profiles have been inferred from the individual response to stress*, by the induction of stress in a controlled experimental context or by acknowledging the development of Post-Traumatic Stress Disorder (PTSD) symptomatology after experiencing real-life (i.e., uncontrolled) traumatic events. Firstly, it is important to acknowledge the brain substrates underlying stress processing. There have been three RSNs in the literature that consistently show to have a direct implication in the processing of acute stress: SN, DMN, and FPN (van Oort et al., 2017; Menon, 2011). A review by van Oort et al. (2017) concluded that the SN plays a crucial role in the coordination of acute stress response, and the DMN is present among most stress induction paradigms. Accordingly, the interactions between these two networks may be important to support emotional memory. Finally, they also proposed that the association between FPN performance and stress may follow a non-linear U-shaped trend.

Concerning resilience-vulnerability in this experimental context, van Oort et al. (2020) found vulnerability to stress to be predicted by the absence of a decrease in within DMN FC when exposed to aversive visual stimuli. While patients of stress-related and neurodevelopmental disorders underwent a more negatively stressful experience, accompanied by a decrease in FPN FC, healthy controls showed downregulation of the DMN during stress induction. Restricted to healthy individuals, hippocampal networks modulate the subjective feeling of stress in front of an induced stressor (Goldfarb et al., 2020). Particularly, higher FC from hippocamp to dorsolateral PFC, postcentral gyrus, and cerebellum, along with lower FC to the hypothalamus, parahippocampal cortex, and inferior temporal gyrus, predicted more resilient responses (i.e., less feeling of stress). Finally, Sinha et al. (2016) elucidated subjective, physiological, and endocrine responses to induced stress (by visualizing an aversive movie) to be linked to particular patterns of neural activation. These patterns mainly involved higher connectivity of ventromedial PFC areas and adjacent PFC areas (anterior and dorsolateral), that may facilitate executive control and attention. Additionally, ventromedial PFC areas were suggested to mediate emotional regulation processes via enhanced negative inhibition of subcortical structures (amygdala, hippocampus, striatum, and insula).

(iv) Resilience according to the response to traumatic events

Lastly, studies on the *individual response to real-life exposure to traumatic events* provide a powerful source of information about brain mechanisms underlying psychological resilience. Bolsigner et al. (2018) reviewed the state of the art in this sub-field, trying to discern between vulnerability markers or plastic consequences derived from trauma. Regarding structural features, reduced volume on areas of the hippocampus, the ACC, and the ventromedial PFC, are considered both consequences of traumatic environments (e.g., Woodward et al. 2006) and vulnerability indicators for upcoming dealing with stress. Considering brain function, hippocampal activation during a fear inhibition task was associated with higher trait resilience and better recovery from trauma (i.e., a decrease in PTSD symptomatology in the medium term; van Rooij et al., 2021). In terms of connectivity at rest, van der Werff et al. (2013) detected higher negative connectivity between the left dorsal ACC and the lingual and occipital fusiform gyrus. This resilient group was defined according to the absence of PTSD, anxiety, and depressive symptoms even though they had a history of childhood trauma. Analyses contrasted FC patterns between the resilient group and two groups: a healthy control with no childhood trauma and a vulnerable group with childhood trauma and also stress-related diagnoses.

Table 1. Review of research articles about brain mechanisms of psychological resilience, grouped by the utilized approach to resilience.

<table>
<tr><th>First author</th><th>Year</th><th>Approach to resilience</th><th colspan="2">Brain area(s) / network(s)</th><th colspan="2">Resilient feature</th><th>MRI modality</th><th>Population</th></tr>
<tr><td rowspan="4">Long Y</td><td rowspan="4">2019</td><td rowspan="4">Trait (CD-RISC)</td><td colspan="2">Whole brain</td><td colspan="2" rowspan="4">⇩Flexibility*</td><td rowspan="4">rs-fMRI</td><td rowspan="4">n=41
age ~22
healthy</td></tr>
<tr><td colspan="2">VN</td></tr>
<tr><td colspan="2">ROIs ∈ VN</td></tr>
<tr><td colspan="2">ROIs ∈ DMN</td></tr>
<tr><td rowspan="3">Richter A</td><td rowspan="3">2019</td><td rowspan="3">Trait (WYRS)</td><td colspan="2">VS</td><td colspan="2">⇩Activation</td><td rowspan="3">tb-fMRI
(reward)</td><td rowspan="3">n=97
age: 25-57
at-risk</td></tr>
<tr><td colspan="2">Hippocampus</td><td colspan="2" rowspan="2">⇧Activation</td></tr>
<tr><td colspan="2">VTA</td></tr>
<tr><td rowspan="4">Iadipaolo AS</td><td rowspan="4">2018</td><td rowspan="4">Trait (CD-RISC)</td><td rowspan="2">aDMN</td><td>vDMN</td><td rowspan="2">⇧FC</td><td rowspan="2">⇩Dynamic
state duration</td><td rowspan="4">rs-fMRI</td><td rowspan="4">n=55
age: 6-17
at-risk</td></tr>
<tr><td>rCEN</td></tr>
<tr><td rowspan="2">SN</td><td>rCEN</td><td colspan="2" rowspan="2">⇩ State-specific FC</td></tr>
<tr><td>aDMN</td></tr>
<tr><td rowspan="5">Gupta A</td><td rowspan="5">2017</td><td rowspan="5">Trait (CD-RISC)</td><td colspan="2">ROIs ∈ PPC</td><td colspan="2">⇧/⇩ GMvol & SurfA</td><td rowspan="5">T1-w</td><td rowspan="5">n=48
age: ~26
healthy</td></tr>
<tr><td colspan="2">Right ACC</td><td colspan="2">⇧CTh</td></tr>
<tr><td colspan="2">Right aMCC</td><td colspan="2">⇩CTh</td></tr>
<tr><td colspan="2">Left sgACC</td><td colspan="2">⇩SurfA</td></tr>
<tr><td colspan="2">Amygdala</td><td colspan="2">⇧GMvol</td></tr>
<tr><td rowspan="3">Kong F</td><td rowspan="3">2015</td><td rowspan="3">Trait (CD-RISC)</td><td colspan="2">Bilateral Insula</td><td colspan="2" rowspan="3">⇩ReHo</td><td rowspan="3">rs-fMRI</td><td rowspan="3">n=276
age: ~21
healthy</td></tr>
<tr><td colspan="2">Right dACC</td></tr>
<tr><td colspan="2">Right rACC</td></tr>
</table>

Santarnecchi E	2018	Psychological factors: Coping styles (COPE)	ACC	Bilateral mPFC	⇧Negative FC (avoidance)	rs-fMRI	n=102 age: ~27 healthy
				Bilateral Precuneus			
			Left angular gyrus	Visual Cortex	⇧ FC (problem-oriented)		
			Left frontopolar cortex	Right Temporal Pole	⇧Negative FC (social support)		
Holz NE	2016	Psychological factors: Positive coping (GSCQ)	ACC		⇧GMvol	T1-w	n=181 age: ~25 healthy
Dolcos S	2015	Psychological factors: Optimism (LOT)	OFC		⇧GMvol	T1-w	n=61 age: 18-24 healthy
Goldfarb EV	2020	Response to induced stress	Hippocampus	Hypothalamus	⇩FC	tb-fMRI (aversive visual stimuli)	n=60 age: ~29 healthy
				Parahippocampal cortex			
				Inferior temporal gyrus			
				Dorsolateral PFC	⇧FC		
				Postcentral gyrus			
				Cerebellum			
van Oort J	2020	Response to induced stress (controls vs. patients)	DMN		⇩ within-FC	tb-fMRI (aversive visual stimuli)	n=214 age: 18-74 168 patients (stress-related and neuro-developmental) 46 controls
			FPN		Absence of ⇩ within-FC		

Sinha R	2016	Response to induced stress	vmPFC		⇧Dynamical activity	tb-fMRI (aversive visual stimuli)	n=30 age~26 healthy
			vmPFC	Left aPFC	⇧FC		
				Dorsolateral PFC	⇧Negative FC		
				Amygdala			
				Hippocampus			
				Striatum			
				Insula			
van Rooij SJH	2021	Response to trauma: PTSD symptoms & Trait (CD-RISC)	Hippocampus		⇧Activation	tb-fMRI (fear inhibition)	n=28 age: ~39 healthy
van der Werff SJA	2013	Response to trauma: PTSD, anxiety and depression symptoms (childhood trauma)	Left dACC	Lingual gyrus	⇧Negative FC	rs-fMRI	n=33 age: ~40 11 resilient out of 22 childhood trauma, 11 healthy controls
				Occipital fusiform gyrus			

*Flexibility, within the context of dynamic connectivity analyses, is understood as the frequency with which a ROI (or ROIs within a network) switches from one modular community structure to another.

Abbreviations: Anterior Cingulate Cortex, ACC; anterior Default Mode Network, aDMN; anterior Midcingulate Cortex, aMCC; anterior Prefrontal Cortex, aPFC; Default Mode Network, DMN; dorsal ACC, dACC; Functional Connectivity, FC; functional Magnetic Resonance Imaging, fMRI; medial Prefrontal Cortex, mPFC; Posterior Parietal Cortex, PPC; right Control Executive Network, rCEN; Regional Homogeneity, ReHo; Region of Interest, ROI; resting-state functional Magnetic Resonance Imaging, rs-fMRI; Salience Network, SN; T1-weighted, T1-w; task-based functional Magnetic Resonance Imaging, tb-fMRI; ventral Default Mode Network, DMN; Ventral Tegmental Area, VTA; ventromedial Prefrontal Cortex, vmPFC; Visual Network, VN.

Scales: Connor-Davidson Resilience Scale, CD-RISC; Wagnild and Young Resilience Scale, WYRS; COPE; German Stress Coping Questionnaire, GSCQ; Life Orientation Test, LOT.

All in all, the literature describes a variety of brain regions and associated characteristics underlying resilience when facing psychological stress. These repeatedly involve areas within the DMN, the SN, and the FPN but also other RSNs that are less frequently explored (i.e., the VN). On the whole, these studies present both advantages and disadvantages with regard to different aspects. But in general, the size of the samples among the studies is small, which is understandable especially when needing complex study designs (mainly task-based fMRI studies) or recruiting participants in such a specific situation as having experienced traumatic events and developing PTSD. In a very important way, there is an overall lack of studies that contemplate pre-trauma MRI data, which is also comprehensible due to the unpredictability of such events. Therefore, studies analyzing pre-trauma data in the framework of big cohorts are of immense value in expanding knowledge in the field of psychological resilience. Here, pandemics and other natural disasters pose an interesting opportunity to face this challenge. For this reason, the following section is focused on the contextualization of the CoronaVirus Disease 2019 (COVID-19) pandemic as an experimental scenario to study psychological resilience.

3. The COVID-19 pandemic

At the end of December 2019, a number of cases of patients with pneumonia, of a priori unknown cause, were reported in Wuhan (province of Hubei, China), where a few weeks later the first case of COVID-19 (a disease caused by the Severe Acute Respiratory Syndrome-CoronaVirus 2 [SARS-CoV-2]) was identified (Hongzhou et al., 2020). The SARS-CoV-2 has never been a total stranger. This virus belongs to the *Orthocoronavirinae* subfamily of *Coronaviridae* viruses which have been known to provoke infection in both human and other animals for many years. First reports of human coronaviruses date around the decade of 1960s (Tyrell & Bynoe, 1966). Nonetheless, not all coronaviruses lead to the same symptomatology neither with the same severity for the infected organism. Later in 2002 and 2012 respectively, two coronaviruses: SARS-CoV and Middle East Respiratory Syndrome-CoronaVirus (MERS-CoV), posed a new public health concern by causing fatal respiratory illness to those infected (Cui et al., 2019). For the case of SARS-CoV-2, which shares 50% genome sequence identity with MERS-CoV and 79% with SARS-CoV, the transmissibility is much higher. It is transmitted by the inhalation or direct contact with infected respiratory droplets (including coughing, speaking, or breathing) through mouth, eyes, or nose. The symptomatology of the derived infection can vary in severity but typically includes fever, fatigue, dry cough, and pneumonia. More critical cases can lead to multi-organ failure and cause the death of the patient (Hu et al., 2021). Additionally, on some occasions, it can result in a systemic affectation which means that can modify the normal functioning of other groups of organs such as the nervous system. Importantly for the context of this Doctoral Thesis, it should be mentioned that many have been the studies analyzing the effects of the SARS-CoV-2 infection in the brain (Czarnowska et al., 2023, Dai et al., 2023). However, beyond the infection caused by the virus, the whole situation around the pandemic has been shown to challenge the stability of a proportion of the population that is likely to be bigger than the one that has been infected and developed physical complications.

The rapid spread of the virus and the consequent collapse of the sanitary and economic systems of the affected cities (Naseer et al., 2023), led the World Health Organization (WHO) to declare the situation as a public health emergency of international concern on the 30th January 2020. This terminology changed to a global pandemic on 11th March 2020 (WHO, 2023), when around 120,000 cases and 4,600 deaths were registered in the world, of which 2,000 and 42 occurred in Spain. These numbers increased exponentially, reaching peaks of around 20,000 deaths per day. More than three years later, by May 2023, 7 million people have perished due to COVID-19 notwithstanding all the measures that have been taken to control the spread of the virus (Our World in Data, 2023).

Since the WHO raised the alarm, government entities of each country have put into place different actions to control the spread of the virus and minimize its impact on their systems. These actions included a variety of containment measures that mainly limited social interactions, including severe restrictions such as interleaving periods of strict lockdowns, curfews, or even the closure of businesses, schools, or public places (ISCIII, 2023). During the whole pandemic period, these actions have been changing with the aim of adapting to the

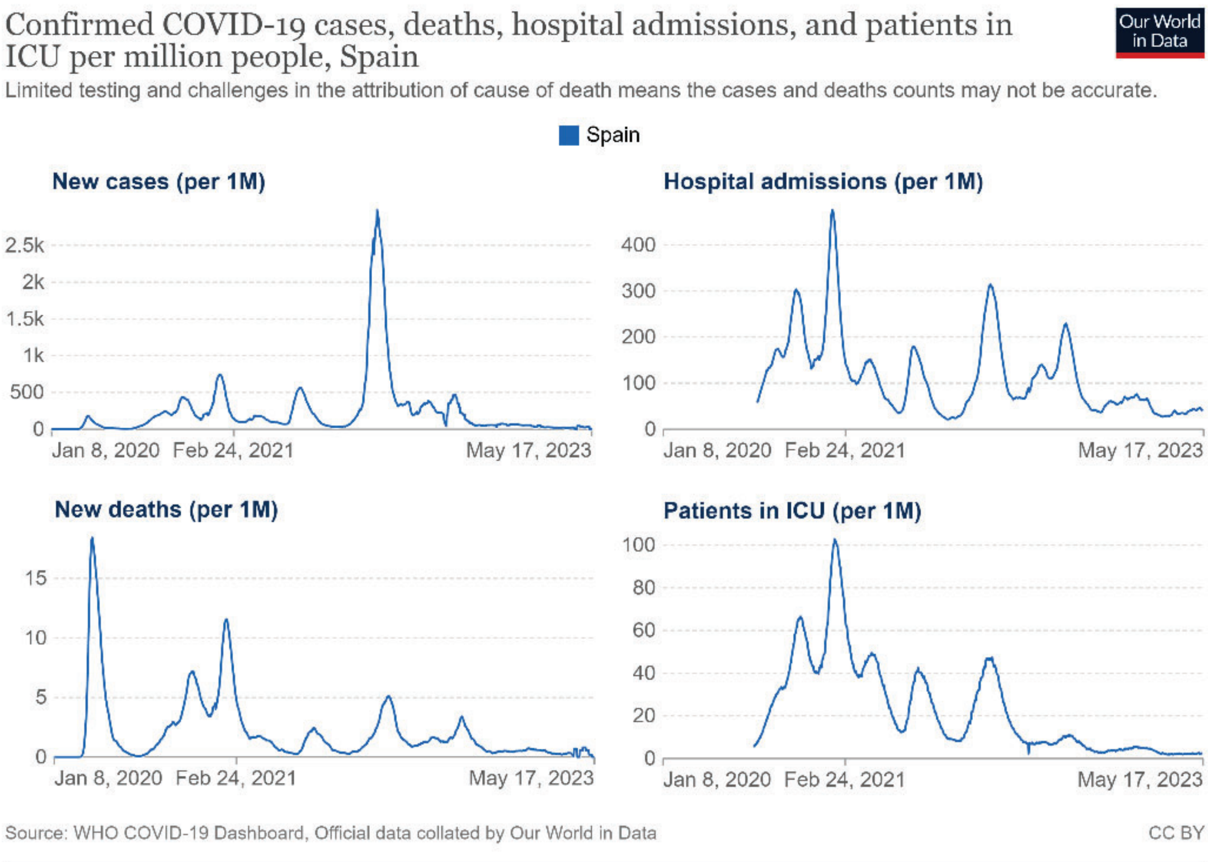

Figure 8. Amount of diagnosis, deaths, hospital admissions and patients in ICU due to COVID-19 per million people in the Spanish population from January 2020 to May 2023.

variable circumstances that have characterized different waves or periods of the pandemic. As the virus replicated and spread, its molecular evolution (Wolf et al., 2023) and the actions taken by the population such as the mentioned containment measures and the development of a vaccine (Li et al., 2022), have characterized the different waves observed worldwide. Some of the variants have shown greater transmissibility, contributing to the occurrence of more intense waves of infection. Notable examples include the Alpha variant (B.1.1.7), first identified in the United Kingdom (UK Health Security Agency, 2023), and the Delta variant (B.1.617.2), initially detected in India (CDC, 2023). Furthermore, some variants have also demonstrated a potential decrease in the effectiveness of certain treatments or vaccines.

Spain has faced several waves of contagion that have had a significant impact on the healthcare system of the country. As can be seen in Figure 1.1, the number of cases, deaths, hospital admissions, and patients in the intensive care unit (ICU) oscillated progressively, and do not always correlate. Thus, the combination of the four indicators should be considered together to have a clearer idea of the situation. Particularly, the most challenging periods occurred in 2020 and early 2021. In the first wave, which took place between March and May 2020, there was a sharp increase in hospital admissions and patients requiring intensive care unit (ICU) treatment (Ministry of Health of Spain, 2020). Hospital occupancy reached its peak in April 2020, with thousands of individuals hospitalized and immense pressure on healthcare services (Ministry of Health of Spain, 2020) and the highest number of deaths. Subsequently, a second wave was experienced in October and November 2020, which also resulted in a high demand for hospital admissions and ICU care (Ministry of Health of Spain, 2020). Finally, in January and February 2021, a third wave hit, reaching record numbers of hospitalizations and ICU bed occupancy (Ministry of Health of Spain, 2021). These periods presented unprecedented challenges for the Spanish healthcare system, which made tremendous efforts to attend to all patients affected by the disease. As control measures were implemented and the vaccination campaign progressed, the situation began to stabilize, gradually reducing the pressure on the healthcare system (Ministry of Health of Spain, 2021).

3.1. A threat for mental health

As it has just been mentioned, beyond the direct harmful repercussions of COVID-19, a major health and societal threat, there have been the negative psychological and psychosocial sequelae of imposed quarantines and mass confinements (Pfefferbaum & North et al., 2020) potentially affecting a much larger segment of our populations (Torales et al., 2020). The pervasive negative health impact of infringing personal freedom during the extended periods of a pandemic outbreak has most likely led to significant changes in lifestyles, behavioral patterns, and other potential negative consequences such as the incurrence of financial losses for families (e.g., Brooks al., 2020, Holmes et al., 2020). More precisely, confinement orders analogous to the one dictated by the Spanish government in mid-March 2020, have been linked to a persistent emergence of symptoms and conditions, such as anxiety and fear, depression, insomnia, suicidal ideation, or feelings of loneliness amongst others (e.g., van Tilburg et al., 2021; García-Prado et al., 2021).

From a public health perspective, the potential negative impact of extended periods of confinement and social distancing has been judged to be an extremely important threat. Nonetheless, it has been proved that the degree of strictness of the restrictions influenced the degree to which the citizens have a negative impact on their mental health (Ingram et al., 2022). Altogether this had led to the call for the development of preventive and interventional strategies (Galea et al., 2020) and policies that carefully balance infection control benefits against the psychological costs of mandatory quarantine and other restrictions (Shrivastava &

Shrivastava, 2021; Rubin & Wessely, 2020), for this pandemic and for future analogous emergencies to come.

A clear proof of the impact or concern about mental health that this pandemic poses to our communities is the vast literature that has emanated to study such phenomenon. At the end of May 2023, when a search on PubMed is done by using the terms "(COVID-19) AND (Mental Health)", around 27 thousand results are raised (and these have been published between 2020 and 2023; PubMed, 2023, accessed 26th May 2023). Many of these articles indicated the negative impact of the pandemic and confinement on mental health. For example, a meta-review by de Sousa et al. (2021) found an increase in mental health problems with prevalence ranging from 20 to 36%. However, they also emphasized the heterogeneity of the findings. In a more recent review, Penninx et al. (2022) concluded that the effect of the pandemic on mental health is small and heterogeneous. They also pointed out that this effect is negative and greater during the first wave of the pandemic, or even greater in following waves if the contingency measures applied were equally restrictive (as in Patel et al., 2022). Another review by Aknin et al. (2022) concludes that the negative effect of the pandemic outbreak is mainly concentrated on the first periods of it, but uniquely as regards experiencing higher psychological distress rates. However, the population seems to be resilient in terms of loneliness, social connection, and self-harm behaviors (e.g., suicide; Aknin et al., 2022).

Due to the complexity of a phenomenon that in fact has affected a population as big as the one contained by the whole globe, it is also expected that each country or nation experience diverse realities. Besides the general lack of studies encompassing evidence from all nations, especially when talking about the more underdeveloped countries, some studies have also made efforts to assess these possible differences. Particularly, a meta-analysis including 64 articles with data from North America, Europe, Latin America, Asia-Pacific, and Africa, sustains the existence of a global spike in different components of mental health during the first wave of the sanitary crisis, which was followed by a decrease in July 2020 in North America and Europe (Cénat et al., 2022). Interestingly, both symptomatology and the extension of its increase seem to be different when regarding different countries or nations. North America particularly showed the more aggravating tendencies in all domains, while Latin America and Europe headed insomnia problems. Under this appreciation, it could be hypothesized that having a robust and fairly accessible public sanitary system may play a crucial role in handling a social crisis, in this case especially when talking about repercussions on mental well-being (Cénat et al., 2022).

As well as the impact of such natural disasters can be studied at the level of communities (i.e., nations and countries), many efforts have been made to discern what happens at a more specific level: the individual. When assessing the determinants leading to an individual having a stronger worsening in mental health, two of the most predominant factors of risk (or protection) are age and sex/gender (Aknin et al., 2022; Cénat et al., 2022). Particularly, women have shown to experience generally greater distress during the pandemic. This, in line with the usual tendency of this sector of the population to have a higher prevalence of emotional distress in non-pandemic contexts (Kuehner, 2017), has been discussed to be a consequence of gender roles in society and how these are in interaction with the pandemic situation (Aknin et al., 2022). As regards age, although elder individuals have been expected to be those most negatively impacted, the experience has shown the opposite. Older adults have, indeed, experienced highly negative outcomes for example as a consequence of being a more vulnerable population sector when considering COVID-19 complications (Lu et al., 2022), or as a result of having less access to social interaction during confinements (Sepúlveda-Loyola et al., 2020). However, a review of 134 studies evidenced this negative impact to be inferior to the one experienced by the younger population (Lebrasseur et al., 2021). The most common rationale to explain such phenomenon is the degree of disruption that the pandemic, and particularly the restrictions imposed to control its spread, have supposed for their daily life (Faulkner et al., 2022). Additionally, the personal experience of each individual (e.g., the loss of a loved one due to COVID-19 or being laid off) and also the interactions of each one with these experiences (e.g., seeking help or information, protecting themselves from the infection or worrying about its possibility; Heiat et al., 2021) could be strong determinants of their trajectory. Particularly for the latter, these are in a strong relationship with psychological and biological determinants of the individual (more detail on this line is paid in the following sections).

In addition to the above, it is worth discussing how the commented-upon worsening in mental well-being during the pandemic has been assessed. Most studies focus on outcomes regarding emotional distress, such as anxiety and depression (e.g., meta-analyses by Salari et al., 2020 or Luo et al., 2020; Kimhi et al., 2021), and post-traumatic stress symptomatology (Chen et al., 2022; Chen et al., 2022-b). However, mental health and well-being must be understood as a more complex construct than de absence of emotional psychopathology. Keyes et al. (2005) discussed that "the absence of mental disorders like depression does not mean the presence of mental health" (Keyes et al., 2005; see also Keyes et al., 2020) and instead advocated the existence of three principal pillars upon which mental well-being is built: emotional well-being, psychological well-being, and social well-being (see the following sections for further details). The literature on this topic for the pandemic outbreak is, as mentioned, mainly oriented to the emotional aspects of mental health. Nonetheless, there is also an important size of research regarding loneliness during the outbreak, while almost nothing has been studied concerning psychological well-being. As regards loneliness, Aknin et al. (2022) conclude a general resilient tendency. Very interestingly, a study on the Spanish population revealed a paradoxical effect on the subjective perception of social isolation during the first weeks of the outbreak. Subjective loneliness significantly decreased in comparison to pre-pandemic levels, which could be a result of the sense of community emerging by going through the same challenge or having a common enemy (Bartrés-Faz et al., 2021).

3.2. What can be learned? Seeking the keys of resilience

Until here, we can conclude that the COVID-19 pandemic has posed a tremendous challenge to humanity, not only compromising physical health but testing the mental stability of the global population. In this context, Pascual-Leone & Bartrés-Faz (2021) compare the pandemic with the "black swans" that Nassim Taleb used to talk about in his book. These black swans relate to events that are highly improbable but that actually happen and that we must learn from for the future. Moreover, as they commented:

> "[...] not everyone would deal with them in the same way, either by their personal context or by their individual psychological and biological profile. This is nothing else but the resilience vs. vulnerability tug of war." (Pascual-Leone & Bartrés-Faz, 2021)

In front of a situation such as the one caused by the pandemic, in addition to expecting a general worsening of mental health, it can also be anticipated the existence of variability in the population response (Chen & Bonanno, 2020; Bonanno et al., 2004). In fact, the above-mentioned findings in the literature already point out high heterogeneity, meaning that more vulnerable to more resilient individuals face uncontrollable and oppressive events with greater or lesser success. The keys to a resilient life have been sought for decades by the scientific community (Bonanno, 2004). Understanding how some people can maintain their health even when the environment or their own system challenges its integrity could lead to better interventions to promote this kind of desirable outcomes in those that, on the contrary, are more vulnerable. Importantly, this could be applied to daily interventions or to diminish damage in future “black swans” appearing.

When facing highly aversive life events, such as pandemics, most people remain resilient (Chen & Bonanno, 2020). This could be hard to believe due to the bias of studying trauma and post-traumatic stress affections as the main focus of many studies, but resilience is a very extended reality (Bonanno, 2004). Particularly for the COVID-19 pandemic, around three out of four parts of the population have shown resilient trajectories (Chen et al., 2022; Chen et al., 2022-b). To reliably assess the response to a potentially traumatic event, it is crucial to have a longitudinal design with pre-aversive circumstances (i.e., pre-pandemic) and enough follow-up span to consistently capture different profiles of vulnerability or resilience. As proposed by Bonanno (2004), these profiles, or trajectories, could be agglomerated into four possible tendencies: chronicity, delay, recovery, and resilience. While chronic and resilient individuals will sustain their pre-pandemic status (whether this was clinical or not), minimal oscillations are expected (see Figure 9; Chen & Bonanno, 2020). There are a few studies that have followed similar approaches to discern the mentioned trajectories during the COVID-19 pandemic (mainly latent growth analyses) and then characterizing them (i.e., finding variables that are able to predict them; Chen et al., 2022-b). At this level, the most common predictors regard sociodemographic (e.g., sex, age, socioeconomic status) and at some points psychological aspects of the individuals (e.g., personality and coping strategies; Vannini et al., 2021). Importantly, and as it is explained in the following sections, resilience must be understood as the interplay of factors of different natures (neurobiological, psychological, and environmental; Feder et al., 2019). Brain mechanisms as predictors of longitudinal resilient vs. vulnerable tendencies have been especially understudied in the context of COVID-19 and in the general literature.

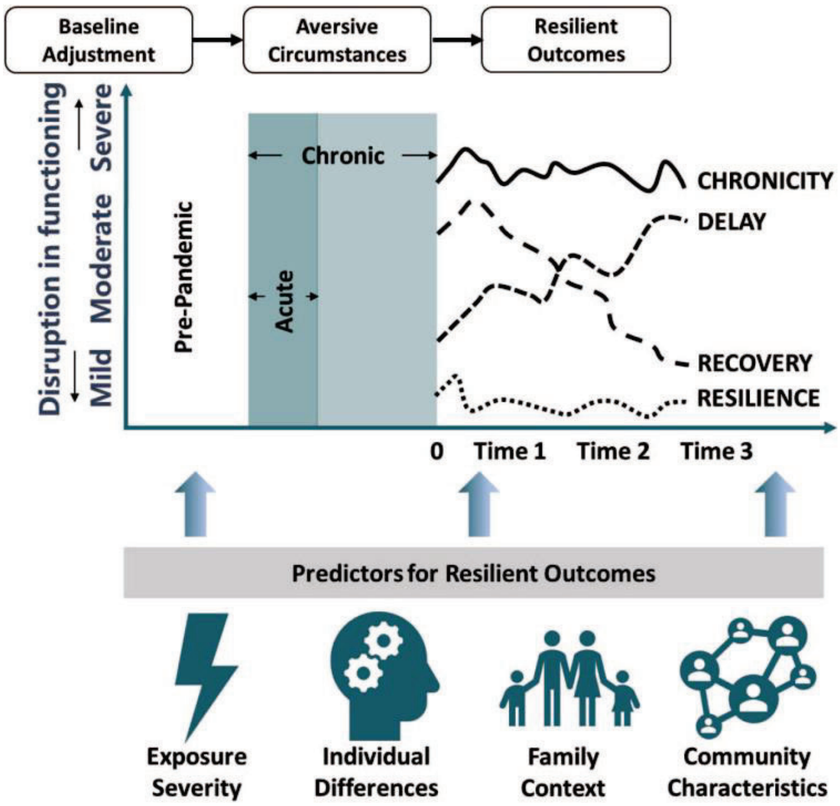

Figure 9. Temporal elements of psychological resilience. Extracted from Chen & Bonanno (2020).

All in all, the scenario established by the pandemic is remarkably well suited to study differences between those more resilient and those more vulnerable.

Rationale

Resilience is a dynamic process conditioned by complex interactions between multiple factors, regarding psychological and biological mechanisms, along with environmental influences. However, the study of resilience as a whole has important limitations when it comes to the low variety of psychological and brain measures, and the interplay between them, as well as the heterogeneity and small size of the samples experiencing stressful events that may be ideally comparable among individuals. Opportunely, the COVID-19 pandemic established a scenario well-suited to investigate this phenomenon avoiding such limitations.

Most studies characterizing the brain mechanism of resilience (by means of MRI analyses) focus on structural properties such as gray matter volume, and functional aspects such as activation of a priori chosen brain areas or connectivity between pairs of particular areas. However, analytical approaches encompassing a broader view of the functioning of the brain, such as those balancing segregation-integration mechanisms, would open new paths and promising outlooks to disentangle the phenomenon of resilience. Particularly, as can be reasonably inferred from the contextualization provided in previous sections, resilience is a dynamic process that can be better understood through the detection of highly plastic brain properties, and functional MRI is a well-suited technique for achieving this. On the other hand, most studies in the context include a small number of psychological properties (i.e., frequently ranging from one to three variables) to be associated with the MRI features and hardly ever analyze the interplay between the multiple features that condition resilience, for instance, sociodemographic variables, psychological factors, and other environmental features influencing the individual well-being and development (Feder et al., 2019; see again figure 1). Therefore, studies with a wider view in regard to including a richer phenotyping of the participants would be of special interest.

CHAPTER 2

Hypotheses and objectives

Hypotheses

In consideration of the contextual background provided, a series of hypotheses will now be outlined to further explore brain mechanisms and psychological determinants of mental health resilience within the context of the COVID-19 pandemic:

- Differences on mental health outcomes will be found in the response to pandemic-related stressors. Based on these differences, it will be possible to differentiate individuals with resilient or vulnerable profiles.

- Considering the variation in individuals' responses to pandemic-related stressors, most of them are expected to follow a resilient trajectory.

- This response and its predisposing factors will be different according to the different domains of mental health: emotional, psychological, and social.

- Vulnerable or resilient trajectories will be predicted by different protective and risk factors including psychological, sociodemographic, lifestyle, and rs-fMRI measures, and their interactions.

Objectives

Main Objective

The main objective of this Doctoral Thesis is to understand the brain mechanisms and psychological determinants explaining interindividual variability as regards the response to stressful situations, such as those derived by a global pandemic, which may lead to more vulnerable or resilient profiles in terms of mental well-being.

Specific Objectives

In order to reach the main objective of this Doctoral Thesis, four specific objectives were derived:

1) To capture the individual variability regarding mental health outcomes (i.e., vulnerability vs. resilience) to the stressful situations derived by the COVID-19 pandemic, by comparing pre- and during-pandemic assessments.

2) To investigate whether components of mental health (i.e., psychological, social, and emotional) are differently impacted during the COVID-19 pandemic.

3) To identify the predisposition factors leading to more vulnerable or resilient responses in line with the main different components of mental health (i.e., psychological, social, and emotional), at the level of sociodemographic and psychological variables, lifestyles, and RSNs segregation-integration measures.

4) To analyze the interplay between psychological factors (i.e., perceived stress and coping strategies) and the connectivity status of brain networks (i.e., segregation-integration measures) leading to more vulnerable or resilient responses.

CHAPTER 3

Studies

Study 1

COVID-19 after two years: trajectories of different components of mental health in the Spanish population

Bayes-Marin I, **Cabello-Toscano M**, Cattaneo G, Solana-Sánchez J, Fernández D, Portellano-Ortiz C, Tormos JM, Pascual-Leone A, Bartrés-Faz D..

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COVID-19 after two years: trajectories of different components of mental health in the Spanish population

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Abstract

Aims. Our study aimed to (1) identify trajectories on different mental health components during a two-year follow-up of the COVID-19 pandemic and contextualise them according to pandemic periods; (2) investigate the associations between mental health trajectories and several exposures, and determine whether there were differences among the different mental health outcomes regarding these associations.

Methods. We included 5535 healthy individuals, aged 40–65 years old, from the Barcelona Brain Health Initiative (BBHI). Growth mixture models (GMM) were fitted to classify individuals into different trajectories for three mental health-related outcomes (psychological distress, personal growth and loneliness). Moreover, we fitted a multinomial regression model for each outcome considering class membership as the independent variable to assess the association with the predictors.

Results. For the outcomes studied we identified three latent trajectories, differentiating two major trends, a large proportion of participants was classified into 'resilient' trajectories, and a smaller proportion into 'chronic-worsening' trajectories. For the former, we observed a lower susceptibility to the changes, whereas, for the latter, we noticed greater heterogeneity and susceptibility to different periods of the pandemic. From the multinomial regression models, we found global and cognitive health, and coping strategies as common protective factors among the studied mental health components. Nevertheless, some differences were found regarding the risk factors. Living alone was only significant for those classified into 'chronic' trajectories of loneliness, but not for the other outcomes. Similarly, secondary or higher education was only a risk factor for the 'worsening' trajectory of personal growth. Finally, smoking and sleeping problems were risk factors which were associated with the 'chronic' trajectory of psychological distress.

Conclusions. Our results support heterogeneity in reactions to the pandemic and the need to study different mental health-related components over a longer follow-up period, as each one evolves differently depending on the pandemic period. In addition, the understanding of modifiable protective and risk factors associated with these trajectories would allow the characterisation of these segments of the population to create targeted interventions.

Introduction

The COVID-19 pandemic posed an extraordinary health, social and economic challenge to the world. Due to the rapid spread of the virus, governments had to implement restrictive policies such as lockdowns or stay-at-home orders (COVID-19 Mental Disorders Collaborators, 2021). Although these restrictive policies varied between countries, they affected people's daily lives globally, in terms of their work, livelihood, leisure activities and social interactions (Prati and Mancini, 2021). In the case of Spain, in the two years following the start of the pandemic, different containment measures were put into place, interleaving periods of strict lock-down confinement (e.g., home confinement, closure of schools and businesses, use of facemasks outdoors/indoors) with those of more relaxed measures (progressive return to work, the opening of restaurants and shops, use of facemasks only in some enclosed spaces, etc.) (Red Nacional de Vigilancia Epidemiológica. Instituto de Salud Carlos III, 2022).

A large body of knowledge has been generated regarding the impact of the pandemic and confinement in relation to mental health (Salari *et al.*, 2020; Prati and Mancini, 2021; Wu *et al.*, 2021). Whether through cross-sectional or longitudinal studies, it has been reported prevalence rates or mean scores of depressive or anxiety symptoms, assuming that the response to the pandemic is homogeneous, i.e., the same among individuals (Shevlin *et al.*, 2023). In contrast, a systematic review based on longitudinal studies declared that the effect of lockdowns on depression and anxiety was small and significant, but also highly heterogenous (Prati and Mancini, 2021). Similarly, a meta-review of mental health during the COVID-19 pandemic, found an increase of mental health problems from 20 to 36%, but also a high heterogeneity among studies (de Sousa *et al.*, 2021). It is worth mentioning that this evidence come from studies carried out at most up to one year after the pandemic, with a lack of studies that have analysed longer-term consequences on mental health. According to Taylor (2019), pandemics are dynamic events and as such their reactions were likely to vary over time (Taylor, 2019). For this reason, the results should be contextualised at different times of the pandemic and the events occurring in each period. In addition, in order to evaluate change from pre-pandemic status, baseline information is needed, and this condition has been less available in the performed research (Ahrens *et al.*, 2021; Ellwardt and Präg, 2021; Pierce *et al.*, 2021).

In agreement with the assumption that psychological adjustment in front of an adverse event is heterogeneous and may vary over time, different studies have been carried out on mental health trajectories (Ahrens *et al.*, 2021; Batterham *et al.*, 2021; Ellwardt and Präg, 2021; Joshi *et al.*, 2021; Pellerin *et al.*, 2021; Pierce *et al.*, 2021; Saunders *et al.*, 2021; Shilton *et al.*, 2021). Most of these studies identified trajectories based on depression and anxiety symptoms measures, using individual-centred statistical techniques, as growth mixture models (GMM) or latent class growth analysis. These techniques rely on the assumption that individuals can be assigned to homogeneous subgroups (i.e., distinct trajectories) based on similarities on given outcomes (Nguena Nguefack *et al.*, 2020). The abovementioned investigations identified from two (Joshi *et al.*, 2021) to five trajectories of depression or/and anxiety symptoms (Ahrens *et al.*, 2021; Batterham *et al.*, 2021; Ellwardt and Präg, 2021; Pellerin *et al.*, 2021; Pierce *et al.*, 2021; Saunders *et al.*, 2021; Shilton *et al.*, 2021). In general terms, the results showed that a large proportion of the sample was classified in a stable trajectory over time (called 'resilient trajectory'), while a smaller proportion showed worse scores or worsening over the follow-up period ('chronic' and 'deteriorating trajectories') (Ahrens *et al.*, 2021; Batterham *et al.*, 2021; Ellwardt and Präg, 2021; Joshi *et al.*, 2021; Pellerin *et al.*, 2021; Pierce *et al.*, 2021; Saunders *et al.*, 2021; Shilton *et al.*, 2021). These results support the model put forward by Bonanno (2004), which argued that resilience is extremely common, finding higher proportions in the so-called 'resilient' trajectory, where hardly any changes were observed throughout the follow-up in the face of a stressor (Bonanno, 2004).

Nevertheless, these studies focused on psychological distress as outcome measure, using mostly sociodemographic variables, and in some cases personality (Saunders *et al.*, 2021), loneliness (Ahrens *et al.*, 2021; Shevlin *et al.*, 2023), coping strategies (Joshi *et al.*, 2021; Lin *et al.*, 2021; Pellerin *et al.*, 2021) and subjective well-being variables (Pellerin *et al.*, 2021) as predictors of these trajectories. According to Keyes *et al.* (2020), mental health is a conjunction of emotional (positive and negative affect and psychological distress), psychological (positive functioning variables, as meaning in life, personal growth, autonomy and environmental mastery) and social wellbeing (social integration, social contribution and social acceptance), being more than just the absence of psychopathology (Keyes *et al.*, 2020). Accordingly, it might be hypothesised that we could find changes in these other components of mental health. For example, Baños *et al.* (2022) found in a sample of Spanish residents that the scores on positive functioning variables (meaning in life, gratitude, resilience, compassion and life satisfaction) worsened from the beginning of the lockdown, whereas emotional distress improved by the end of the first Spanish state of alarm (June 21st, 2020) (Baños *et al.*, 2022). Thus, an in-depth study of the impact of the COVID-19 pandemic on mental health should not be limited to its effect on psychological distress, but on the different components of wellbeing affecting mental health.

Likewise, people classified into different trajectories differed in terms of several predictors at baseline. As reported in previous research, being younger, female, reporting lower income, less education and having a previous mental health diagnosis, were factors consistently associated with 'chronic' and 'worsening' trajectories (Pierce *et al.*, 2021; Saunders *et al.*, 2021; Shilton *et al.*, 2021). Fewer research studies examined modifiable determinants associated with these mental health patterns such as emotion regulation, coping strategies and locus of control (Ahrens *et al.*, 2021; Joshi *et al.*, 2021; Shilton *et al.*, 2021).

Altogether, the study of the impact of the pandemic on mental health should take into account the heterogeneity of responses to a crisis situation. Prevalence or incidence rates would not be sufficient to estimate its impact. In this sense, the study of mental health trajectories over a long follow-up would make it possible to identify subgroups of the population in a situation of greater vulnerability, as well as to visualise the most critical moments of the pandemic. Furthermore, the understanding of modifiable protective and risk factors associated with these trajectories would allow the characterisation of these segments of the population to create targeted interventions. The resulting body of knowledge would have considerable practical implications for pressing public health efforts.

Therefore, this study aimed to (1) identify trajectories based on different mental health components (emotional, psychological and social wellbeing) during a two-year follow-up of the COVID-19 pandemic, and contextualise them according to relevant events in each pandemic period; (2) investigate the associations between mental health trajectories and sociodemographic, personality, coping, subjective well-being and lifestyles variables, and to determine whether there were differences among the different mental health outcomes regarding these associations.

Method

Study design and participants

Middle- aged volunteers (40 to 65 years) participating in the Barcelona Brain Health Initiative (BBHI), an ongoing prospective longitudinal study that aims to understand and characterise the determinants of brain health maintenance, were invited to participate in the current study. Briefly, BBHI study participants are community-dwelling individuals, free from any self-reported neurological or psychiatric diagnosis at the time of the recruitment, who answer annual questionnaires regarding demographic, socio-economic, self-perceived health and lifestyles (general health, physical activity, cognitive ability, socialisation, sleep, nutrition and vital plan) information. The BBHI recruitment took place in 2017 through an intensive dissemination campaign including conferences, radio and TV interviews and social media advertisements. For further details of the cohort and study protocol see Cattaneo *et al.* (Cattaneo *et al.*, 2018).

The present work refers to a BBHI sub-study designed to investigate mental health during the COVID-19 pandemic (Bartrés-Faz *et al.*, 2021; Pascual-Leone *et al.*, 2021). BBHI participants who had completed the annual questionnaires before the COVID-19 widespread were invited to participate in subsequent brief evaluations (March, April, June and October 2020, March, July and October 2021 and February 2022) during the different periods of the COVID-19 pandemic (See Fig. 1). In this sub-study, several measures regarding mental health, subjective well-being, quality of life and coping strategies, were included to explore the effects of the pandemic on health and well-being.

In the present study, we included both the annual general follow-up questionnaires and the COVID-19 assessments, considering the observations two years before the pandemic (2018 and 2019 annual questionnaires) as baseline data. We decided not to include the 2017 annual questionnaire as we considered the information from two points before the pandemic as a good baseline on the individual's mental health status.

Figure 1 summarises the periods covered by our study (from early 2018 to February 2022), highlighting the time points when the questionnaires were launched (orange dots), the relevant highlights of the pandemic (blue dots) and their correspondence with the epidemic periods established by the national epidemiological surveillance network of the Carlos III National Health Institute (Red Nacional de Vigilancia Epidemiológica. Instituto de Salud Carlos III, 2022). These periods were defined by this national epidemiological surveillance network by analysing the evolution of incidence rates in the Spanish population.

The study was approved by the Catalan Union of Hospitals ethics committee [Unió Catalana d'Hospitals] (approval references: CEIC 17/06 and CEI 18/07). Moreover, written informed consent was obtained from all participants in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Measures

Outcomes

According to Keyes *et al.* (2020) definition of mental health, we selected different variables as proxies for the emotional, psychological and social components. This selection was made according to the availability of longitudinal measures including baseline data and similarity to the constructs assessed (Keyes *et al.*, 2020).

Emotional

To assess psychological distress, we used the Patient Health Questionnaire 4 items (PHQ-4) (Kroenke *et al.*, 2009), a screening and accurate measurement of core symptoms or signs of depression ('be bothered by little interest or pleasure in doing things', 'be bothered by feeling down, depressed, or hopeless') and anxiety ('feeling nervous, anxious or on edge', 'be bothered by not being able to stop or control worrying'). Participants were asked to indicate how often they have been bothered by four possible symptoms in the last 2 weeks, rated 0 'not at all', 1 'several days', 2 'more than half the days', or 3 'nearly every day'. A score of six or higher represent the cut-off point for a potential case of depression/anxiety (Kroenke *et al.*, 2009). However, in our analyses, we used the continuous form where higher scores mean greater psychological distress.

Psychological

This domain was constituted by 'personal growth', one of the positive functioning variables extracted from the Ryff Psychological wellbeing scale (SPWB) (Ryff, 1995; Ryff and Keyes, 1995). SPWB measure consists of 39 items, constituted by six sub-scales evaluating six aspects of positive functioning. Participants are asked to indicate how accurately each item describes themselves by rating on a 5-level Likert scale ranging from 1 'least like me' to 5 'most like me'. Higher scores indicate better positive functioning. In particular, 'personal growth', is constituted by seven items and refers to one's openness to new experiences and growth.

Social

Keyes' social wellbeing definition includes different factors of the subjective evaluation of personal life circumstances and functioning in society, such as social contribution, integration, actualisation, acceptance and coherence. In the present study, we used the UCLA 3-Item Loneliness Scale (Rico-Uribe *et al.*, 2016), as a proxy measure of social well-being. The UCLA items are related to social integration since refer to the feeling of being excluded or isolated from others. (Rico-Uribe *et al.*, 2016).In this brief questionnaire, respondents were asked how often they felt that they: lacked companionship, were left out, and were isolated from others, on a 3-level Likert scale coded from 1 'hardly ever', to 3 'often'. Higher scores indicate greater loneliness.

Exposures

We included other variables, such as sociodemographic, self-perceived quality of life and health, lifestyles related to health, among other psychological measures to characterise the mental health trajectories.

The following sociodemographic variables were considered: sex (male/female), age (continuous), current marital status (single, married, divorced, widowed), living alone (yes/no), educational level (primary or less, secondary, higher education), occupation (employed, unemployed, retired), monthly family income (<1000€, 1000–2000€, 2000–5000€, >5000€), and if the person lives in a town or in a city (town/city).

Furthermore, to evaluate self-perceived general health and cognitive function we used the Patient-Reported Outcomes Measurement Information System (PROMIS) of global health (Ader, 2007) and the PROMIS Applied Cognition – General Concerns scale (Fieo *et al.*, 2016), respectively. The PROMIS Global Health is composed by ten items representing five domains (physical function, pain, fatigue, emotional distress, social health) that are used to assess global physical health. Concerning the cognitive function scale, is comprised by eight items assessing self-reported cognitive troubles or deficits. In both measures, higher scores mean better general health and better cognitive functioning.

In addition, we included some variables related to lifestyles, as sleeping problems and tobacco consumption. Sleeping problems (i.e., difficulty to fall asleep, wake up at night) were assessed

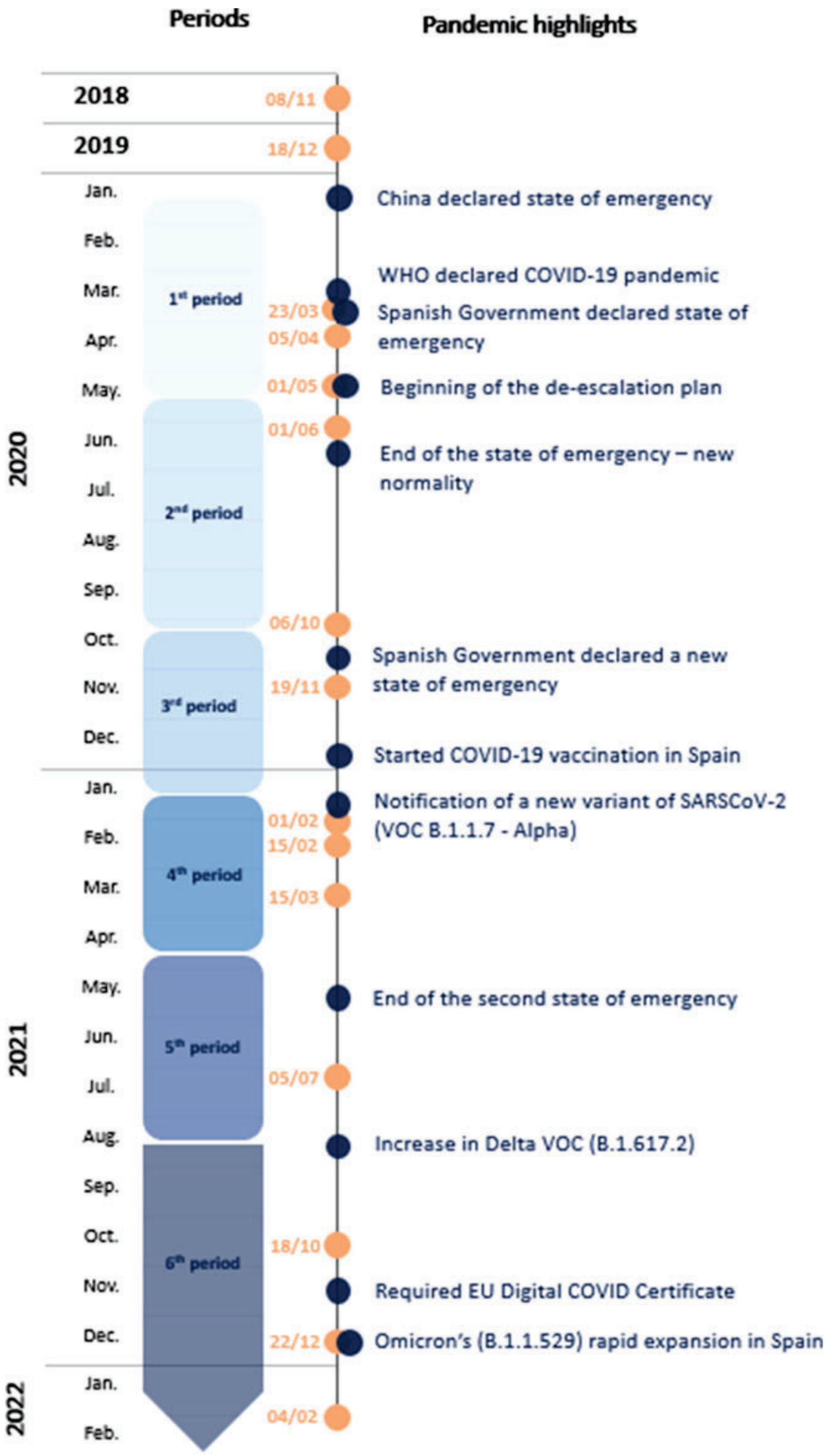

Figure 1. Timing of data acquisition and periods relative to the development of the COVID-19 pandemic in Spain.
Note: Timeline showing the periods covered by the present study, according to the epidemic periods in Spain, as defined by the national epidemiological surveillance network of the Carlos III National Health Institute. Questionnaires launching is presented with orange dots, whereas blue dots represent relevant highlights of the pandemic.

through the Jenkins Sleep Evaluation Questionnaire, a 4-item questionnaire with scores ranging from 0 (no sleep problems) to 20 (most sleep problems) (Jenkins *et al.*, 1988). Moreover, tobacco coded as *yes/no* was included in our analyses.

We also considered the big five personality traits (extraversion, emotional stability, agreeableness, conscientiousness and openness to experience), assessed via the International Personality Item Pool (Goldberg, 1992). Resilience and coping strategies were evaluated with the Brief Resilience and Coping Scale (BRCS) (Sinclair and Wallston, 2004), where higher scores mean better resilience and coping ability.

Related to this, we added the Engaged Living Scale to assess an engaged response style (Trompetter *et al.*, 2013), and three of the six scales from the SPWB: autonomy (a sense of autonomy in thought and action), environmental mastery (the ability to manage complex environments to suit personal needs and values) and positive relations with others (the establishment of quality ties to other) (Ryff, 1995). For each of these scales, higher scores are indicative of better functioning.

Furthermore, perceived stress (the Perceived Stress Scale (Cohen *et al.*, 1983)) was included as a continuous measure. In this case, higher scores mean worse level of that construct.

Statistical analysis

We performed a descriptive analysis of the exposures at baseline. Continuous variables were described by mean ± s.d. values, while categorical variables were presented by the absolute number of individuals and its corresponding percentage (%) within the sample. We considered the information extracted from the annual questionnaires before the COVID-19 pandemic as the baseline. In the case of the variables 'resilience and coping strategies' and 'perceived stress', no pre-pandemic data were available. These two variables were collected in different assessments and to increase the sample size, we considered as baseline the first available observation of each subject on each of these two variables.

To identify mental health trajectories, we first fitted multiple general mixed effects models for each outcome (psychological distress, personal growth and feelings of loneliness), to explore the extent of between-individual heterogeneities (as also recommended in (Herle *et al.*, 2020)). These models separately can allow the estimation of random intercepts, random slopes or both. In this line, these models were compared using a Chi-squared test to find the best design option and do model selection (i.e., the one with the lowest residual sum of squares) (online Supplementary material, Table 2). Second and guided by the results in the previous step, we fitted a GMM with random intercepts and slopes for each outcome to classify individuals into latent trajectories based on their score on the outcome variables without covariates (Nagin and Tremblay, 2005; Berlin *et al.*, 2014; Nagin, 2014). The number of trajectories was determined by analysing group models from 1 to 5 trajectories. According to the Bayesian information criterion (BIC) and the Akaike information criterion (AIC), where the lowest value indicates the better fit, the optimal model was selected (Schwarz, 1978; Akaike, 1998). Moreover, average posterior probabilities above 0.70 were considered as indicators of optimal fit (Tein *et al.*, 2013; Nylund-Gibson and Choi, 2018). Trajectories sample size was also considered since inadequate sample size (lower than 5% can lead to convergence problems, insufficient power to identify classes and changing solutions) (Nylund-Gibson and Choi, 2018). The time variable within the GMM was 'months of the study', although for a clearer presentation of the results, we used the pandemic periods established by the national epidemiological surveillance network of the Carlos III National Health Institute when plotting these.

Then, multiple imputation by chained equations was used to deal with missing data in some of the exposures (online Supplementary Table 3), assuming missing-at-random (MAR), which can handle variables of varying types (Lepkowski *et al.*, 2001; van Buuren, 2007). The imputation model included the outcome (i.e., trajectories membership) and all the variables described in the exposures section, generating 20 imputed datasets (He, 2010). To check imputation quality, we compared imputed and observed data using density and stripplots of van Buuren and Greenacre (van Buren and Greenacre, 2018) (online Supplementary Figs 1 and 2, respectively).

To study the relationship between latent trajectory membership and the described exposures, we first fitted univariable models for each outcome variable (online Supplementary Table 4). We aimed to explore interactions or possible confounding effects to avoid misinterpretations. Then, we conducted a multinomial regression model for each outcome considering class membership as the independent variable to assess the association with several exposures. For each model, the most stable-resilient trajectory was considered the reference category. These multivariable models were additionally adjusted for sex, age, living alone, monthly family income and educational level. Due to potential multicollinearity between some of the exposures we checked the significance and magnitude of correlations through a correlation matrix before running the model (online Supplementary Fig. 3). Regression models were run in 20 imputed datasets and results combined using Rubin's rules (Little and Rubin, 2002).

Additional tests were performed to ensure internal consistency (Cronbach's alpha) and intraclass reliability (intraclass correlation coefficient, ICC) of all the scales in the study, since these were administered in their translated version (Spanish and Catalan). ICC was only calculated for longitudinal assessments (i.e., PHQ-4, UCLA-3 and 'personal growth' from SPWB) and limited to pre-pandemic observations.

All statistical analyses were performed in R version 3.6.2 (R Core Team, 2019), and run in RStudio, version 1.3.1093 (RStudio Team, 2020).

Results

In Table 1 are presented the main characteristics of the total sample ($N = 5536$) at baseline. Our analytical sample was characterised by higher number of females than males (67.39% vs. 32.60%) and by a high proportion of persons with high education (70.82%). The mean age was 51.17 (s.d. = 6.93). From the total sample, 14.43% were living alone, 8.83% were unemployed and 4.11% had a monthly household income lower than 1000€, whereas in 15.93% it was more than 5000€. Moreover, most of the sample (73.80%) was living in an urban area. All scales showed high internal consistencies (Cronbach's alpha ranging from 0.75 to 0.95) and good intraclass reliability (UCLA-3: ICC = 0.75, PHQ-4: ICC = 0.75, 'personal growth' from SPWD: ICC = 0.79).

Mental health trajectories

The first step was to determine the optimal number of latent trajectories according to the fit indices (online Supplementary material Tables from 5 to 7). Although in most outcomes the information criteria (BIC and AIC) pointed to the five- and four-class solutions, the size of the latent classes (<5.00%) and the posterior probabilities (<0.70), lead these solutions to be discarded. Consequently, the 3-class solution provided the best fit. In the case of 'personal growth', one of the posterior probabilities was slightly lower than 0.70, but the three-class solution was selected to allow comparability with the other outcomes and to explore this sub-sample characteristics.

In the case of psychological distress ($N = 5530$, see Fig. 2a), we identified a trajectory composed by individuals with PHQ-4 scores above the clinical cut-off pre and during the pandemic. This sub-group was termed 'chronic' trajectory (*1*: $n = 518$ (9.36%)) and showed some fluctuations across periods (e.g., there was a significant increase of psychological distress when

Table 1. Main characteristics of the sample at baseline

Characteristics	$N = 5536$	
Sex, *n* (%)		
Male	1805 (32.60)	
Female	3731 (67.39)	
Age, mean (s.d.)	51.17 (6.93)	
Marital status, *n* (%)		
Married	3358 (60.65)	
Single	1015 (18.33)	
Divorced	1029 (18.58)	
Widowed	134 (2.42)	
Living alone (yes), *n* (%)	799 (14.43)	
Educational level, *n* (%)		
Primary education or less	248 (4.49)	
Secondary education	1367 (24.69)	
Higher education	3921 (70.82)	
Occupation, *n* (%)		
Employed	4492 (81.14)	
Unemployed	489 (8.83)	
Retired	555 (10.02)	
Household income, *n* (%)		
<1000€	228 (4.11)	
1000–2000€	1238 (22.36)	
2000–5000€	3188 (57.58)	
>5000€	882 (15.93)	
Living in a city (yes), *n* (%)	4086 (73.80)	
Smoking (yes), *n* (%)	753 (13.60)	Cronbach's α
Global health, mean (s.d.)	37.96 (5.62)	0.84
Cognitive function, mean (s.d.)	49.23 (8.97)	0.95
Sleeping problems, mean (s.d.)	8.69 (4.01)	0.68
Personality traits, mean (s.d.)		
Extraversion	31.72 (7.08)	0.85
Emotional stability	33.64 (7.82)	0.88
Agreeableness	41.08 (5.20)	0.78
Conscientiousness	38.31 (6.01)	0.78
Openness to experience	36.23 (6.03)	0.79
Engaged living scale, mean (s.d.)	60.74 (9.35)	0.93
Autonomy, mean (s.d.)	47.35 (1.79)	0.75
Environmental mastery, mean (s.d.)	36.17 (2.28)	0.75
Positive relations with others, mean (s.d.)	27.83 (6.45)	0.84
Brief resilience and coping scale, mean (s.d.)	15.52 (2.38)	0.75
Perceived stress, mean (s.d.)	17.63 (7.25)	0.88

Note. The analyses were performed after the multiple imputation, combining 20 imputed datasets using Rubin's rules as described in the 'Statistical Analysis' section.

the de-escalation plan took place (period 2 > period 1: $t = 2.383$ $p = 0.017$) and with the notification of a new variant of SARS-CoV-2 (VOC B.1.1.7 -Alpha)) (period 4 > period 3: $t = 2.869$ $p = 0.004$). Conversely, most individuals showed stable trajectories (*2*: n = 1940 (35.08%) and *3*: n = 3072 (55.55%)) across the follow-up period. These trajectories differed essentially in the intercept, but we considered them as 'resilient' trajectories according to Bonanno's (2004) definition and were named as 'resilient' and 'moderately resilient', respectively.

From the three-trajectories of 'personal growth' ($N = 5{,}535$, see Fig. 2b), one group (*3*: $n = 1996$ (36.06%)) was characterised by higher levels of this construct (meaning better perception of personal growth), that was sustained over time, so we termed the 'resilient' trajectory. Conversely, we identified another group ('worsening' trajectory, *1*: $n = 423$ (7.64%)) that had higher scores before the pandemic and that decreased significantly at the first period of the pandemic (i.e., when the Spanish Government declared the state of emergency; period 1 > pre: $t = 8.885$ $p < 0.001$) and reported a steady and sustained decline over the follow-up. Finally, most of the sample (*2*: $n = 3116$ (56.29%)) was classified into a group ('progressively ascending' trajectory) characterised by lower scores at baseline with a slight increase during the studied period. However, this change was not significant and its name was merely descriptive.

Finally, of the three trajectories of loneliness ($N = 4{,}066$, see Fig. 2c), two of them (*2*: 'chronic – high loneliness', $n = 468$ (11.51%), and *3*: 'chronic – medium loneliness', $n = 828$ (20.36%)) showed a similar pattern, such that those with higher scores of perceived loneliness before the pandemic showed a decrease at the beginning of the pandemic (i.e., when Spanish Government declared the state of emergency and lockdown was implemented; period 1 > pre: *2* $t = 4.331$ $p < 0.001$, *3* $t = 10.329$ $p < 0.001$), which increased again in period 2 (when the de-escalation plan began; period 2 > period 1: *2* $t = -4.699$ $p < 0.001$, *3* $t = -1.975$ $p = 0.048$). From the third period on, there was a decrease until the sixth period, where there was newly an increase in perceived loneliness. Conversely, most of the sample (*1*: 'resilient – no loneliness', $n = 2770$ (68.12%)) had low and stable scores during the study-period, meaning low perceived loneliness.

In addition, we calculated the proportions of participants classified in the resilient trajectories of each mental health outcome and the overlap among them. We aimed to see whether those individuals who were resilient in one mental health component were also resilient in the others. Of these results, it should be noted that 65.91% of the participants classified in the trajectory 'resilient - no loneliness' were the same individuals as those classified in the trajectories 'resilient' and ' moderately resilient' of the psychological distress variable.

Association between mental health trajectories and exposures

To explore possible interactions or confounding effects among the exposure variables, we performed univariable regression models for each mental health component (online Supplementary Table 4). From these results, highlight the significant associations found in some socio-demographic variables, such as living alone, occupation, household income and educational level, smoking, sleeping problems and some personality traits. These associations largely disappear in the multivariable models when we adjusted for sex, age, living alone, monthly family income and educational level.

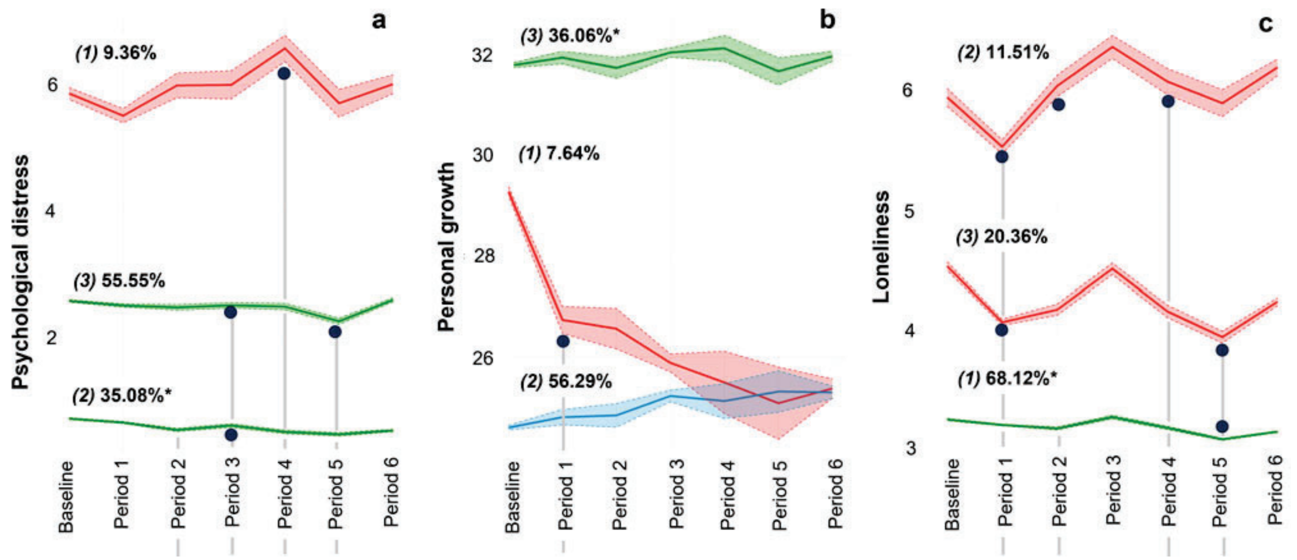

Figure 2. Latent trajectories of different components of mental health.
Note: The different trajectories were termed as follow: psychological distress (1: 'chronic' (n = 518), 2: 'resilient' (n = 1,940), and 3: 'moderately resilient' (n = 3,072)), personal growth (1: 'worsening' (n = 423), 2: 'progressively ascending' (n = 3,116), and 3: 'resilient' (n = 1,996)), and loneliness (1: 'resilient – no loneliness' (n = 2,770), 2: 'chronic – high loneliness' (n = 468), and 3: 'chronic – medium loneliness' (n = 828)). *Trajectories used as the reference category when multinomial regression models were performed. Blue dots indicate significant changes along the trajectories according to relevant highlights of the pandemic. In particular, we found significant changes in the following periods: period 1 (Spanish Government declared state of emergency), period 2 (beginning of the de-escalation plan), period 3 (Spanish Government declared a new state of emergency), period 4 (notification of a new variant of SARSCoV-2 (VOC B.1.1.7 – Alpha), and started COVID-19 vaccination in Spain), and period 5 (end of the second state of emergency).

In Table 2 the significant results from the multinomial regression models performed for each of the mental health outcomes are presented, expressed as relative risk ratios with 95% confidence intervals (CI). We excluded marital status from the analyses due to a high collinearity (0.72) with the variable living alone (online Supplementary Fig. 3).

For psychological distress, females, former smokers, having sleeping problems and higher perceived stress, were risk factors to be classified into the 'chronic' trajectory but also for the 'moderately resilient' trajectory, compared to those in the 'resilient' one. Conversely, higher age, better global health and cognitive function, higher emotional stability (personality trait and coping strategies (BRCS), were protective factors for the 'chronic' and 'moderately resilient' trajectories, taking as a reference the 'resilient' class.

In the case of 'personal growth', in addition to some similarities, we observed differences in the risk and protective factors of the 'worsening' and 'progressively ascending' trajectories, compared to the 'resilient' class. Regarding similarities, we observed that older age was a risk factor, and that variables such as personality trait 'openness to experience' and higher scores on the BRCS (i.e., better resilience and coping strategies) were protective factors. Concerning the differences, those with lower scores in 'personal growth' and who experienced a small increase during follow-up ('progressively ascending' trajectory), also have as protective factors a better health status, better cognitive function and higher scores in the SPWB scales of 'positive relations with others' and 'environmental mastery'. Conversely, higher and secondary education were risk factors for those classified in the 'worsening' trajectory, compared to primary education or less.

As for the loneliness results, we observed similarities between the two trajectories with high scores ('chronic – high loneliness' and 'chronic – medium loneliness'). In both trajectories, variables such as being a female, living alone, and higher perceived stress were risk factors for being classified in these trajectories. Among the protective factors, we found better health status, higher scores on the 'engagement with life' and the SPWB 'positive relations with others' scales, and in the case of those classified into the 'chronic – high loneliness', higher scores on the resilience and coping strategies scale (BRCS), compared to those classified in the 'resilient – no loneliness' class.

Discussion

Mental health during the COVID-19 pandemic attracted much attention, and numerous studies on this topic have been conducted (Salari *et al.*, 2020; Prati and Mancini, 2021; Wu *et al.*, 2021). However, the vast majority focused on psychological distress as a measure of mental health (Ahrens *et al.*, 2021; Batterham *et al.*, 2021; Ellwardt and Präg, 2021; Joshi *et al.*, 2021; Pellerin *et al.*, 2021; Pierce *et al.*, 2021; Saunders *et al.*, 2021; Shilton *et al.*, 2021), which is a conjunction of emotional, psychological and social components (Keyes *et al.*, 2020). Our objective was to identify mental health trajectories considering these components as indicators of mental health and to determine whether they were affected in the same way during the different stages of the pandemic. Moreover, we aimed to investigate if the associated variables differed or coincided among the different trajectories.

For the three outcomes studied (psychological distress, personal growth and feelings of loneliness), we identified three latent trajectories. Of these, we differentiated two major trends, a large proportion of people who were in 'resilient' trajectories (i.e., better previous functioning with stable trajectories during the follow-up period), and a smaller proportion of participants who were part of 'chronic-worsening' trajectories (i.e., low functioning and/or with changes during follow-up). For the 'resilient' trajectories, we also observed a lower susceptibility to the changes that occurred in

Table 2. Results from the multivariable models to explore the association between latent trajectory membership and exposures in the mental health constructs

	Psychological distress		Personal growth		Loneliness	
Variables	'Chronic'	'Moderately resilient'	'Worsening'	'Progressively ascending'	'Chronic – high loneliness'	'Chronic – medium loneliness'
Sex						
Male (ref.)	–	–	–	–	–	–
Female	**2.59 (1.91–3.51)**	**1.71 (1.48–1.99)**	1.07 (0.14–2.45)	**0.82 (0.71–0.95)**	**1.36 (1.02–1.81)**	**1.29 (1.06–1.56)**
Age	**0.95 (0.93–0.97)**	**0.97 (0.96–0.98)**	**1.02 (0.83–1.37)**	**1.02 (1.01–1.04)**	1.00 (0.98–1.02)	0.99 (0.98–1.00)
Living alone						
No (ref.)	–	–	–	–	–	–
Yes	1.32 (0.91–1.91)	0.95 (0.77–1.17)	1.06 (0.77–1.46)	0.91 (0.74–1.11)	**3.15 (2.33–4.28)**	**2.06 (1.63–2.61)**
Occupation						
Employed (ref.)	–	–	–	–	–	–
Unemployed	1.06 (0.68–1.65)	0.96 (0.74–1.25)	1.40 (0.95–2.07)	1.07 (0.83–1.38)	1.09 (0.71–1.67)	1.12 (0.82–1.52)
Retired	0.88 (0.52–1.50)	1.00 (0.77–1.29)	0.95 (0.62–1.45)	0.98 (0.76–1.11)	0.94 (0.59–1.48)	1.27 (0.95–1.72)
Household income						
<1000€ (ref.)	–	–	–	–	–	–
1000–2000€	0.65 (0.35–1.21)	1.15 (0.77–1.71)	1.40 (0.77–2.57)	1.42 (0.99–2.04)	0.91 (0.53–1.57)	1.02 (0.66–1.58)
2000–5000€	0.62 (0.34–1.15)	0.92 (0.62–1.36)	1.35 (0.74–2.46)	**1.52 (1.06–2.17)**	**0.56 (0.31–0.98)**	0.85 (0.54–1.32)
>5000€	0.73 (0.36–1.46)	0.85 (0.56–1.30)	1.03 (0.53–1.99)	1.40 (0.95–2.07)	0.63 (0.33–1.20)	0.75 (0.46–1.22)
Living in a city						
No (ref.)	–	–	–	–	–	–
Yes	1.17 (0.87–1.57)	1.07 (0.92–1.25)	0.88 (0.69–1.12)	1.05 (0.91–1.22)	1.08 (0.82–1.41)	2.06 (0.84–1.22)
Educational level						
Primary education or less (ref.)	–	–	–	–	–	–
Secondary education	0.76 (0.42–1.40)	0.94 (0.65–1.37)	**2.79 (1.11–7.02)**	**0.62 (0.43–0.90)**	0.93 (0.52–1.65)	0.99 (0.61–1.62)
Higher education	0.81 (0.45–1.45)	1.14 (0.79–1.64)	**2.55 (1.02–6.36)**	**0.45 (0.32–0.65)**	1.16 (0.66–2.06)	1.09 (0.69–1.74)
Global health	**0.88 (0.85–0.90)**	**0.94 (0.92–0.96)**	1.00 (0.98–1.03)	**0.97 (0.95–0.98)**	**0.95 (0.92–0.97)**	**0.96 (0.94–0.98)**
Cognitive function	**0.90 (0.89–0.92)**	**0.94 (0.93–0.95)**	1.00 (0.98–1.02)	**0.98 (0.97–0.99)**	**0.97 (0.96–0.99)**	0.99 (0.98–1.00)
Smoking						
No (ref.)	–	–	–	–	–	–
Yes	**1.96 (1.38–2.79)**	**1.27 (1.03–1.56)**	1.07 (0.78–1.47)	1.06 (0.87–1.29)	1.35 (0.99–1.84)	1.02 (0.80–1.30)
Sleeping problems	**1.15 (1.11–1.19)**	**1.07 (1.05–1.10)**	0.97 (0.94–1.00)	0.98 (0.96–1.00)	1.01 (0.98–1.04)	1.01 (0.98–1.03)
Personality traits						
Extraversion	1.00 (0.97–1.02)	0.99 (0.98–1.01)	0.99 (0.97–1.01)	**0.98 (0.97–0.99)**	0.99 (0.97–1.01)	0.99 (0.98–1.01)
Emotional stability	**0.92 (0.89–0.94)**	**0.95 (0.93–0.96)**	0.98 (0.96–1.00)	0.99 (0.98–1.01)	**0.95 (0.93–0.97)**	**0.97 (0.95–0.98)**
Agreeableness	1.02 (0.99–1.06)	**1.01 (1.00–1.03)**	1.00 (0.97–1.03)	0.98 (0.96–1.00)	1.00 (0.97–1.03)	1.00 (0.98–1.02)
Conscientiousness	1.00 (0.97–1.03)	0.99 (0.98–1.01)	0.99 (0.97–1.01)	0.99 (0.98–1.01)	**0.99 (0.97–1.02)**	0.99 (0.97–1.00)
Openness to experience	**1.03 (1.00–1.06)**	1.00 (0.99–1.02)	**0.96 (0.93–0.98)**	**0.95 (0.94–0.97)**	**1.04 (1.01–1.06)**	**1.02 (1.00–1.04)**
Engaged living scale	**0.96 (0.94–0.98)**	**0.98 (0.97–0.99)**	0.99 (0.97–1.00)	**0.96 (0.95–0.97)**	**0.97 (0.96–0.99)**	**0.98 (0.96–0.99)**
Autonomy	0.98 (0.92–1.04)	0.98 (0.95–1.02)	1.03 (0.98–1.08)	1.00 (0.96–1.04)	1.03 (0.97–1.11)	0.99 (0.94–1.04)
Environmental mastery	0.98 (0.92–1.05)	1.00 (0.96–1.04)	0.96 (0.90–1.02)	**0.88 (0.84–0.92)**	1.00 (0.94–1.07)	1.03 (0.98–1.08)
Positive relationships with others	**0.94 (0.92–0.97)**	0.98 (0.97–1.00)	0.99 (0.97–1.01)	**0.98 (0.96–0.99)**	**0.86 (0.84–0.88)**	**0.93 (0.91–0.94)**

(*Continued*)

Table 2. (*Continued.*)

Variables	Psychological distress		Personal growth		Loneliness	
	'Chronic'	'Moderately resilient'	'Worsening'	'Progressively ascending'	'Chronic – high loneliness'	'Chronic – medium loneliness'
Brief resilience and coping scale	**0.87 (0.81–0.93)**	0.96 (0.92–1.00)	**0.88 (0.83–0.95)**	**0.89 (0.85–0.93)**	**0.91 (0.86–0.97)**	0.98 (0.94–1.03)
Perceived stress	**1.12 (1.09–1.15)**	**1.06 (1.04–1.07)**	1.01 (0.99–1.03)	1.00 (0.99–1.01)	**1.07 (1.05–1.10)**	**1.04 (1.02–1.05)**

Note. Relative risk ratios (95% CI) from multinomial logistic regression models. Models were run in 20 imputed datasets and results combined using Rubin's rules. Models were adjusted for sex, age, living alone, monthly family income, and educational level. Boldface indicates statistically significant results.

each period of the pandemic, reaffirming Bonanno's (2004) model and the results of research conducted on mental health trajectories during the COVID-19 pandemic (Ahrens *et al*., 2021; Batterham *et al*., 2021; Ellwardt and Präg, 2021; Joshi *et al*., 2021; Pellerin *et al*., 2021; Pierce *et al*., 2021; Saunders *et al*., 2021; Shilton *et al*., 2021). In the case of the so-called 'chronic-worsening' trajectories, we observed greater heterogeneity and susceptibility to different periods of the pandemic. For example, regarding psychological distress (emotional component), those participants classified in the 'chronic' trajectory had higher scores at baseline than when the state of alarm was declared (period 1), and these scores increased at later points in the pandemic (e.g., period 2, when the de-escalation plan was initiated ('new normality'); or period 4, when the Alpha variant was reported). However, in the social component (loneliness variable), those people who felt lonelier before the pandemic (chronic - high loneliness), reduced their scores when the state of alarm was decreed (period 1) and home confinement was imposed, returning to their previous scores when the de-escalation and the period of new normality began (period 2).

With respect to psychological distress, one possible explanation for the results obtained is that people classified within this trajectory already had levels of anxious-depressive symptoms above the cut-off point before the pandemic, predisposing them to higher vulnerability. This explanation is further supported by the results of the multinomial regression models, where we observed higher perceived stress as a risk factor and a negative association with higher scores in resilience and coping strategies, and with the personality trait 'emotional stability'. Our results were in line with previous research. For instance, higher perceived stress during COVID-19 lockdown was found to be a predictor for worse mental health (based on GHQ-28 scores) in a longitudinal study conducted in Germany (Ahrens *et al*., 2021). In the same way, previous mental health diagnosis has been consistently associated to 'chronic' or 'worsening' trajectories (Pierce *et al*., 2021; Saunders *et al*., 2021), which could be extrapolated to the scores above the PHQ-4 cut-off at baseline in our study. Furthermore, in the investigation conducted by Saunders *et al*. (2021), personality traits such as 'emotional stability' was also associated with trajectories with worse anxiety scores (based on the GAD-7), in particular trajectories called 'moderate/moderately-severe symptoms that become severe over time' and 'severe initial anxiety that decreases to normal range, predominantly during lockdown' (Saunders *et al*., 2021). Taken together, all these factors may be acting synergistically posing these individuals in a more vulnerable situation.

Regarding loneliness, the decrease in scores in the initial period of the pandemic (period 1), was also observed in a previous report by our group, attributing this initial change to the spirit of togetherness that was generated to deal with stay-at-home orders, such as video calls to family and friends or the '20:00 h applause', where thousands of people applauded frontline health professionals from windows or balconies acknowledging them their work and commitment. All these aspects may have helped to intensify social bounds, cooperation and a sense of belonging in the initial stages of the pandemic outbreak. However, in the present study including a much-extended follow-up assessment, indicated that this initial effect declined after the end of home confinement until the initial levels of loneliness were reached (Bartrés-Faz *et al*., 2021). When we characterised these groups of individuals (i.e., 'chronic – high loneliness' and 'chronic – medium loneliness'), we observed that they were mostly females, people who were living alone and individuals with high perceived stress. Unlike for psychological distress, fewer studies have been carried out on loneliness. In much of the research, it has been used as a predictor of mental health and rarely as an outcome (Ahrens *et al*., 2021; Shevlin *et al*., 2023). Studies performed in different countries, that have focused on loneliness during the pandemic, have found somewhat controversial results. Some research found an increase of loneliness during the acute phase of the outbreak (Bu *et al*., 2020; Luchetti *et al*., 2020), whereas other reported a reduction in perceived loneliness in this phase (Bartrés-Faz *et al*., 2021). These findings suggest that the results need to be contextualised, as the effect of the pandemic on loneliness may depend on contextual aspects, such as the restrictions applied in each country.

In the case of the psychological dimension of mental health ('personal growth'), we identified fewer changes during follow-up, yet some aspects deserve to be mentioned. According to our results, we found that more than half of the sample (those classified in the 'progressively ascending' class) had low scores in 'personal growth', being people with a feeling of personal stagnation or lack of a sense of improvement or expansion in life. These participants experienced an improvement at follow-up, although not statistically significant. In contrast, a small proportion of the sample ('worsening' trajectory) presented a large decrease in scores from the onset of the pandemic (period 1) compared to their baseline scores. Faced with both scenarios, we wondered what variables would be associated with these trajectories to characterise them. In both cases, older age was a risk factor compared to the 'resilient' class. This differed from what was found in the literature in studies on emotional distress variables during the pandemic, where younger subjects were more vulnerable (Ellwardt and Präg, 2021; Pierce *et al*., 2021; Saunders *et al*., 2021; Shilton *et al*., 2021). Nevertheless, a review concerning the impact of age on mental health changes during the pandemic found heterogeneous findings in the literature, suggesting that the effect of age may depend on contextual variables but also on the mental health outcome studied (Lebrasseur *et al.*, 2021). Our study allows to contextualise these findings in terms of a particular age group (40 to 65 years) and one of the domains of mental health. In addition, both trajectories ('worsening' and 'progressively ascending'), had in common higher resilience and coping strategies, and the personality trait 'openness to experience' as positive factors associated to these trajectories. This could be translated into a lower adaptive capacity as well as a tendency towards conservativeness and less openness to experience. However, they differed in a lower risk of being classified in the 'progressively ascending' class in the case of better self-reported health, better cognition and higher scores in 'positive relations with others' and 'environmental mastery', i.e., quality ties to others and the ability to manage complex situations, respectively.

Given these results, and with the calculation of the overlapping of individuals classified in trajectories considered 'resilient', we reaffirm our initial hypothesis that the different components of mental health should be analysed separately. We found that within so-called 'resilience' there was also heterogeneity, as the proportion of overlapping in the 'resilient' individuals among outcomes was only above 50% for psychological distress and loneliness, while for 'personal growth' and loneliness it was 26.29%. The greatest overlap, that was found between loneliness and emotional distress, was consistent with that reported in the literature, where both variables have been consistently related (Bu *et al.*, 2020; Ahrens *et al.*, 2021). Moreover, each outcome was susceptible to different stages of the pandemic and the variables associated with the trajectories presented some differences. These variations included that living alone was only a significant risk factor for loneliness ('chronic-high/medium loneliness' trajectories), but not for the other outcomes. Likewise, monthly household income was only related to one of the trajectories of 'personal growth' in the adjusted models. Furthermore, lifestyles such as smoking behaviour and sleeping problems were associated with the 'chronic' class of the psychological distress measure, which could be related to a maladaptive strategy and a consequence of experienced distress, respectively. For the same class, predictors as 'emotional stability' and perceived stress, well-known distress-related variables, were found to be risk factors also for the 'chronic' trajectories of loneliness, but not for 'personal growth'. In addition, from the analysis of the variables associated with the different trajectories, we also observed some similarities. Predictors such as better overall health and better cognitive function were protective factors in all of the studied variables. The relationship between physical and mental health status has been commonly reported in the literature, suggesting a bidirectional relationship (Druss and Walker, 2011). Likewise, anxious-depressive symptomatology has been widely recognised as a risk factor for cognitive impairment (Chodosh *et al.*, 2010; Zaninotto *et al.*, 2018). Similarly, the personality trait 'openness to experience', and some SPWB scales ('engaged living scale' and 'positive relations with others') were positively associated with better mental health outcomes (i.e., 'resilient' trajectories). Finally, emphasise the role of coping strategies, as it was positively associated with those trajectories with better functioning in all the analysed outcomes. Previous research found frequent use of dysfunctional coping strategies and less frequent use of emotion-focused coping strategies in those participants classified into the trajectory 'high-increasing depressive symptoms' (Joshi *et al.*, 2021). The role of coping strategies is of particular interest as it is a modifiable factor, which can be trained and serve as a preventive strategy for future crises.

From the perspective of practice and policy, our study provides useful information for risk identification. Our research allows to identify and characterise groups of more resilient people and others who are in a situation of chronicity or vulnerability. Furthermore, the fact that we have separated different aspects of mental health (psychological distress, personal growth and feelings of loneliness) and contextualised the fluctuations by considering the relevant events of the pandemic, makes our study of potential great value. In this sense, it allows for the detection of key temporal moments in which to target interventions to strategically prevent to promote a better emotional, psychological and social status. This knowledge could be extrapolated to the current situation, where other social and economic threats have increased, such as the rising price of basic needs (electricity, gas and food), inflation and eventual recession. Exposure to these factors could affect people's health, and the results of these studies could be used to guide preventive strategies.

Strengths and limitations

The strengths of the present work include a two-year follow-up from the start of the COVID-19 pandemic and the inclusion of baseline information. To the best of our knowledge, no previous study has carried out such a long follow-up (Ahrens *et al.*, 2021; Batterham *et al.*, 2021; Ellwardt and Präg, 2021; Joshi *et al.*, 2021; Pellerin *et al.*, 2021; Pierce *et al.*, 2021; Saunders *et al.*, 2021; Shilton *et al.*, 2021). In our study, we analysed data considering the previous two years as the baseline, until February 2022, when the large expansion of the Omicron variant occurred. This is particularly important because, according to Taylor, pandemics are dynamic events and therefore changes in mental health outcomes are expected to occur over time, including a return to baseline levels (Taylor, 2019). This could be observed with a long follow-up and not just at the beginning of the pandemic when lockdown and other covid measures were implemented. Furthermore, we interpreted the fluctuations in the trajectories in terms of the periods of greatest interest for the pandemic, contextualising the changes in the analysed mental health outcomes, suggesting that certain changes might be related to the events taking place in each covid period. This made our study a richer investigation as it was not limited to two major periods (e.g., pre-covid/covid or lockdown/new normality), but allowed us to observe the evolution of psychological, emotional and social outcomes at different points and to identify the most critical moments of the pandemic. Moreover, as we mentioned earlier, we identified trajectories based on proxy measures of different components of mental health, not just psychological distress, since mental health is more than the absence of anxious-depressive symptoms. Therefore, the approach of our study was under Keyes *et al.*'s (2020) definition of mental health and considered emotional, psychological and social elements as indicators of mental health (Keyes *et al.*, 2020). The fact that we found differences in trajectories and associated variables among mental health outcomes reinforces our hypothesis and the need for more holistic studies on mental health. Finally, the inclusion of several predictors, such as socio-demographic variables, personality traits, some lifestyles and variables regarding subjective well-being and coping strategies, provided a good overview of the risk and protective factors that characterise each of the trajectories.

However, some limitations deserve to be mentioned. First, we did not use a random sample and it could have introduced some bias limiting the sample representativeness and result generalisability. For example, there was an oversampling of females and participants with higher education. Ideally, we should have fitted the models in a randomised design, but such design is not possible to pursue in the current context. Future research could use post-randomisation techniques based on matching or weighting-based random sampling methods that specifically target potentially varying background characteristics. Secondly, there were differences in the number of observations among periods and variables collected. This fact, although inherent to a longitudinal study, entailed a large number of missingness in most of the predictors, so multiple imputation procedures were performed. In our case the complete case analysis could not be considered due to a drastic reduction of the sample size. Nevertheless, the use of multiple imputation procedures is widely advocated when missing data occur in one or more covariates in a regression model and under an MAR assumption, and in order to ensure the quality of the imputed data, all necessary diagnostics were performed (Sterne *et al*., 2009; White and Carlin, 2010). Thirdly, despite having longitudinal information on some of the exposure variables, multinomial regression models included only baseline scores. Some of these variables, such as occupation, sleep problems, resilience and coping strategies and perceived stress, might have changed during follow-up. Due to differences in the number of observations and the period of collection of each variable, longitudinal analysis was discarded. However, future studies should consider analysing the exposure variables longitudinally, as their possible changes could explain part of the results found. Finally, the identification of trajectories in two of the mental health components was based on screening measures, such as the PHQ-4 and the UCLA-3. While much of the research in this field has used these or similar measures (Bu *et al*., 2020; Fancourt *et al*., 2021; Pierce *et al*., 2021; Saunders *et al*., 2021; Shevlin *et al*., 2023), researchers and policymakers should be aware of the accuracy limitations with such tools, and interpret the results with caution.

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Conflict of interest. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 200.

Availability of data and materials. The authors encourage interested investigators to reach out and we will honour all reasonable and scientifically motivated requests for data access and make the raw data available when required.

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Supplementary material

Supplementary table 1. STROBE statement checklist for observational studies

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title sheet
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Title sheet
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	1-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4,5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5, figure 1
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4,5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement).	*6-9*
Bias	9	Describe any efforts to address potential sources of bias	9-11
Study size	10	Explain how the study size was arrived at	5, 9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-11

		(*b*) Describe any methods used to examine subgroups and interactions	10-11
		(*c*) Explain how missing data were addressed	10, supplementary table 3, supplementary figures 1 and 2
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	9
		(*e*) Describe any sensitivity analyses	N/A
Results			**Page**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11 and table 1
		(b) Indicate number of participants with missing data for each variable of interest	Supplementary table 3
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Figures 1 and 2
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	11-13, figure 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Supplementary table 4, supplementary figure 3, page 11
		(*b*) Report category boundaries when continuous variables were categorized	Table 2, supplementary table 4
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Supplementary materials
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	21, 22

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-22
Generalisability	21	Discuss the generalisability (external validity) of the study results	21, 22
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

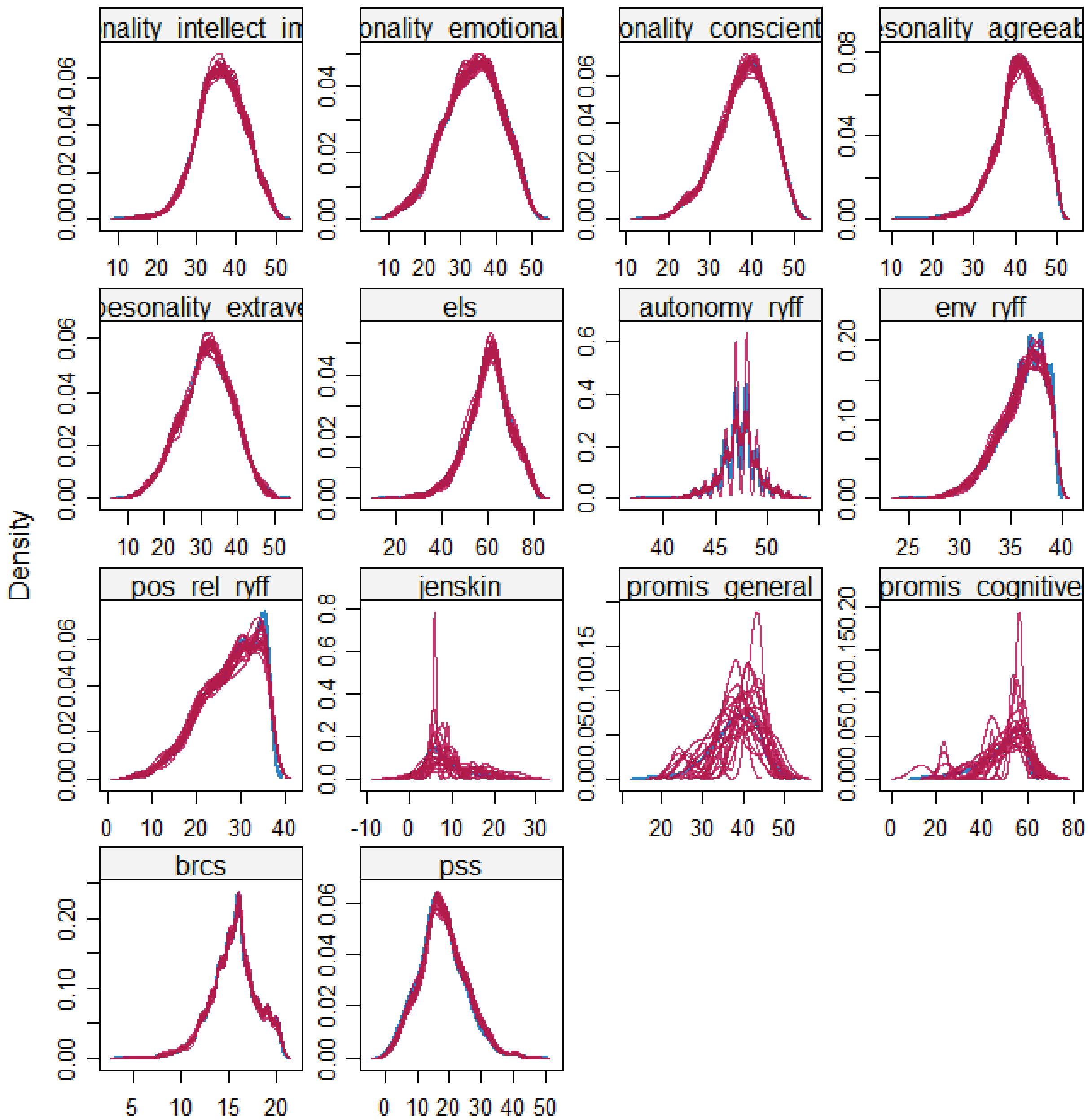
Supplementary table 2. Results from the mixed effects models

Psychological distress (PHQ-4)							
	AIC	BIC	logLik	deviance	Chisq	Df	Pr(>Chisq)
Random intercept only	125663	125696	-62827	125655			
Random slope only	138801	138835	-69397	138793	0	0	
Random slope only	138801	138835	-69397	138793			
Random intercept and slope	125069	125119	-69528	125057	13736	2	<0.0001
Random intercept only	125663	125696	-62827	125655			
Random intercept and slope	125069	125119	-62528	125057	598.21	2	<0.0001
Personal growth							
	AIC	BIC	logLik	deviance	Chisq	Df	Pr(>Chisq)
Random intercept only	88501	88531	-44246	88493			
Random slope only	95322	95353	-47657	95314	0	0	
Random slope only	95322	95353	-47657	95314			
Random intercept and slope	88403	88449	-44195	88391	6923.1	2	<0.0001
Random intercept only	88501	88531	-44246	88493			
Random intercept and slope	88403	88449	-44195	88391	101.75	2	<0.0001
Loneliness (UCLA)							
	AIC	BIC	logLik	deviance	Chisq	Df	Pr(>Chisq)
Random intercept only	74672	74705	-377332	74664			
Random slope only	81076	81109	-40534	81068	0	0	
Random slope only	81076	81109	-40534	81068			
Random intercept and slope	74443	74492	-37215	74431	6637.2	2	<0.0001
Random intercept only	74672	74705	-37332	74664			
Random intercept and slope	74443	74492	-37215	74431	233.23	2	<0.0001

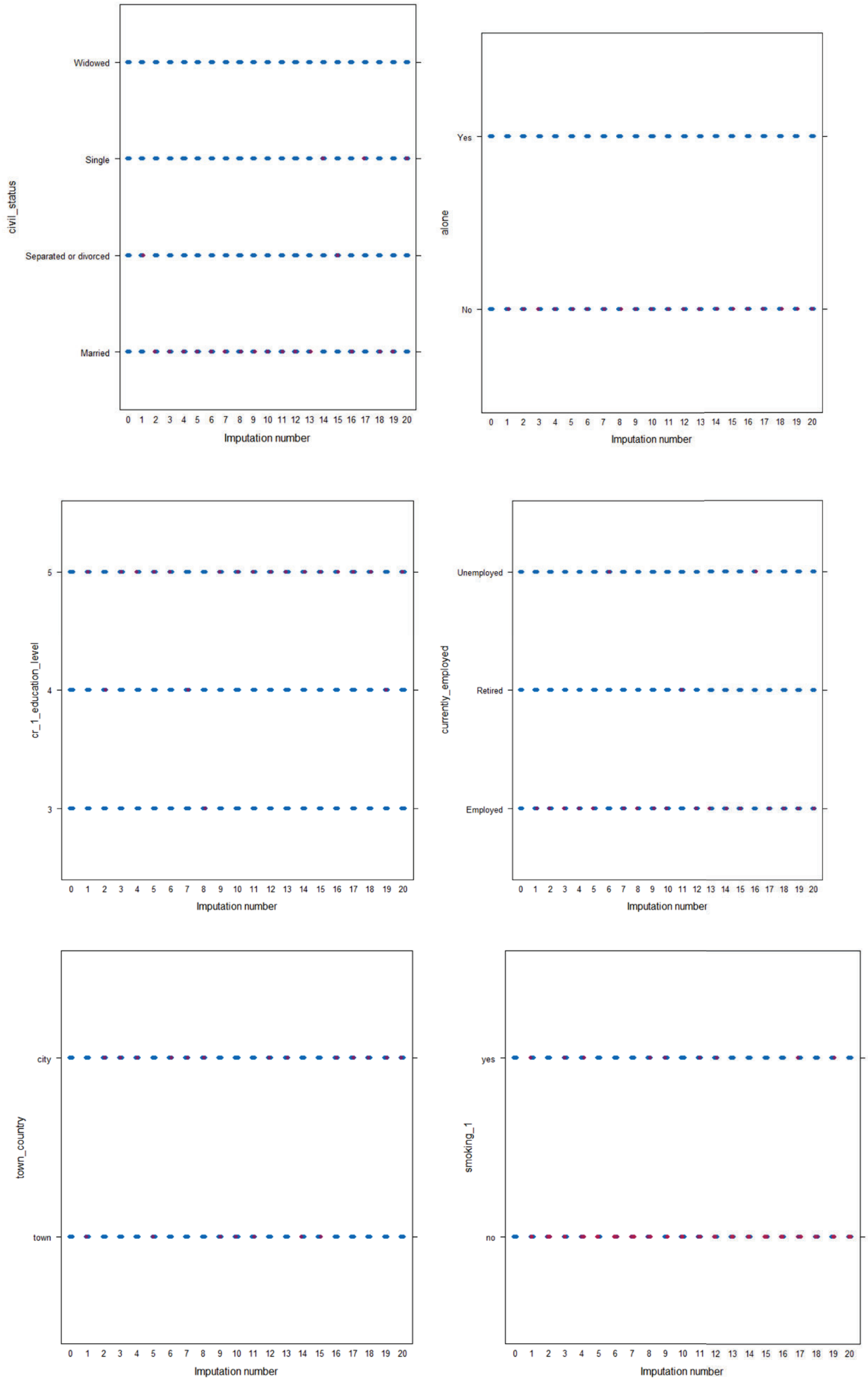
Supplementary table 3. Percentage of missingness in the exposures

Variables	% of missingness
Sex	0.00%
Age	0.00%
Marital status	0.02%
Living alone	0.02%
Educational level	0.02%
Occupation	0.02%
Household income	0.00%
Living in a city	0.02%
Global health	0.11%
Cognitive function	0.11%
Sleeping problems	0.07%
Smoking	0.07%
Personality traits	38.62%
Engaged living scale	12.19%
Autonomy	13.82%
Environmental mastery	13.82%
Positive relationships	13.82%
Brief resilience and coping scale	39.17%
Perceived stress	48.15%

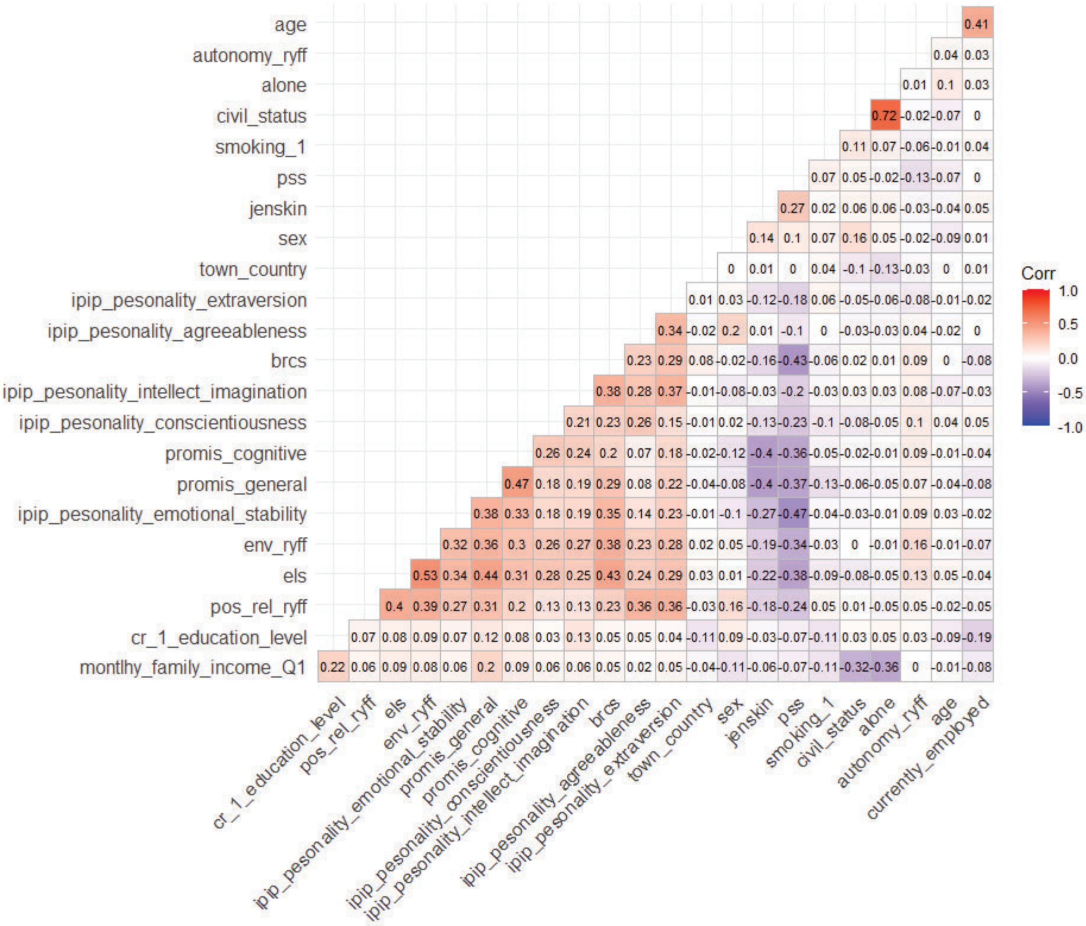
Supplementary figure 1. Density plots for continuous variables conducted to check the imputation quality



Supplementary figure 2. Stripplots for categorical variables conducted to check the imputation quality



Supplementary figure 3. Correlation matrix to assess multicollinearity among the predictors



Supplementary table 4. Results from the univariable models to explore the association between latent trajectory membership and exposures in the mental health constructs

Variables	Psychological distress		Personal growth		Loneliness	
	"Chronic"	**"Moderately resilient"**	**"Worsening"**	**"Improving"**	**"Chronic – high loneliness"**	**"Chronic – medium loneliness"**
Sex						
Male (ref.)	-	-	-	-	-	-
Female	**2.66 (2.11-3.34)**	**1.86 (1.65-2.09)**	1.13 (0.89-1.43)	**0.81 (0.71-0.91)**	**1.26 (1.01-1.57)**	**1.26 (1.07-1.49)**
Age	**0.95 (0.94-0.97)**	**0.97 (0.96-0.98)**	**1.02 (1.00-1.03)**	**1.02 (1.01-1.03)**	0.99 (0.98-1.00)	0.99 (0.98-1.00)
Living alone						
No (ref.)	-	-	-	-	-	-
Yes	**1.45 (1.12-1.87)**	1.02 (0.86-1.20)	1.08 (0.80-1.44)	0.93 (0.79-1.09)	**2.98 (2.40-3.71)**	**1.99 (1.63-2.42)**
Occupation						
Employed (ref.)	-	-	-	-	-	-
Unemployed	**1.73 (1.28-2.35)**	1.07 (0.87-1.32)	1.40 (0.98-2.00)	**1.25 (1.02-1.54)**	**1.57 (1.16-2.12)**	1.29 (0.99-1.68)
Retired	**0.61 (0.42-0.87)**	**0.73 (0.61-0.88)**	1.29 (0.90-1.86)	**1.48 (1.21-1.80)**	0.91 (0.64-1.29)	1.12 (0.88-1.43)
Household income						
<1000€ (ref.)	-	-	-	-	-	-
1000-2000€	**0.57 (0.38-0.88)**	1.26 (0.91-1.75)	1.30 (0.73-2.32)	1.24 (0.92-1.67)	0.73 (0.49-1.08)	0.91 (0.62-1.35)
2000-5000€	**0.32 (0.21-0.48)**	0.93 (0.68-1.27)	1.18 (0.68-2.06)	1.10 (0.82-1.46)	**0.31 (0.21-0.45)**	**0.61 (0.41-0.89)**
>5000€	**0.21 (0.13-0.33)**	**0.65 (0.46-0.91)**	0.84 (0.46-1.54)	0.78 (0.57-1.07)	**0.25 (0.16-0.39)**	**0.43 (0.28-0.65)**
Living in a city						
No (ref.)	-	-	-	-	-	-
Yes	1.05 (0.84-1.31)	1.03 (0.90-1.17)	0.92 (0.73-1.17)	1.05 (0.92-1.19)	1.08 (0.87-1.34)	1.02 (0.86-1.21)
Educational level						
Primary education or less	-	-	-	-	-	-
Secondary education	**0.53 (0.35-0.82)**	0.89 (0.65-1.21)	**2.74 (1.07-7.05)**	**0.61 (0.43-0.84)**	0.67 (0.43-1.03)	0.88 (0.57-1.37)
Higher education	**0.41 (0.28-0.62)**	0.88 (0.65-1.17)	**2.10 (0.83-5.32)**	**0.35 (0.26-0.49)**	**0.60 (0.40-0.91)**	0.82 (0.54-1.23)
Global health	**0.73 (0.71-0.74)**	**0.86 (0.85-0.87)**	**0.96 (0.94-0.98)**	**0.90 (0.89-0.91)**	**0.84 (0.82-0.85)**	**0.90 (0.89-0.91)**
Cognitive function	**0.83 (0.82-0.84)**	**0.90 (0.89-0.91)**	0.98 (0.97-1.00)	**0.94 (0.94-0.95)**	**0.92 (0.91-0.93)**	**0.95 (0.95-0.96)**
Smoking						
No (ref.)	-	-	-	-	-	-

Yes	**2.24 (1.74-2.89)**	**1.37 (1.15-1.63)**	1.12 (0.82-1.52)	**1.18 (1.00-1.40)**	**1.49 (1.17-1.90)**	1.12 (0.91-1.39)
Sleeping problems	**1.39 (1.35-1.42)**	**1.18 (1.15-1.20)**	0.99 (0.97-1.02)	**1.05 (1.03-1.06)**	**1.15 (1.13-1.18)**	**1.08 (1.06-1.10)**
Personality traits						
Extraversion	**0.92 (0.90-0.93)**	**0.96 (0.95-0.97)**	**0.97 (0.95-0.98)**	**0.93 (0.92-0.94)**	**0.92 (0.90-0.93)**	**0.96 (0.95-0.97)**
Emotional stability	**0.81 (0.79-0.82)**	**0.90 (0.89-0.91)**	**0.96 (0.95-0.98)**	**0.94 (0.93-0.95)**	**0.88 (0.86-0.89)**	**0.93 (0.92-0.94)**
Agreeableness	**0.96 (0.94-0.99)**	0.99 (0.97-1.00)	**0.97 (0.95-0.99)**	**0.92 (0.91-0.94)**	**0.93 (0.91-0.95)**	**0.97 (0.96-0.98)**
Conscientiousness	**0.90 (0.89-0.92)**	**0.95 (0.94-0.96)**	**0.97 (0.95-0.99)**	**0.94 (0.93-0.95)**	**0.93 (0.92-0.95)**	**0.96 (0.95-0.97)**
Openness to experience	**0.93 (0.91-0.95)**	**0.96 (0.95-0.97)**	**0.93 (0.91-0.95)**	**0.90 (0.89-0.91)**	**0.96 (0.95-0.98)**	0.99 (0.97-1.00)
Engaged living scale	**0.87 (0.85-0.88)**	**0.93 (0.92-0.94)**	**0.96 (0.95-0.98)**	**0.91 (0.91-0.92)**	**0.90 (0.89-0.91)**	**0.94 (0.93-0.95)**
Autonomy	**0.85 (0.80-0.90)**	**0.92 (0.89-0.95)**	1.00 (0.94-1.06)	**0.93 (0.90-0.96)**	0.95 (0.90-1.00)	**0.94 (0.91-0.98)**
Environmental mastery	**0.64 (0.61-0.67)**	**0.81 (0.78-0.83)**	**0.86 (0.82-0.91)**	**0.71 (0.69-0.74)**	**0.73 (0.70-0.76)**	**0.85 (0.82-0.88)**
Positive relationships with others	**0.87 (0.85-0.88)**	**0.94 (0.93-0.95)**	**0.97 (0.95-0.99)**	**0.92 (0.91-0.93)**	**0.83 (0.82-0.84)**	**0.91 (0.90-0.92)**
Brief resilience and coping scale	**0.64 (0.61-0.67)**	**0.82 (0.79-0.84)**	**0.82 (0.77-0.86)**	**0.74 (0.72-0.77)**	**0.74 (0.70-0.77)**	**0.87 (0.84-0.90)**
Perceived stress	**1.27 (1.24-1.30)**	**1.12 (1.11-1.13)**	**1.04 (1.02-1.06)**	**1.06 (1.05-1.07)**	**1.15 (1.13-1.17)**	**1.07 (1.06-1.09)**

Note. Relative risk ratios (95% CI) from multinomial logistic regression models. Models were run in 20 imputed datasets and results combined using Rubin's rules. Boldface indicates statistically significant results.

Supplementary table 5. Model fit indices for different number of classes solutions for psychological distress (PHQ-4)

No. of classes	Loglik	npm	AIC	BIC	Entropy	class 1 (%)	class 2 (%)	class 3 (%)	class 4 (%)	class 5 (%)	Average posterior probabilities
1	-62528.364	6	125068.728	125108.435	1	100	NA	NA	NA	NA	1.000
2	-61695.263	10	123410.526	123476.705	0.60	11.482	88.517	NA	NA	NA	0.872 0.903
3	**-61374.635**	**14**	**122777.270**	**122869.92**	**0.54**	**9.367**	**35.081**	**55.551**	**NA**	**NA**	**0.860** **0.742** **0.805**
4	-61295.112	18	122626.224	122745.347	0.48	27.142	6.636	34.122	32.097	NA	0.590 0.866 0.737 0.687
5	-61278.940	22	122601.881	122747.476	0.47	4.249	31.320	34.394	23.743	6.292	0.812 0.585 0.734 0.565 0.605

Supplementary table 6. Model fit indices for different number of classes solutions for personal growth

No. of classes	Loglik	npm	AIC	BIC	Entropy	class 1 (%)	class 2 (%)	class 3 (%)	class 4 (%)	class 5 (%)	Average posterior probabilities
1	-44195.484	6	88402.969	88442.682	1	100	NA	NA	NA	NA	1.000
2	-44029.113	10	88078.227	88144.415	0.55	70.551	29.448	NA	NA	NA	0.911 0.714
3	**-44009.436**	**14**	**88046.872**	**88139.536**	**0.48**	**7.642**	**56.296**	**36.061**	**NA**	**NA**	**0.618** **0.812** **0.719**
4	-43987.555	18	88011.110	88130.249	0.56	1.607	59.548	36.224	2.619	NA	0.665 0.788 0.746 0.655
5	-43984.202	22	88012.404	88158.019	0.61	55.447	0.090	3.541	1.282	39.638	0.793 0.688 0.644 0.659 0.744

Supplementary table 7. Model fit indices for different number of classes solutions for loneliness (UCLA)

No. of classes	Loglik	npm	AIC	BIC	Entropy	class 1 (%)	class 2 (%)	class 3 (%)	class 4 (%)	class 5 (%)	Average posterior probabilities
1	-37215.358	6	74442.716	74480.578	1	100	NA	NA	NA	NA	1.000
2	-35390.855	10	70801.711	70864.815	0.68	70.388	29.611	NA	NA	NA	0.915 0.933
3	**-35239.470**	**14**	**70506.940**	**70595.286**	**0.68**	**68.125**	**11.510**	**20.363**	**NA**	**NA**	**0.899** **0.849** **0.768**
4	-35239.470	18	70514.940	70628.527	0.43	65.592	0.00	11.510	22.897	NA	0.519 NA 0.849 0.728
5	-35239.470	22	70522.940	70661.769	0.35	0.000	0.000	11.510	61.288	27.201	NA NA 0.849 0.346 0.661

Study 2

Functional brain connectivity prior to the COVID-19 outbreak predicts mental health trajectories during two years of pandemic.

Cabello-Toscano M, Vaqué-Alcázar L, Bayes-Marin I, Cattaneo G, Solana-Sánchez J, Bargalló N, Tormos JM, Pascual-Leone A, Bartrés-Faz D.

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Functional brain connectivity prior to the COVID-19 outbreak predicts mental healthtrajectories during two years of pandemic.

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While acknowledging the hardships caused by COVID-19, the pandemic also provided a unique opportunity to study mental well-being and individual vulnerability or resilience [1,2]. Sociodemographic, psychological factors, and lifestyles, have been identified as predictors of mental health during COVID-19 [3]. Our previous study demonstrated the relevance of the interplay between psychological measures and brain networks' functional connectivity (FC) [4]. However, important questions remain to be addressed. For example, can FC – alone or in combination with other measures – predict longer- term mental health? Additionally, most studies focus on emotional aspects (i.e., psychological distress), although mental health comprises emotional, psychological (i.e., personal growth, [PG]), and social (i.e., loneliness) well-being components, which were differently impacted during the pandemic [3]. This study aims to investigate if there exists specificity between FC measures and long-term changes across mental health components, knowing the links between brain networks and 'resilience processes' [5,6].

We studied 702 healthy, middle-aged individuals (350 women, age: 50.66 ± 6.98 years) who met criteria in [3]. All participants gave written informed consent according to the Declaration of Helsinki. The study protocol was approved by the Comitè Ètic d'Investigació de la Fundació Unió Catalana d'Hospitals (CEIC-17/06). Resting-state functional magnetic resonance imaging (MRI) images acquired prior to the COVID-19 outbreak were preprocessed, and system segregation (SyS; integration-segregation balance) was calculated for seven resting state networks (RSN) [see 4]. Multinomial logistic regressions were fitted to predict trajectory membership for the three mental health components (Resilient, Chronic, or Worsening trajectories as captured by growth mixture models contrasting pre- vs. during-pandemic observations within a two-year follow-up [see 3 and Figure 1-A]). *RSN models* included FC. *Full models* combined significant RSN measures and significant predictors found in our previous study (age, sex, monthly income, stress coping, personality dimensions, general health, and lifestyle habits) [see 3]. *Non-RSN models* were as *Full models* but without RSN data, in a way that through likelihood ratio tests (*non-RSN* vs. *Full models*) we assessed whether the goodness of fit improved by adding FC measures to sociodemographic, psychological, and lifestyle measures.

The emotional mental health trajectory membership (Figure 1-A) was significantly predicted by FC of the Salience Network (SN) (Figure 1-B), revealing that a more functionally integrated SN (i.e., lower SyS) was more representative of Resilient trajectories in comparison to Chronic and marginally to Moderate-Resilient ones. In the *Full model*, the significance of SN-FC as a predictor was reduced, and the comparison of *Full* vs. *non-RSN models* was non-significant (Figure 1-C).

The psychological component of mental health trajectory membership (Figure 1-A) was significantly predicted by the Dorsal Attention Network (DAN), with a higher probability of belonging to the high-PG trajectory with a greater functionally integrated DAN. Additionally, there were trends to predict this outcome by Limbic Network (LN) and Fronto-Parietal Network (FPN). However, in the *Full model*, only FPN-FC remained significant. Notably, *Full model* was significantly better than the *non-RSN model* (Figure 1-C).

Finally, social well-being mental-health trajectory membership was not significantly predicted by any of the RSN-SyS values (R2=0.008).

Our findings indicate that measures of FC reflecting the integration-segregation of principal brain networks offer distinct predictions for long-term mental health outcomes across the COVID-19 pandemic. Although the emotional well-being trajectory was predicted by basal SN- SyS, the *Full model* was more informative. Building upon our previous findings [4], this suggests that anxious-depressive trends during the pandemic were directly affected by SN-SyS, and indirectly influenced by DMN- and FPN-SyS through psychological mechanisms such as perceived stress, aligning with the triple network perspective [5,6,7]. In contrast, when studying PG, the results showed a much greater relevance of baseline FPN-SyS, adding meaningful information to the model derived from aggregated sociodemographic, psychological factors, and lifestyles. Individual differences in PG maintenance likely reflect the capacity to thrive through reappraising and attaching value and significance to life under stressful situations [8]. As such, the associations found between PG and FPN

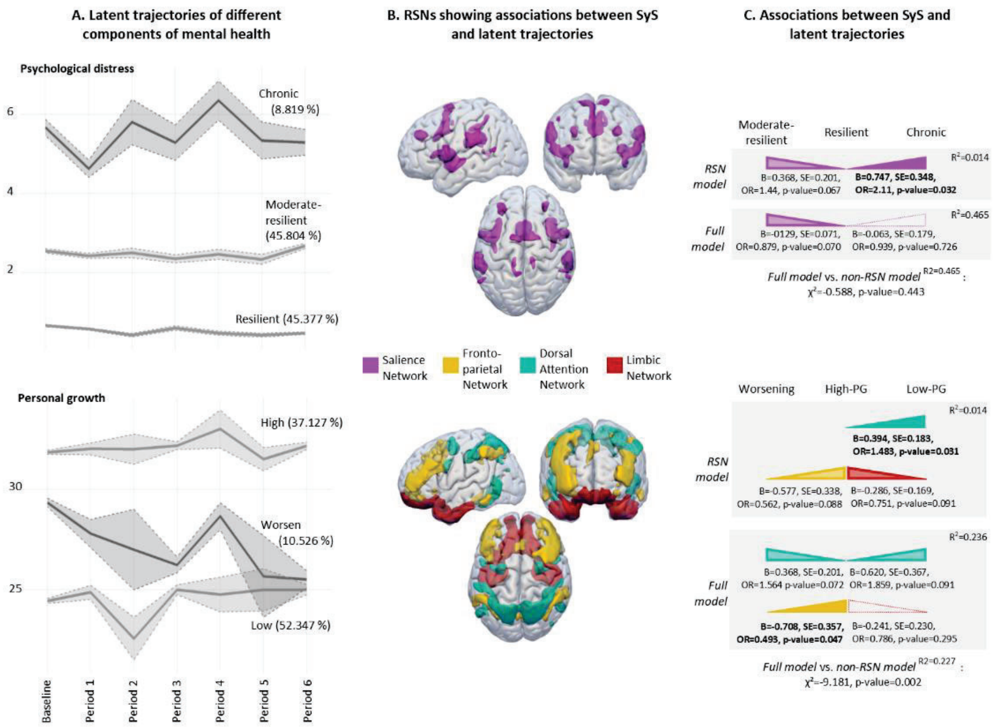

Figure 1. Associations between RSNs SyS and latent trajectories of different components of mental health. Panel A depicts the latent trajectories elucidated by Bayes-Marin et al. (2023)[3] subset to the sample of this study. Note that despite three components of mental health were analyzed(i.e., psychological distress, personal growth, and loneliness), only those significant regarding the RSN analyses are displayed. Panel B shows a three-dimensional representation of the brain regions comprising the four particular RSN networks identified in the results section of this study(i.e., Salience, Fronto-Parietal, Dorsal Attention, and Limbic). Panel C describes the associations between SyS values from the networks in B, and the outcomes in A, as estimated by multinomiallogistic regressions. Colored triangles indicate the direction of the association between the outcome and RSN SyS values with the same color in B. As Resilient and High-PG groups were fixated as references in the logistic models, then triangles indicate whether there is a higher or lower probability to belonging to the reference group when SyS increases. Fully colored trianglesindicate high significance (i.e., p-value<0.05), those with thick borders but less opacity indicate marginal effects (i.e., p-value<0.1), and empty triangles denote effects that were significant in the *RSN model* that were lost in the *Full model*. Finally, results from the comparison between *Full models* and *non-RSN models* are included. This comparison is performed by likelihood ratio tests, with negative X^2 values denoting that the *Full model* is significantly better than the *non- RSN model*. Abbreviations: RSN, resting state network; OR, odd ratio; SE, standard error; SyS, system segregation; PG, personal growth.

connectivity, commonly linked to cognitive flexibility and control processes [9], may reveal the importance of cognitive aspects within this component of mental health. Finally, having not found any RSN-SyS associated with social well- being may be related to the fact that, through loneliness we measured the individual's subjective perception but not the direct engagement in social contacts, and/or that paradoxical effects on loneliness during the outbreak were previously reported [10].

Overall, our findings suggest that assessing brain network integration versus segregation aids in predicting individual resilience and vulnerability across mental health dimensions. Brain connectivity measures allow early identification of at-risk individuals, enabling the design and evaluation of personalized preventive strategies.

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Study 3

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.

Cabello-Toscano M, Vaqué-Alcázar L, Cattaneo G, Solana-Sánchez J, Bayes-Marin I, Abellaneda-Pérez K, Macià-Bros D, Mulet-Pons L, Portellano-Ortiz C, Fullana MA, Oleaga L, González S, Bargalló N, Tormos JM, Pascual-Leone A, Bartrés-Faz D.

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Archival Report

Biological Psychiatry: CNNI

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 $\pm$ 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 $\pm$ 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 ± 2.18 months) and 5 assessments separated on average by 3.04 ± 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).

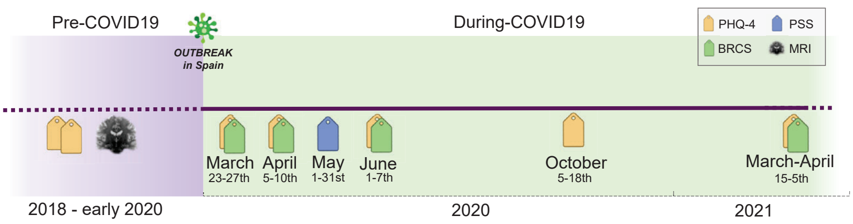

Figure 1. Timeline study design showing baseline (i.e., pre-pandemic) and during-pandemic points of acquisition for the main outcome (i.e., Patient Health Questionnaire-4 [PHQ-4]), magnetic resonance imaging (MRI), and psychological factors (perceived stress measured by the Perceived Stress Scale [PSS] 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 = $[x - \text{mean}]/\text{SD}$). 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

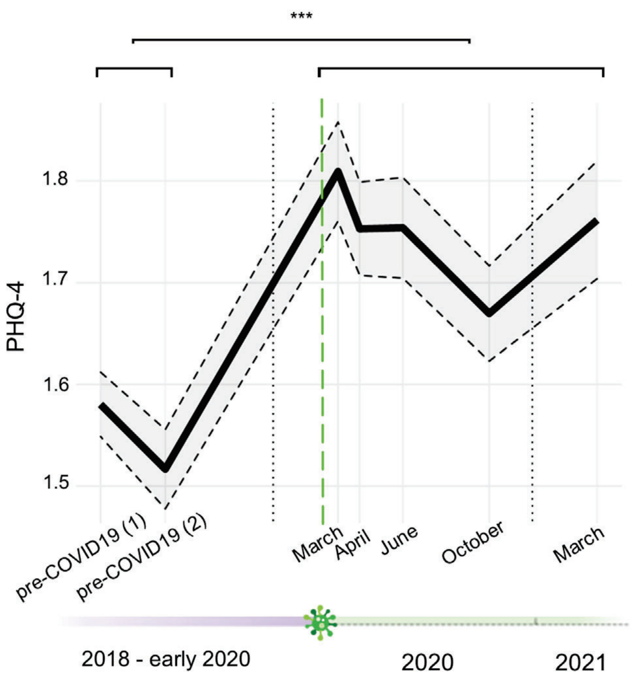

Figure 2. Average values of the Patient Health Questionnaire-4 (PHQ-4) along time point measurements for the whole sample (N = 2023) showing ratings increases. Shadow areas above and below the average PHQ-4 line (i.e., thick line) represent standard errors. Abscissa axes indicate the timeline of observations 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).

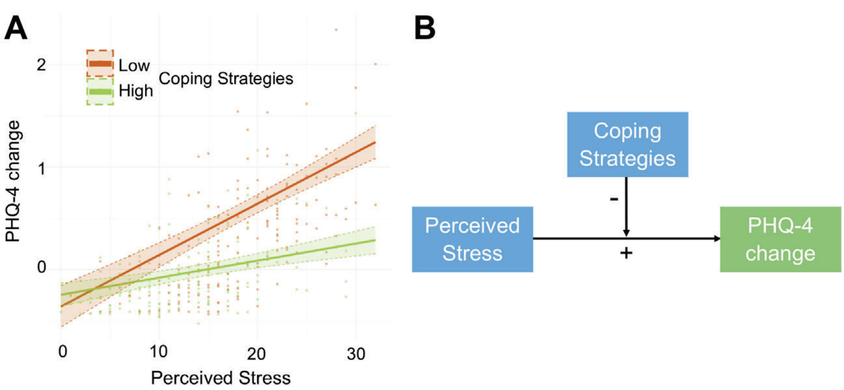

Figure 3. Plots illustrating the associations found between the studied psychological factors (i.e., coping strategies and perceived stress) and psychological distress worsening (i.e., Patient Health Questionnaire-4 [PHQ-4] change). **(A)** Scatter and lines plot showing the association between PHQ-4 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.

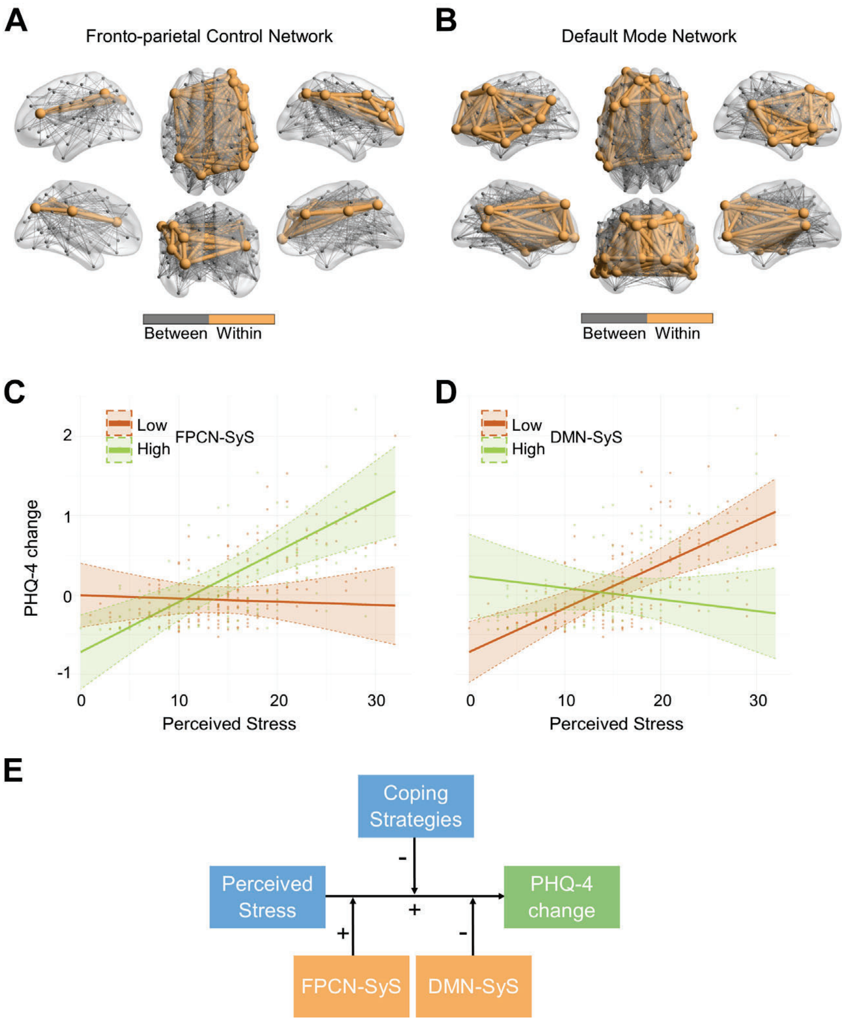

Figure 4. Representation of the modulatory effect of frontoparietal control network (FPCN) and default mode network (DMN) system segregation (SyS) values on the association between perceived stress and Patient Health Questionnaire-4 (PHQ-4) change. **(A, B)** Graphs representing within- and between-network 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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SUPPLEMENTAL INFORMATION

Functional Brain Connectivity Prior to the COVID-19 Outbreak Moderates the Effects of Coping and Perceived Stress on Mental Health Changes

Cabello-Toscano *et al.*

SUPPLEMENTAL METHODS AND MATERIALS

Questionnaires

Patient Health Questionnaire-4 (PHQ-4) is a questionnaire answered on 4 items Likert-type scale combining a two-item measure consisting of core criteria for depression (PHQ-2), as well as a two-item measure for anxiety (GAD-2), both of which have independently been shown to be good brief screening tools.

The Brief Resilient Coping Scale (BRCS) incorporates 4 items, being ‘I look for creative ways to alter difficult situations’; ‘Regardless of what happens to me, I believe I can control my reaction to it’; ‘I believe I can grow in positive ways by dealing with difficult situations’ and ‘I actively look for ways to replace the losses I encounter in life’. The subjects are required to provide a response to each item using a 5 Likert-type scale, ranging from a score of 1 and indicating that the item ‘does not describe me at all’, and a score of 5, stating that the item ‘describes me very well’.

MRI acquisition parameters

Magnetic resonance imaging (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*. MRI session included accelerated multiband sequences adapted from the Human Connectome Project and provided by the Center of Magnetic Resonance Research at the University of Minnesota. For all participants, a high-resolution T1-weighted structural image was obtained with a magnetization prepared rapid acquisition gradient-echo (MPRAGE) three-dimensional protocol and a total of 208 contiguous axial slices obtained in ascending fashion [repetition time (TR)=2400 ms, echo time (TE)=2.22 ms, inversion time=1000 ms, flip angle=8º, field of view (FOV)=256 mm and 0.8 mm isotropic voxel]. Additionally, a high-resolution 3-

dimensional SPACE T2 weighted acquisition was undertaken [TR=3200ms, TE=563ms, flip angle=120º, 0.8 mm isotropic voxel, FOV=256mm]. In the same session, they also underwent resting-state functional MRI (rs-fMRI) multiband (anterior-posterior phase-encoding; acceleration factor=8) interleaved acquisitions [T2*weighted EPI scans, TR=800 ms, TE=37 ms, 750 volumes, 72 slices, slice thickness=2 mm, FOV=208 mm]. All the MRI images were examined by a senior neuroradiologist (N.B) in order to detect any clinically significant pathology (none found). Then, all the acquisitions were visually inspected before analysis (M.C.-T. and L.M.-P.) to ensure that they did not contain MRI artifacts or excessive motion.

MRI preprocessing

The rs-fMRI preprocessing pipeline comprised spatial standardization and nuisance correction by making use of functions from FMRIB Software Library (FSL; version 5.0.11; https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/), FreeSurfer (version 6.0; https://surfer.nmr.mgh.harvard.edu) and Statistical Parametric Mapping (SPM12; https://www.fil.ion.ucl.ac.uk/spm/). To start with, the first 10 scans were removed to ensure magnetization equilibrium. After that, all images were field inhomogeneity corrected (*FSL topup tool*), all scans realigned to a reference image (*FSL MCFLIRT*) and then standardized into native T1-weighted space (*SPM Coregister*). Finally, normalization (*SPM Normalize*) of all fMRI images to Montreal Neuroscience Institute (MNI152) standard space was performed to ensure among-subjects comparability. As for nuisance correction, different components were defined and manually removed from the rs-fMRI images by the "*fsl_regfilt*" tool implemented in FSL. These components correspond to (i) motion regressors of rotation, translation and their derivatives, as estimated during scans' realignment, (ii) a drift estimated by a discrete cosine transform (DCT) as a low-pass frequency filter (<0.01), and (iii) signals from white matter (WM) and cerebrospinal fluid (CSF). In order to extract these, CSF and WM masks were obtained from automatic subcortical segmentation of brain volume, based upon the existence of an atlas containing probabilistic information on the location of structures (1). This step was part of the FreeSurfer *'recon-all'* processing stream, which was run with default parameters, except for the addition of the T2 flag for the improvement of pial surfaces reconstruction. That is to say, both T1- and T2-weighted images were used for processing anatomical information.

As head movement may affect rs-fMRI results (2–5), in-scanner head motion was considered. In this study, the frame-wise displacement (FWD) mean was calculated for every subject. FWD was computed as in (2), using the vectors of rotation and translation estimated during scans' realignment as part of the preprocessing pipeline.

System segregation (SyS) metric

After preprocessing the MRI data, blood-oxygen-level-dependent signal was extracted and averaged across all voxels falling within each region of interest (ROI). Then, ROI-to-ROI rs-FCs were computed as Pearson correlations and subsequently Fisher-z transformed. Negative values were set to zero and autocorrelations were not considered for the calculation of system segregation (SyS), a versatile graph theory-based measure of functional brain network integrity, as expressed in:

$$SyS_{net} = \frac{W_{net} - B_{net}}{W_{net}},$$

W_{net} was computed as the average rs-FC connecting all the nodes within the same network, while B_{net} was computed as the average rs-FC connecting nodes of a network to nodes from the rest of the cortex. SyS_{net} captures the balance between within-network (W_{net}) and between-networks (B_{net}) rs-FC.

SUPPLEMENTAL RESULTS

BBHI vs whole sample

In order to test whether the studied sample was different from the general BBHI cohort, differences in age, sex and pre-pandemic anxiety and depression symptoms (i.e., pre-pandemic PHQ-4) were evaluated. In consequence, it was found that those within the BBHI cohort who did not participate in the COVID-19 follow-up surveys had significantly higher pre-pandemic anxiety and depression symptoms (whole sample < out of the sample: $t=5.276$; $p<0.001$). In contrast, there were no significant differences in terms of age ($t=0.074$; $p=0.941$) nor sex ($\chi^2=0.268$; $p=0.605$) between the groups.

Anxiety and depressive symptoms change: age and sex effects [for the MRI-available sub-sample]

Considering Patient Health Questionnaire-4 (PHQ-4) change within the MRI-available sub-sample (N=433), we found that this variable was not associated with age ($\beta=-0.009$, t=-1.460, p=0.145), but with educational level (β=0.105, t=2.816, p=0.005). This model also revealed that females had a greater psychological distress worsening (i.e., higher PHQ-4 change) than male participants (β=0.073, t=1.986, p=0.048). Additionally, in a separate model we found that age and sex were independently associated to our outcome (age * sex interaction; β=-0.004, t=-0.681, p=0.496). Finally, only considering baseline data, we found younger individuals (age; β =-0.031, t=-3.127, p=0.002) were those with higher pre-pandemic PHQ-4 values, while females and males had similar baseline PHQ-4 values (females > males; β=0.150, t=1.182, p=0.238).

Sociodemographic effects on perceived stress and coping strategies

For the whole sample of participants, two linear regressions showed that perceived stress was associated to age (β=-0.050, t=-2.177, p=0.030), but not to sex (females > males, β=0.571, t=1.732, p=0.084) neither to educational level (β=-1.034, t=-3.075, p=0.002), while coping strategies were not associated to any of the sociodemographic variables we focus on here (age: β=-0.005, t=-0.682, p=0.495; educational level, β=0.114, t=1.279, p=0.201; sex: females > males, β=0.010, t=0.106, p=0.915).

For the MRI-available sub-sample, two linear regressions showed that perceived stress was not associated to any of the sociodemographic factors we focus on here (educational level, β=-0.128, t=-0.206, p=0.837; sex, females > males: β=-0.632, t=-1.042, p=0.298; age: β=-0.006, t=-0.127, p=0.899). Furthermore, coping strategies was only predicted by sex (females > males: β=0.451, t=2.425, p=0.016) but not by any of the others (age: β=-0.006, t=-0.416, p=0.678; educational level: β=0.001, t=0.711, p=0.004).

Effects of perceived stress and coping strategies on anxiety and depressive symptoms change [for the MRI-available sub-sample]

The first model showed a negative association between coping strategies and PHQ-4 change (β=-0.058, t=-6.258, p< 0.001) and the second model showed a positive association between perceived stress and PHQ-4 change (β=0.030, t=8.729, p< 0.001). Finally, the third model revealed that the change was significantly described by an interaction between perceived stress and coping strategies (β=-0.003, t=-2.167, p=0.031). Importantly, in this model, the direct effect of perceived stress on PHQ-4 was reduced but maintained (β=0.073, t=3.314, p< 0.001), while the direct effect of coping strategies on anxiety and depression change disappeared (β=0.007, t=0.291, p=0.771).

SUPPLEMENTAL FIGURES

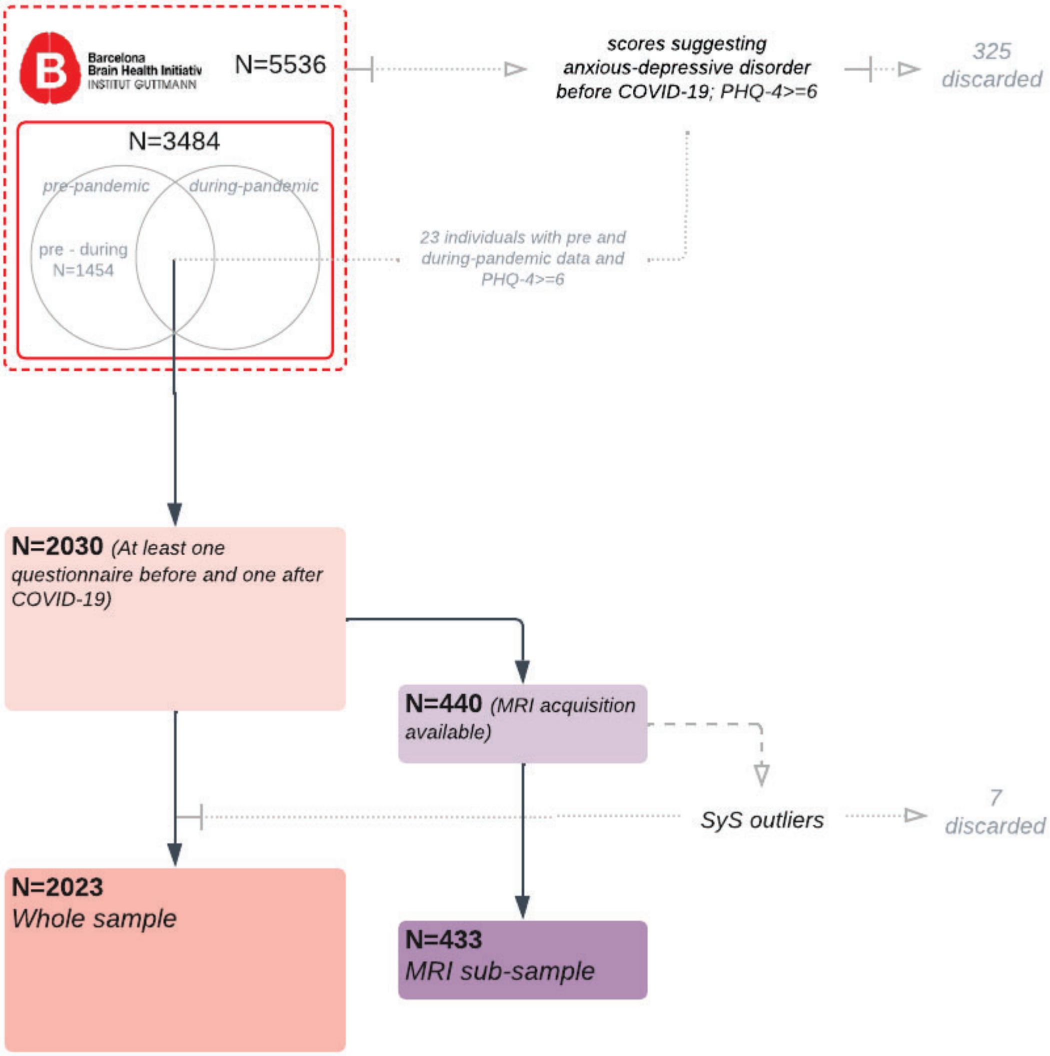


Figure S1. Flowchart illustrating BBHI cohort (in red), the whole sample included in the present article (in salmon) and MRI sub-sample (in purple) population sizes. From the entire BBHI cohort (5536 participants), 325 individuals were discarded according to inclusion criteria, to ensure that a healthy population (i.e., free of anxiety or depression clinical diagnosis) was studied. This removal, along with the availability of PHQ-4 scores, led to a cohort of 3484 individuals. Then, only those who had available data for pre- and during- pandemic follow-up surveys were considered, leading to an N=2030 sample. Note that, before the removal of individuals with “scores suggesting anxious-depressive disorders before COVID-19”, only 23 had available during-pandemic data and then were discarded from participating in the study. Regarding neuroimaging data, a sub-sample of N=440 comprised those who fulfilled inclusion criteria and underwent MRI acquisition before the pandemic outbreak. Finally, seven participants were discarded since they presented outlier values of SyS in at least one of the seven studied RSNs, which led to a final whole sample of 2023 individuals, and an MRI sub-sample of 433 individuals. *Abbreviations: BBHI, Barcelona Brain Health Initiative; Patient Health Questionnaire-4, PHQ-4; MRI, Magnetic Resonance Imaging; SyS, System Segregation; RSN, Resting State Networks.*

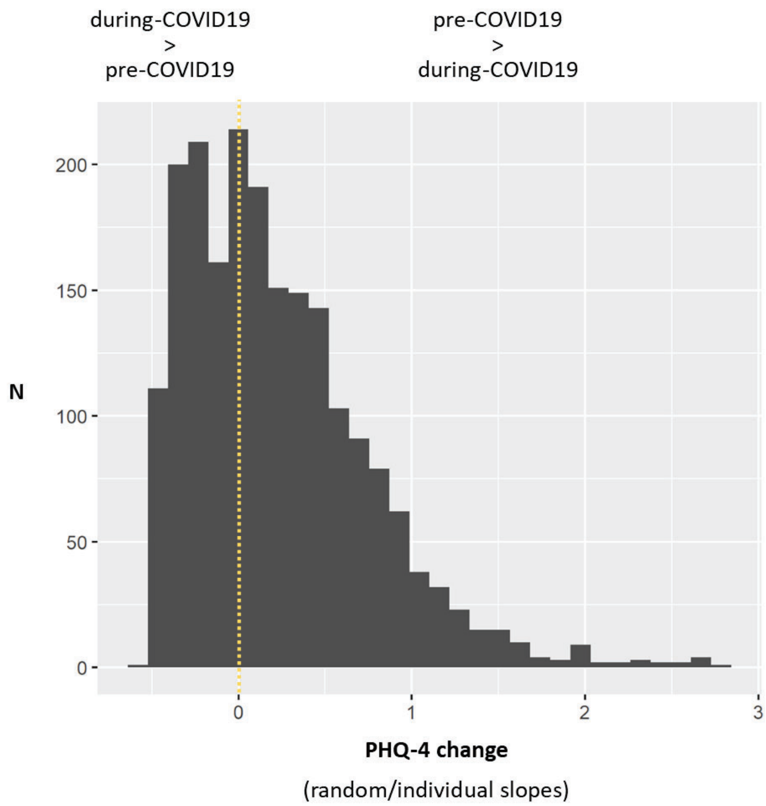


Figure S2. Estimated PHQ-4 change variable. Histogram of the variable PHQ-4 change, which was estimated by fitting a linear mixed effects model of the whole sample of participants (N=2023) with random slope and random intercept at the individual level. Then, each individual was assigned with a different slope according to the estimated change on PHQ-4 between during- and pre-pandemic observations. Lower than zero values of PHQ-4 change represent that PHQ-4 levels were higher along during-pandemic observations than along pre-pandemic, and vice versa. *Abbreviations: Patient Health Questionnaire-4, PHQ-4.*

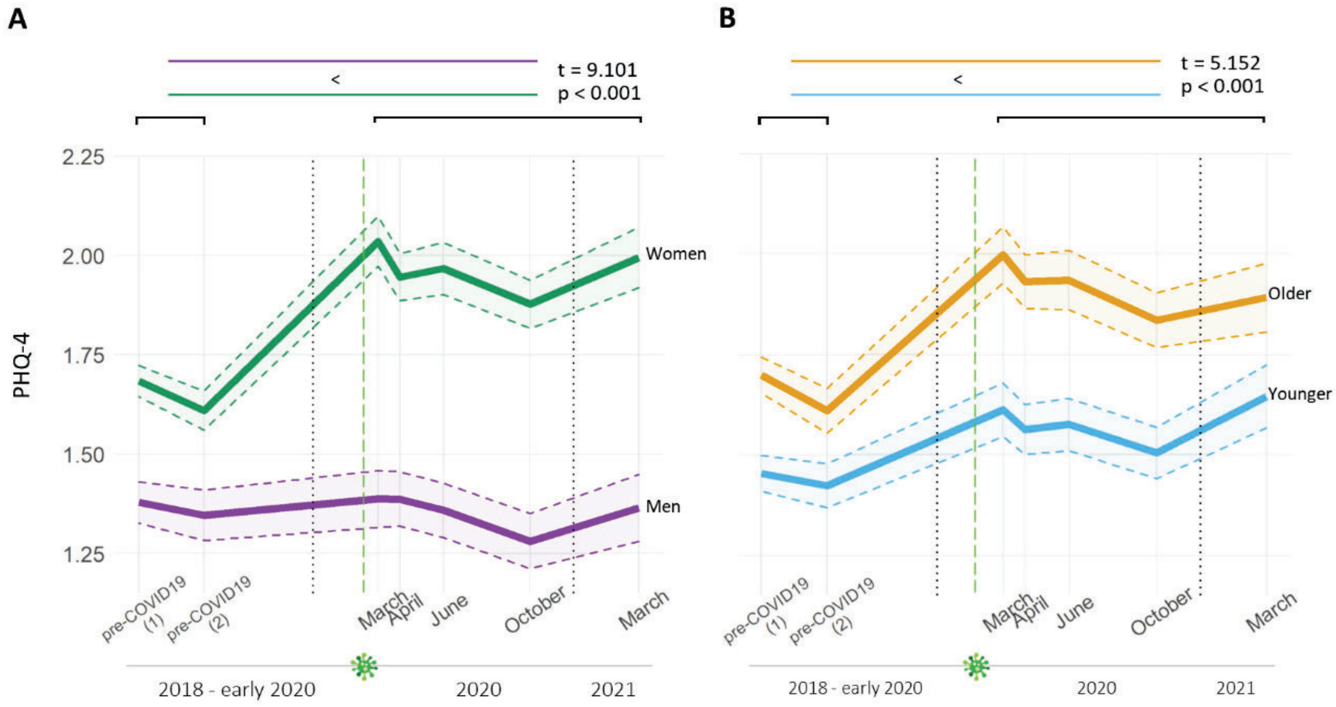
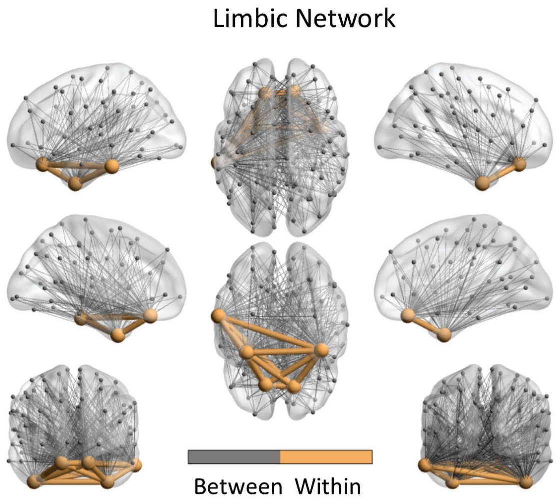


Figure S3. PHQ-4 according to age and sex groups. Abscissa axes indicated the timeline of observations in the study, which are grouped within pre-pandemic (i.e., from 2018 to early 2020) and during-pandemic observations (i.e., those from March 2020 to March 2021). Green line indicates the beginning of the lock-down (14th March 2020 in Spain) and separates pre- and during-pandemic observations. Black vertical dashed lines delimitate 2020 and 2021. Shadow areas above and below average PHQ-4 lines (i.e., thick lines) represent standard errors. Finally, in the upper part of the figure, the difference on PHQ-4 change between groups is illustrated and quantified by a t-student test. (A) Average values of PHQ-4 along time-point measurements for the whole sample (N=2023), as split by (A) two age categories: younger (below mean; i.e., < 54 years) in blue, and older (above or equals to mean; i.e., ≥ 54 years) individuals in yellow, and (B) as split by sex: females in green and males in purple. Note that these age-related categories were created with visualization purposes and were not included in any statistical analysis in the main manuscript. *Abbreviations: Patient Health Questionnaire-4, PHQ-4.*

A



B

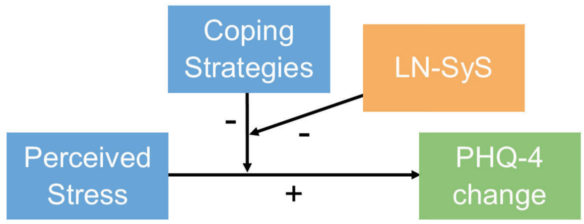


Figure S4. Plots illustrating trend towards significance effect of limbic network SyS (LN-SyS) on the interaction between perceived stress and coping strategies to describe PHQ-4 change (β=-0.024, t=-1.727, p=0.085). (A) Graph representing within and between network connectivity taking part in the computation of LN-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 LN, while those in gray refer to outside network ROIs and the connectivity between them and the LN. This graph was created with the BrainNet Viewer (http://www.nitrc.org/projects/bnv/; Xia et al., 2013). (B) Schema of the interaction between coping strategies and the association between perceived stress and psychological distress worsening, as regulated by LN-SyS. *Abbreviations: LN, limbic network, LN; SyS, system segregation; PHQ-4, Patient Health Questionnaire-4. Anxiety and depression symptoms change as a function of limbic network (LN) status and psychological factors.*

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CHAPTER 4

Global summary of the results

Barcelona, 21st September 2023

Dr. David Bartrés Faz, professor at the University of Barcelona and director of this Doctoral Thesis certify that it is the result of three studies, of which two have been published as peer-reviewed articles and one manuscript submitted for publication. As regard to authorship, the Ph.D. candidate was first author of two of the studies, and second author with equal contribution in the other one. More precisely:

Study 1 was published as a peer-reviewed article and the Ph.D. candidate was second author with equal contribution:

> Bayes-Marin I, **Cabello-Toscano M**, Cattaneo G, Solana-Sánchez J, Fernández D, Portellano-Ortiz C, Tormos JM, Pascual-Leone A, Bartrés-Faz D. COVID-19 after two years: trajectories of different components of mental health in the Spanish population. Epidemiol Psychiatr Sci. 2023 Apr 17;32:e19. [Impact Factor (IF): 7.818 - Q1]

Study 2 was submitted for publication as a research letter, where the Ph.D. candidate was first author:

> **Cabello-Toscano M**, Vaqué-Alcázar L, Bayes-Marin I, Cattaneo G, Solana-Sánchez J, Mulet-Pons L, Bargalló N, Tormos JM, Pascual-Leone A, Bartrés-Faz D. Functional brain connectivity prior to the COVID-19 outbreak predicts mental health trajectories during two years of pandemic.

Study 3 was published as a peer-reviewed article and the Ph.D. candidate was first author:

> **Cabello-Toscano M**, Vaqué-Alcázar L, Cattaneo G, Solana-Sánchez J, Bayes-Marin I, Abellaneda-Pérez K, Macià-Bros D, Mulet-Pons L, Portellano-Ortiz C, Fullana MA, Oleaga L, González S, Bargalló N, Tormos JM, Pascual-Leone A, Bartrés-Faz D. 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. Biol Psychiatry Cogn Neurosci Neuroimaging. 2023 Feb; 8(2):200-209. [IF: 6.050 - Q1]

Finally, none of the co-authors utilized this work for the realization of any other Doctoral Thesis.

Signatures,

DAVID BARTRES FAZ - DNI 34757964 L Digitally signed by DAVID BARTRES FAZ - DNI 34757964L Date: 2023.09.21 15:04:19 +02'00'	VAQUE ALCAZA R, LIDIA (FIRMA) Digitally signed by VAQUE ALCAZAR, LIDIA (FIRMA) Date: 2023.09.21 14:25:09 +02'00'
Dr. David Bartrés Faz	Dr. Lídia Vaqué Alcázar

SUMMARY OF RESULTS

Study 1:

Leveraging data from up to 5,535 healthy middle-aged individuals, during two years of the COVID-19 pandemic and two years before the outbreak, Growth Mixture Models (GMM) were fitted to classify individuals into different trajectories for three mental health-related outcomes (psychological distress, personal growth, and loneliness). Trajectories of change were elucidated for each of the three components of mental health (i.e., emotional, social, and psychological). According to these, we differentiated two major trends in our sample. While a large proportion of participants was classified into 'resilient' trajectories, less dense trajectory groups experienced 'chronic-worsening' trends. Multinomial logistic regressions were fitted to characterize these groups as regards predisposition factors. The three components were associated with cognitive function, general health, and coping strategies. Psychological well-being trajectory was predicted by age, education, personality traits of being open to experience, environmental mastery, and having positive relations with others. Emotional well-being trajectory was predicted by age, sex, sleeping problems, smoking, perceived stress, and emotional stability. Finally, social well-being trajectory was predicted by whether the individual lives alone or not, sex, perceived stress, emotional stability, having positive relations with others, and engagement with living responses.

Study 2:

Following the results in study 1, a sub-sample of 702 individuals with resting state fMRI data available was analyzed. Particularly, multinomial logistic regressions were fitted to study the predictability of the trajectories of mental well-being during the pandemic from basal RSN-SyS data (i.e., the status of FC integration-segregation). It was found that psychological well-being trajectory was predicted by FPN-SyS, although this association was lost when the predictors in study 1 were included in the model. On the contrary, emotional well-being trajectory was predicted by SN and DMN-SyS, effects that did not disappear in the presence of sociodemographic, psychological, and other lifestyle factors. Finally, the social well-being trajectory was not predicted by any measure of RSN-SyS.

Study 3:

Finally, we wanted to focus on the study of anxious-depressive symptoms associated with the situation derived by the COVID-19 during the first year of the pandemic (understood as the most extreme period of social restriction). Leveraging data from 2,023 healthy middle-aged individuals, during one year of the pandemic and two years before the outbreak, a linear mixed model was fitted to assess individual change (i.e., estimating random slopes). The results showed a small but significant increase in symptoms (mainly at a subclinical level) that was predicted by sex, age, coping strategies, and perceived stress. Importantly, coping strategies and perceived stress interacted to predict psychological distress change in a way in which individuals with more coping strategies did not experience a worsening even when perceiving high levels of stress. This was replicated in a sub-sample of 433 individuals that had rs-fMRI data available. Analyses on this sub-sample showed that while psychological distress change was not directly related to any RSN-SyS basal measure, DMN and FPN-SyS moderated the association between perceived stress and the outcome, in an analogous way to coping strategies. Additionally, coping strategies and perceived stress were not predicted by any RSN-SyS variable either.

CHAPTER 5

General discussion

There are several points of special interest for discussion in the context of this Doctoral Thesis. First, the variability in the stress response of the different components of mental health allows us to discern between resilient and vulnerable individuals. Secondly, the importance of studying the different components of mental health separately. In third place, the different predisposing factors that predicted resilient vs. vulnerable responses regarding different components of mental health. Among these predisposing elements, we found different factors of risk and protection regarding sociodemographic, psychological characteristics, lifestyles, and brain mechanisms. Figure 5.1 integrates protection and risk factors for the three components of mental health as suggested by the results in studies 1, 2, and 3. Due to the novelty in the field of the results regarding brain mechanisms, an important part of this discussion is devoted to commenting on these findings and their interpretation. Finally, all conclusions derived from this work must be situated within the context of the COVID-19 pandemic as a threat to mental health, but they hold value beyond that specific context. Interventions aimed at promoting resilience in future similar global emergency situations, as well as in more general contexts of stress, can derive benefit from these conclusions.

1. The variability in the response to pandemic stressors

The first specific goal of this Doctoral Thesis was to capture the variability in the response to pandemic stressors in order to, afterwards, study what is associated with the observed differences. Two main approaches were adopted for this purpose, by which longitudinal data was analyzed. Both approaches accounted for longitudinal change as the contrast between observations belonging to pre- and during-pandemic periods and are based on the use of multilevel regression analyses (Herle et al., 2020; Goldstein, 2002). However, the models estimated followed slightly different strategies. While study 3 was oriented to quantify mental health changes at the individual level (i.e., individual slopes from mixed effects models), studies 1 and 2 focused on the change itself to define groups of similar variation (i.e., trajectories estimated by GMM; Herle et al., 2020). Most of the literature regarding longitudinal analyses in the context of the COVID-19 pandemic followed methodologies in the line of discovering trajectories (i.e., as in studies 1 and 2). However, the findings in the literature are heterogeneous and occasionally contradictory (Shevlin et al., 2023), crucially lacking from pre-pandemic data which severely hampers the interpretation of the discoveries.

At the individual level, our findings showed significant negative changes in the emotional domain, as accounted for by increases in subclinical symptoms of anxiety and depression (study 3). However, during the pandemic only around 10% of people were discovered to have scores higher than the established clinical cut-off points (Kroenke et al., 2009). This result represents lower estimates that are in line with recent reviews (Prati & Mancini, 2021) that range from 20% to 30% (Luo et al., 2020; Salari et al., 2020) and also raises the possibility that there is a significant number of resilient outcomes overall (Chen et al., 2022; Kimhi et al., 2021; Gambin et al., 2021). Then, the individual effect associated with a worsening of psychological distress was consistent but small, which needs to be interpreted alongside the general shape of the elucidated trajectories (study 1), and vice versa. These primarily consisted of flat trends primarily depicting resilient responses, accompanied less frequently by chronic tendencies. This aligns with the idea that the general population is expected to be largely resilient in front of loss or life-threatening events (Bonanno, 2004), and importantly facing the pandemic (Chen & Bonanno, 2020). It also acknowledges arguments against the potential surge in mental illness brought about by the pandemic (i.e., the absence of a 'tsunami' of mental illness, Shevlin et al., 2023). It is possible that, regarding the small number of vulnerable individuals in the studied cohort (i.e., those experiencing a detrimental effect on their emotional well-being) and substantial period of follow-up, the ability of approaches such as GMM to identify such subtle details is limited. Subsequently, employing a complementary approach to quantify individual changes provided us with a deeper understanding.

2. Different components of mental health need to be studied separately

It is well-established that mental health encompasses emotional, psychological, and social aspects of an individual's life (Wren-Lewis & Alexandrova, 2021; Keyes et al., 2020; Keyes et al., 2005). Even so, the study of mental health during the COVID-19 pandemic has been primarily focused on analysing psychological distress as the main indicator of well-being or illness (Pellerin et al., 2022; Saunders et al., 2022; Ahrens et al., 2021; Batterham et al., 2021; Ellwardt & Präg, 2021; Joshi et al., 2021; Pierce et al., 2021; Shilton et al., 2021). This is not a solitary occurrence, but it is also very frequent in the literature on psychological resilience, where the primary outcomes are oriented toward PTSD symptoms (e.g., Bolsinger et al., 2018) and stress-related disorders (e.g., Goldfarb et al., 2020). In this vein, the second specific objective of this Doctoral Thesis was to explore the trio of aspects that constitute mental well-being, what is novel within the field of mental health studies in the COVID-19 context, and also within the field of psychological resilience.

Our findings in study 1 precisely reinforce the need for including a multi-domain perspective of mental health. Three different trajectories were consistently elucidated for each of the three components. Although these were essentially resilient or chronic trends, except for a section of the sample experiencing a decrease in their scores on personal growth (i.e., the psychological component), individuals generally followed non-matching trajectories for the different components. In other words, being classified as with higher levels of personal growth did not necessarily mean belonging to the emotionally or socially resilient group. In fact, we discovered that the percentage of shared characteristics among resilient individuals was higher than 50% solely in the case of psychological distress and loneliness. Conversely, the overlap was only 26.29% between personal growth and loneliness. The most significant similarity, observed between loneliness and emotional distress, aligns with findings in existing literature where these two variables have consistently demonstrated a connection (Bu et al., 2020; Ahrens et al., 2021). Additionally, each outcome displayed varying sensitivity to different phases of the pandemic. Another piece of evidence supporting this notion is the fact that each outcome was predicted by several factors of risk and protection (in studies 1, 2, and 3), some shared but others component-specific, and the interaction between some of them (in study 3), covering sociodemographic, psychological and neural factors (Feder et al., 2019). The following sections are devoted to discussing the shared and specific predisposing factors of the three components of mental health in the context of the COVID-19 pandemic and psychological resilience, as part of what we aimed with the second objective of this Doctoral Thesis.

3. Shared predisposing factors among components of mental health

Notably, coping strategies, cognitive function, and general health were shared protective factors for the three components. The connection between physical and mental health status has been frequently documented in the literature, implying a mutual influence (Druss and Walker, 2011). Similarly, the presence of anxiety and depressive symptoms has been acknowledged as a potential threat to cognitive decline (Zaninotto et al., 2018; Chodosh et al., 2010). As regards the findings in the context of psychological well-being, a study by Bartrés-

Faz et al. (2018) described the mediation role of psychological factors such as purpose in life and sense of coherence (in strong relation with personal growth), in the association between cognitive reserve and cognition (Bartrés-Faz et al., 2018). Considering coping strategies, these have been frequently described as conditioned by cognitive function, in line with the results in this thesis, essential for psychological resilience (Lazarus & Folkman, 1991).

Other factors were shared for pairs of components. Emotional and social resilience vs. vulnerability shared the most predisposition factors: emotional stability, perceived stress, and sex. This aligns with the fact that resilient/vulnerable trajectories in studies 1 and 2 for these two components showed the highest overlap of individuals. Both personality traits, emotional stability, as a protective factor, and subjective measure of perceived stress, as a risk factor, were found to be associated with worse emotional well-being pre- and during- the pandemic (i.e.,

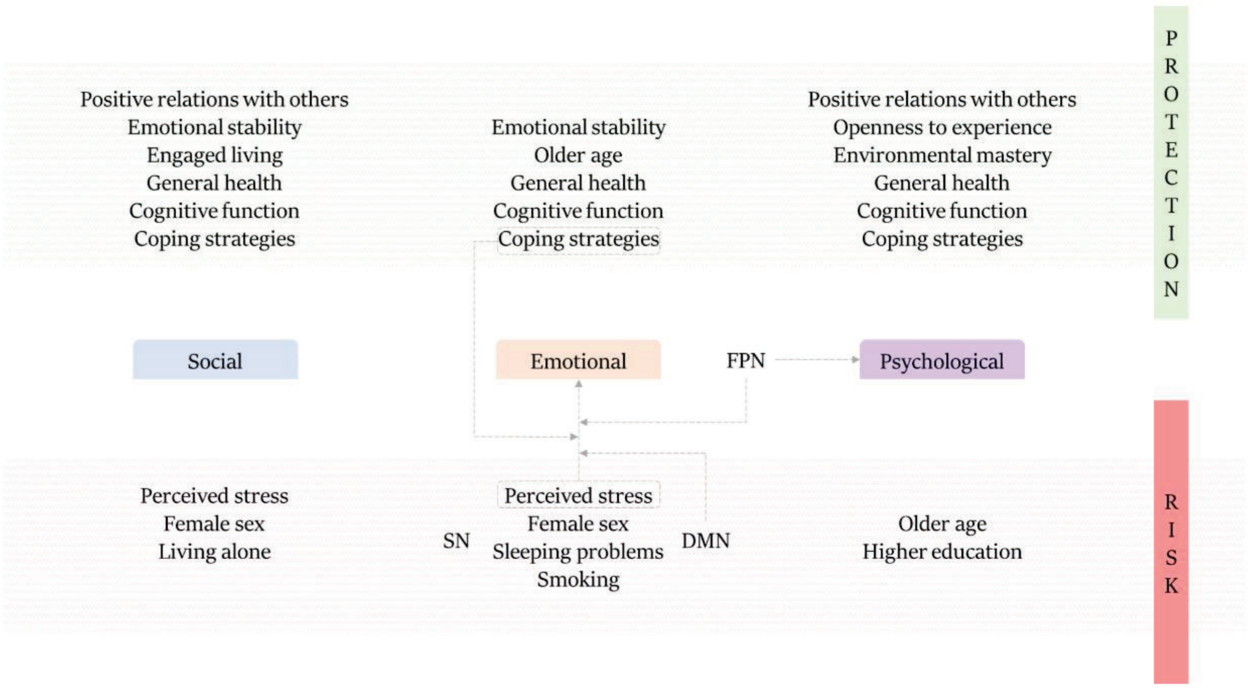

Figure 10. Summary of results regarding protective and risk factors for the three components of mental health as derived by the three studies derived from this Doctoral Thesis.

chronic trajectories; Saunders et al., 2022; Ahrens et al., 2021). As regards sex, in our sample female population represented a higher probability of being at risk (study 1) and accordingly experienced a greater increase in anxious-depressive symptomatology associated with the beginning of the outbreak (study 3), matching with multiple articles in the context of the pandemic (Saunders et al., 2022; Pierce et al., 2021; Shilton et al., 2021). In fact, there is a large literature about the prevalence of depression being much greater in women than in men, also outside the context of the pandemic (Kuehner, 2017). The gender gap in depression may be explained by a complex combination of psychological and biological factors with a strong conditioning of environmental influences (e.g., societal structural gender inequities or higher exposure to sex-related violence; Kuehner, 2017). Accordingly, there are also indicators of a gender gap regarding loneliness, which could have widened during the pandemic (Lepinteur et al., 2022) but have been reported likewise in general contexts (Beutel et al., 2017).

In another vein, age was a predisposing factor for the emotional and psychological components. Controversially, older age was found to be a protective factor for depression and anxiety (studies 1 and 3), but a risk factor for the psychological component (study 1), as those experiencing a longitudinal decrease in their personal growth scores (i.e., worsening), were also the older ones in the sample. Many studies found younger individuals are more vulnerable in the face of the pandemic (Saunders et al., 2022; Ellwardt & Präg, 2021; Pierce et al., 2021; Shilton et al., 2021). However, our results and the conclusions of a review focusing on how age influences a shift in mental health during the pandemic (i.e., Lebrasseur et al., 2021), suggest that the impact of age might be contingent on contextual variables as well as the particular aspect of mental health being studied.

Additionally, positive relations with others were shared as a protective factor for both loneliness and personal growth (i.e., was a predictor of resilient trajectories). Such aspect as having positive relations with others was assessed by a scale assessing different areas of psychological well-being (Ryff, 1995). Particularly, this sub-scale scores higher when the individual is capable of strong empathy, which facilitates the feeling of being more connected (i.e., less lonely; Beadle et al., 2012).

Finally, emotional, and psychological responses to the pandemic were predicted by the functional balance between integration and segregation of the FPN at rest (i.e., FPN-SyS). Similarly to age, lower FPN-SyS (i.e., lower segregation and/or higher integration of the network) could be interpreted as a factor of protection in the emotional domain (study 3), but as a factor of risk for the psychological component (study 2). Particularly, in study 3 we found that lower FPN-SyS was characteristic of individuals who underwent small to no-worsening in anxious-depressive symptomatology associated with the pandemic outbreak, even when they reported experiencing high levels of stress. Thereby, FPN-SyS seemed to protect the emotional well-being of our sample by reducing the risk that implied perceiving the pandemic as stressful. This could be comparable to the mechanism described for coping strategies in the same study. Furthermore, we found in study 2 that the group experiencing a decrease in personal growth (i.e., psychological worsening, therefore a more vulnerable group) was more likely to have lower FPN-SyS. Reiterating the previous argument, predisposing factors of resilience and vulnerability may depend on the particular aspect of mental health being studied. Either protection or risk by higher SyS, this network has been widely associated with psychological resilience (Bolsinger et al., 2018; Holz et al., 2020), and the response to acute stress (van Oort et al., 2017).

Altogether, these predisposition factors represent essential pathways for the implementation of strategies that promote resilience in mental health, especially for individuals at risk in multiple aspects (emotional, psychological, and social) at a time, and personalized for those being at risk in particular domains. Furthermore, they contribute to the understanding of the relationship between the separate components of mental well-being.

4. Specific predisposing factors of mental health components

Apart from those factors that were found to be shared by two or three of the components, there were specific aspects that were related to only one of these in a particular component, again reinforcing the need for considering them separately.

Loneliness was predicted by engagement with living and living alone, as factors of protection and risk respectively. It is to be expected that living alone may constitute a factor of risk for experiencing loneliness, which has been widely confirmed by studies such as the one by Beutel et al. (2017). Here, data from around fifteen thousand individuals confirmed that living alone, without a partner, or, without children, among other factors, was associated with higher levels of subjective loneliness (Beutel et al., 2017). Nonetheless, an engaged response in life may overcome the negative impact of living alone or any other form of social restriction (such as the ones imposed to control the spread of a virus during the COVID-19 pandemic). An engaged response is aligned with the idea of mindfully accepting undesired experiences and taking actions, which is opposite to an avoidant coping style and enhances psychological flexibility (Trompetter et al., 2013). In fact, psychological inflexibility and avoidance have been shown to mediate the association between loneliness and perceived stress (Ortega-Jiménez et al., 2021). In a similar vein, previous studies have shown that the associations between gratitude and loneliness were mediated by psychological flexibility and engaged living (e.g., Frinking et al., 2020), both within the sample studied in this thesis and in a separate study conducted outside the context of the pandemic (Bartrés-Faz et al., 2021). During the COVID-19 pandemic, similar findings highlighted the importance of psychological flexibility in mental health (e.g., regarding anxiety and depression; Pellerin et al., 2022). For example, in a population of veterans with substance abuse problems which increased when feeling lonelier, having greater psychological flexibility reduced the negative impact on physical and mental health due to the pandemic (Kelly et al., 2022).

Psychological distress was predicted by sleeping problems, smoking, and connectivity measures of the SN and DMN. Sleep habits and smoking, which may be related to better global health, were still independent significant predictors of emotional trajectories to separate resilient vs. chronic individuals. There is a large literature demonstrating that smoking is associated with poorer mental health and that quitting may reduce symptomatology and risk for future psychopathology (Taylor et al., 2021; Taylor & Munafò, 2019). Additionally, during the pandemic, there were reports of smokers perceiving the infection as riskier for themselves (Loud et al., 2021), which could increase fear of infection and consequently worsen emotional well-being. Sleep also holds significant implications for mental health, exerting notable influence on the operation of the HPA axis and neuroplasticity (Palagini et al., 2022). In fact, numerous articles analyze the links between sleep alterations, such as deprivation or insomnia, and brain connectivity (Zou et al., 2021; Yang et al., 2018; Khazaie et al., 2017), particularly affecting areas associated with psychological resilience (e.g., the mPFC, the DMN or the SN; Bolsinger et al., 2018), with consequences on cognitive function (Chen et al., 2018; Khazaie et al., 2017) and mental health (e.g., depressive symptoms; Sutherland et al., 2022; Khazaie et al., 2017). In line with brain connectivity, the results in studies 2 and 3 described particular associations between psychological distress resilience and segregation-integration baseline status of the DMN, the SN, and the FPN. More details about these findings can be found in the following sections.

5. The interplay between psychological factors and brain mechanisms

As for addressing the fourth specific objective of this Doctoral Thesis, study 3 aimed to analyze the interplay between psychological factors and connectivity status leading to more vulnerable or resilient responses. In particular, the findings underscore the regulatory role of both psychological (i.e., coping strategies) and brain mechanisms (i.e., segregation-integration status) on the negative effects of stress perceived during the pandemic into anxious-depressive symptoms (see Figure 10).

Regarding the psychological mechanisms, within this Doctoral Thesis, it was observed that coping techniques reduced the influence of perceived stress on mental well-being. The findings validate the significance of coping behaviors and emphasize their potential to improve mental health, primarily by lessening the adverse effects of perceived stress (Vannini et al. 2021; Iadipaolo et al., 2018; Minahan et al., 2021; Lazarus & Folkman, 1984).

Concerning the brain mechanisms, as far as our understanding goes, study 3 represents the first occurrence of identifying the modulation in how perceived stress affects anxious and depressive reactions using the baseline balance in connectivity between the FPN and DMN networks. The FPN, more specifically the dorsolateral PFC, has been suggested to orchestrate a regulatory role over other cortical and subcortical regions related to cognitive emotion regulation (Gagnepain et al., 2017; Kohn et al., 2014; Depue et al., 2007). These aspects could thus aid in comprehending the finding of the FPCN's modulatory function in mitigating the detrimental impacts of perceived stress on the manifestation of anxiety and depressive symptoms. More precisely, the results showed that lower SyS (i.e., more integrated, or less segregated network) of the FPN was a factor of protection analogous to the described via of stress-emotion regulation. The DMN showed an opposite regulatory function, with higher values of SyS (i.e., less integrated, or more segregated network) predicting resilient responses even when high levels of perceived stress. This opposition to the effects may be explained by other studies where there were inverse FC changes for the two networks during exposure to sustained stress (van Oort et al., 2017). The DMN may help maintain behavioral homeostasis in response to induced stressors (Veer et al., 2011) and is involved in interindividual variation in stress responsiveness (Zhang et al., 2019).

6. Networks of Resilience: FC segregation-integration as a predictor of resilience

In this Doctoral Thesis, three main networks of resilience have been identified: the DMN, the SN, and the FPN. The literature on psychological resilience has already proposed this triple network model as supporting mental health in the face of stress both at the clinical and subclinical level (van Rooij et al., 2021; Goldfarb et al., 2020; van Oort et al., 2020; Long et al., 2019; Richter et al., 2019; Santarnecchi et al., 2018; Iadipaolo et al., 2018; Gupta et al., 2017; Holz et al., 2016; Sinha et al., 2016; Kong et al., 2015; Dolcos et al., 2015; van der Werff et al., 2013). However, the novelty of our findings lies in the context of the COVID-19 pandemic being used as a framework to induce stress within a large cohort. In addition, we utilized an FC-based approach to assess the balance between the integrity and segregation of key brain networks, which had never been used before in the field. Finally, all analyses within this thesis were data-driven, which prevented our result to have been forced by only analyzing data from those networks that were expected to be associated with the outcomes.

Salience Network

Results in study 2 showed that individuals with lower values of SN-SyS (i.e., less segregated, or more integrated SN) were more likely to depict a resilient trajectory regarding psychological distress during the pandemic. This RSN is activated in response to stimuli and orients attention to external/internal information. When stress is present, it is related to a hypervigilant state for threat detection (Yoon & Weierich, 2016). Particularly, it comprises areas such as the anterior insula, dorsal ACC, amygdala, and temporal poles, along with VS, hypothalamus, thalamus, substantia nigra, midbrain, temporoparietal junction, and precentral gyrus. Numerous articles have found structural and functional brain aspects of these areas to be associated with stress resilience. For example, Kong et al. (2015) found lower regional homogeneity (i.e., spatial coherence in BOLD signal) among individuals with higher trait resilience. Regarding the actual experience of induced acute stress, higher connectivity between SN areas (amygdala, striatum, and insula) and the vmPFC predicted a more resilient response (Sinha et al., 2016). These later findings could be analogous to a reduction in SN segregation (i.e., lower regional homogeneity) and an increase in SN integration (i.e., higher between network connectivity), which is in line with our findings.

However, study 2 also explored whether the predictability of RSN measures remained significant when analyzed in combination with psychological, sociodemographic, and other predisposing factors for resilience vs. vulnerability. In the case of SN and psychological distress, adding non-brain measures to the model eliminated the significance of SN-SyS as a predictor. To fully understand this shift, further analyses would be required. Nonetheless, some hypotheses could be generated from the view of the literature and the results in study 1. One possibility might be that one, or some, of the variables included in the model could present a correlation with SN-SyS, or interact with this measure to predict the outcome. For example, sleep problems have been already described in a previous section as related to FC within areas comprising the SN (e.g., Zou et al., 2021). While other candidates would be perceived stress or coping strategies, these could be discarded by the results in study 3. Neither perceived stress nor coping strategies were directly predicted by the SyS of any RSN. When testing whether there was a modulatory offset of these psychological factors by those brain mechanisms, SN-SyS was not involved in any significant interaction.

Default Mode Network:

Results in study 3, as described in the previous section, indicated a modulatory role of the DMN on how perceived stress affects anxiety and depression increases in front of potential pandemic stressors. Individual anatomic and functional differences within this circuit contribute to individual differences in psychological resilience (Bolsinger et al., 2018). Abnormal DMN functionality (along with FPCN and SN dysfunctions) is characteristic of anxiety and depression disorders (Menon, 2011; Zhang et al., 2020). Results involving the DMN are generally interpreted as reflecting reduced immersion in unpleasant internalized experiences (e.g., a shorter fraction of time in the dynamic state discovered by Iadipaolo et al., 2018) because this network has been linked to self-referential processes (Knyazev, 2012). Those engaging the SN, on the other hand, frequently show a lesser vulnerability to maladaptive saliency processing or negative self-referential thoughts, especially when interacting with the anterior DMN (Iadipaolo et al., 2018).

Fonto-Parietal Network

The FPN was simultaneously associated with psychological and emotional resilience, as indicated by results in studies 2 and 3, respectively. As regards personal growth (i.e., psychological resilience), the findings indicated that baseline FPN-SyS was a very relevant predictor, contributing valuable information to the model consisting of aggregated sociodemographic, psychological, and lifestyle characteristics. Individual differences in personal growth maintenance are believed to reflect the ability to thrive in stressful times by reappraising and attaching worth and purpose to life (Bartrés-Faz et al., 2018). As a result, the connections discovered between personal growth and FPN connectivity, which are often associated with flexibility and control processes (Cole et al., 2013), may highlight the importance of cognitive components within this component of mental health.

On the other hand, FPN-SyS implications on emotional resilience were the result of a modulatory role of this network through the effects of perceived stress on psychological distress (as for DMN-SyS). During the COVID-19 pandemic, we discovered that areas from the FPCN (which substantially overlap with the CEN) could be recognized as significant neurobiological indicators of individual differences in mental health outcomes. This network, which connects the prefrontal dorsolateral and superior parietal cortices, supports executive functions, is essential for optimal social navigation and long-term goal fulfillment (Bettcher et al., 2016), and has been linked to resilience mechanisms (Bolsinger et al., 2018; Holz et al., 2020; McEwen et al., 2013).

Overall, our findings suggest that examining brain network integrity vs. segregation can help predict future individual variations in resilience vs. vulnerability across the different dimensions of mental health. Consideration of connectivity metrics may aid in the early detection of at-risk individuals, allowing for the development of individualized preventive programs. Importantly, the networks are related to emotional regulation, executive control, and cognitive processes (Menon, 2011), and not to sensorial or motor functions. On a further note, it is worth mentioning that areas overlapping within the networks, such as the anterior cingulate cortex, have also been highlighted as regions subtending cognitive reserve and resilience in advanced age and in the context of Alzheimer's Disease (Arenaza-Urquijo et al., 2019; Stern et al., 2018). Albeit these findings refer to two clearly different fields of research, further investigations could address the question of whether there are core cortical regions that provide a 'resilience signature' across different dimensions of mental and brain health.

7. Personalized interventions beyond the COVID-19 pandemic

Taken together, the findings of this Doctoral Thesis highlight the importance of studying resilience using a person-centered approach, in which relevant contributing factors (psychological, lifestyle, sociocultural, and neurodevelopmental aspects) are eventually integrated, and the effects of neurobiological markers are interpreted within this context (Vannini et al., 2021). Our findings could pave the way for preventive strategies not only for the current COVID-19 pandemic but also for comparable future outbreaks or any analogous circumstances. The unearthed findings can be extrapolated to any situation where mental health is at risk due to exposure to high levels of stress. The conclusions drawn not only provide valuable insights into understanding and addressing the psychological challenges we faced during the COVID-19 pandemic but also offer a solid foundation for formulating strategies and policies to promote mental well-being in high-stress environments, whether these are other pandemics or natural disasters or not. In this line, it is worth emphasizing that all the findings have been endorsed by literature in both contexts (i.e., pandemic or not).

Our research provides valuable insights for identifying and mitigating risks. Particularly, it is relevant since it showed the possibility to categorize individuals according to multiple aspects into those with greater resilience, and those who are consistently unwell or vulnerable. Additionally, our ability to isolate distinct facets of mental health (such as psychological distress, personal growth, and feelings of loneliness) and incorporate pandemic-related factors enhances the significance of our findings. Consequently, this framework enables the identification of crucial time-frames during which interventions can be strategically directed to prevent and enhance emotional, psychological, and social well-being.

First, cognitive behavioral interventions to improve coping strategies in combination with stress reduction approaches (e.g., mindfulness-based stress reduction) may be beneficial, especially for individuals at risk, such as those living alone, experiencing high levels of stress, women, younger adults, or smokers (see Figure 10). Importantly, in the view of our results, this line of intervention has the potential to be beneficial for the three components of mental health. Second, the status of functional brain networks has been demonstrated to be a valuable predictor of the likelihood of response to psychological interventions [see Picó-Perez et al. (2022) for a meta-analysis] and can reveal neural mechanistic effects of effective treatments

(Picó-Perez et al., 2017; Marwood et al., 2018). Our finding that such functional aspects modulate the influence of psychological resources on mental health, especially for the emotional and psychological aspects of mental well-being, implies that a combined strategy involving brain imaging to assess whether the effects of therapies targeting such important circuits may be of special interest. The FPN, in particular, has been proposed to underlie resilient mechanisms for both emotional and psychological dimensions, making it a highly competitive neuroanatomical target.

Finally, this approximation may benefit from technologies that allow for direct control of brain network connections. Non-invasive brain stimulation may directly reduce anxiety (Cirillo et al., 2019) and depressive symptoms (Walsh & Pascual-Leone, 2003). Notably, the integration of such approaches with electroencephalography and/or fMRI allows for customized manipulation of the spatiotemporal dynamics of specific brain networks (Fox et al., 2012). Furthermore, brain responses elicited by stimulation may be predictive of clinical and behavioral outcomes (Abellaneda-Pérez et al., 2021; Abellaneda-Pérez et al., 2022; Shafi et al., 2014; Shafi et al., 2012; Pascual-Leone et al., 2011). As a result, such experimentally controlled procedures could be combined with other characteristics to forecast an individual's probability of experiencing unfavorable mental health effects in the face of unexpected and long-term stresses (Vannini et al., 2021). The findings within this work contribute to the discovery of these “other characteristics” with which to combine experimental interventions since it has shown the potentiality of simultaneously considering multimodal variables (sociodemographic, lifestyle, and psychological factors but also brain mechanisms) to describe resilience.

8. Limitations and strengths

The studies within this doctoral thesis are not without limitations, which must be considered for the better interpretation of the results. Importantly, the studied population possesses specific attributes, probably explained by the way we recruited participants. Notably, it consists of individuals who have a strong interest in their own brain health, with a lower representation of those experiencing lower mental health levels, and with a high level of education and socioeconomical status. This, for example, could limit interpretations regarding the effects of education on mental health. It may also condition that the results may not be generalizable to other populations such as teenagers or elder individuals, those with a lower socioeconomic status. In this line, it must be acknowledged that only sex and not gender was assessed among the population, assuming that the individuals identify themselves with both coincident sex and gender (e.g., female and women). Then, interpretations regarding the gender gap in the previous sections are subjected to this assumption.

Other consideration is that the analyses did not contemplate the effects that having been infected with SARS-CoV-2 could have on the nervous system and cognition (e.g., Ariza et al., 2023; Campabadal et al., 2023; Ariza et al., 2022). Since the study design included multiple assessments along an extensive period of the pandemic, during which most individuals got infected at least once, it was very difficult to control this variable. Additionally, MRI acquisition was prior to the pandemic and then free of potential affectations due to infection. In line with the MRI acquisition, it must be also remarked that due to public restrictions (to control the spread of the virus), it was not possible acquire this data during the moments of highest levels of stress of the pandemic, making not possible to study the actual brain state while experiencing the stressors. However, the precedence of this data to the outbreak is at the same time a strength of the study, since it allows to explore the mechanisms of protection or risk that could underlie being potentially more resilient or vulnerable subsequently.

Additionally, multiple neuroimaging metrics could have been utilized. However, SyS was chosen by its ability to condense essential properties of the brain functioning in a single value (Wig et al., 2017). SyS was recently associated with resilience in other contexts (e.g., Ewers et al., 2021), but it had never been related to mental health until the present work. This is at the same time a limitation and a strength since it opens a new realm of hypotheses to be studied, but its interpretation is limited to little work in the field.

Finally, one of the most significant strengths of this doctoral thesis is the inclusion of longitudinal data spanning both pre-pandemic and pandemic periods, with a total follow-up of up to four years. This extensive dataset comprises approximately two thousand participants, with magnetic resonance imaging available for around seven hundreds of them. Such a large and well-characterized cohort is rare and adds unique value to the obtained results.

Chapter 6

Conclusions

Through the combined analysis of the studies included in this Doctoral Thesis, we can conclude that:

1. The response in terms of mental health changes to the pandemic outbreak was variable among a middle-aged healthy population, who exhibited primarily resilient longitudinal responses.
2. Emotional, psychological, and social components were differentially impacted during the pandemic and influenced by specific risk and protective factors, suggesting that they need to be considered separately for future, more personalized, preventive strategies.
3. Non-modifiable factors a priori, such as personality, age, and gender, were identified as key markers for defining individuals at higher risk.
4. Modifiable factors such as coping strategies and other aspects of psychological well-being, as well as factors promoting physical and cognitive health (e.g., healthy sleep habits or abstaining from smoking) serve as catalysts for resilience in the context of the COVID-19 pandemic, and therefore should represent modifiable targets for interventions.
5. The functional segregation vs. integration balance of specific brain networks (i.e., DMN, SN, and FPN) were related to mental health response during COVID-19 pandemic.
6. The FPN was involved both in emotional and psychological mental health changes, whereas the DMN and SN were specific for psychological distress interindividual differences.
7. The DMN and FPN system segregation values, measured prior to the COVID-19 pandemic, modulate the negative impact of perceived stress on depression and anxiety symptoms.

Overall, the results of the present dissertation stressed that it is imperative to consider psychological, lifestyle, and sociodemographic factors along with brain mechanisms, with particular emphasis on their interactions, to comprehend the phenomena of resilience and vulnerability and thereby promote more effective interventions.

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