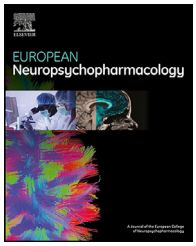
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

European Neuropsychopharmacology 53 (2021) 7–18



www.elsevier.com/locate/euroneuro

Self-reported neurocognitive symptoms during COVID-19 lockdown and its associated factors in a sample of psychiatric patients. Results from the BRIS-MHC study

Laura Montejo[a,1], Brisa Solé[a,1], Norma Verdolini[a], Anabel Martínez-Arán[a], Caterina del Mar Bonnín[a], Joaquim Radua[c,d,e,f], Inés Martín-Villalba[a], Evelin Williams[a], Clemente García-Rizo[b], Gisela Mezquida[b], Miguel Bernardo[b], Eduard Vieta[a,*], Carla Torrent[a,*], Silvia Amoretti[a,b], BRIS-MHC research group

[a] *Bipolar and Depressive Disorders Unit, Hospital Clinic, University of Barcelona, Institute of Neuroscience, IDIBAPS, CIBERSAM, c/Villarroel, 170, 12-0, 08036 Barcelona, Catalonia, Spain*
[b] *Barcelona Clinic Schizophrenia Unit, Hospital Clinic of Barcelona, University of Barcelona, Neuroscience Institute, IDIBAPS, CIBERSAM, Barcelona, Spain*
[c] *Imaging of Mood- and Anxiety-Related Disorders (IMARD) Group, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain*
[d] *CIBERSAM, Madrid, Spain*
[e] *Early Psychosis: Interventions and Clinical-detection (EPIC) Lab, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK*
[f] *Department of Clinical Neuroscience, Stockholm Health Care Services, Stockholm County Council, Karolinska Institutet, Stockholm, Sweden*

Received 17 May 2021; received in revised form 8 July 2021; accepted 10 July 2021

KEYWORDS
COVID-19;
Lockdown;
Cognition;

Abstract
Lockdown caused by COVID-19 pandemic has a negative impact on mental health. The aim was to assess self-reported neurocognitive symptoms during the lockdown and identify associated vulnerable and protective factors in a sample of psychiatric patients in a Spanish population.

* Corresponding authors.
E-mail addresses: evieta@clinic.cat (E. Vieta), ctorrent@clinic.cat (C. Torrent).
[1] The first two authors contributed equally to this work.

https://doi.org/10.1016/j.euroneuro.2021.07.006

Bipolar disorder;
Psychiatric disorders;
Mental illness

These results are part of the Barcelona ResIlience Survey for Mental Health COVID-19 (BRISMHC) project. Neurocognitive symptoms were assessed through an online survey considering the five items that represented self-reported neurocognitive complaints. We split the sample into two groups based on the severity of the self-reported neurocognitive complaints: intact cognitive function/mild cognitive impairment (CI-) and moderate/severe cognitive impairment (CI+). Univariate analyses were used to compare both groups in terms of sociodemographic and clinical variables. Multiple logistic regression models were carried out to identify clinical variables and coping strategies associated with neurocognitive symptoms. 198 patients with different psychiatric diagnoses were included in this study. One hundred seventeen patients were classified in the CI- group and 81 in the CI+ group. Depressive symptoms and negative psychotic-like symptoms were vulnerable factors for neurocognitive impairment. Coping strategies of performing physical activity, carrying out relaxing activities and maintaining a routine were protective factors against cognitive impairment. Lockdown situation negatively impact on neurocognitive function. Psychopathological symptoms and coping strategies were associated with neurocognitive symptoms during lockdown in subjects with psychiatric illness. The early treatment of psychopathological symptoms in psychiatric patients and promoting coping strategies during lockdown should be considered an intervention strategy against cognitive impairment.

1. Introduction

Since the first case of coronavirus disease COVID-19 was detected in China in December 2019, the disease has spread globally and has led to be recognized as a world pandemic, many countries have taken a series of measures to prevent its spread, with strict restrictions. In Spain, on March 14, 2020, the state of emergency was decreed and the total lockdown was imposed throughout the country; this implied only leaving home for essential activities (buying essential products, health care or attending job). The total lockdown lasted until the end of May while activities allowed outside were progressively increased until reaching the "new normality" at the end of June.

To date, many studies demonstrate a cognitive impairment after a diagnosis of COVID-19 that shows deficits in memory, attention and executive function domains (Almeria et al., 2020; Alonso-Lana et al., 2020). However, the causes of these impairments are unclear and could be from various sources, for instance; directly from the COVID-19 itself, due to the pharmacological treatment for the disease, to the effects of cytokine storm syndrome, to the hyperinflammatory process (Cothran et al., 2020), hospital admission, etc. A report of Miskowiak et al (2021) identified cognitive impairment in 59-65% of patients with COVID-19 diagnosis showing deficits in memory and executive functions which were associated with the severity of the lung affection. Patients with a previous diagnosis of a neurodegenerative disease (i.e. dementia) are especially vulnerable to the effects of COVID-19 and show different clinical patterns (Alonso-Lana et al., 2020; Heneka et al., 2020). Neuropsychiatric disorders are also prevalent as a symptom of the COVID-19 disease, in one study (Varatharaj et al., 2020) it was identified 59% of the cases with several neuropsychiatric disorders (altered mental status, new-onset psychosis, neurocognitive (dementia-like) syndrome, and affective disorder) and, of those, around 23% had neurocognitive impairment.

The lockdown situation and isolation itself implies a series of changes in people's daily lives (i.e: working at home, decreased activity and leisure, reduction of social and family life, etc.) which could have a negative impact on psychosocial functioning, socioeconomic status and clearly in mental health. Due to that, researchers are making an effort to analyze the impact of this special situation on many social and psychological variables. Various studies conducted during the current pandemic suggest the presence of psychopathological symptoms as a result of lockdown, especially stress, anxiety and depression in community subjects (Brooks et al., 2020; Fullana et al., 2020; Salari et al., 2020) with worse effects on healthcare workers (Alonso et al., 2021; Mortier et al., 2021). Also, psychiatric patients are considered a vulnerable population to this kind of situation and could negatively impact on their mental health with a worsening of symptoms and relapses (Moreno et al., 2020; Vieta et al., 2020). As a result a significant increase in the percentage of acute psychiatric hospitalization during the lockdown was found (Gómez-Ramiro et al., 2021).

Cognitive performance is usually impaired in the psychiatric population (Millan et al., 2012) and could be negatively affected by other variables such as the presence or exacerbations of psychopathological symptoms (Ganguli et al., 2006; Huang et al., 2016; Talreja et al., 2013). Therefore, situations such as the current one are very prone to cause changes in psychiatric symptoms. In this sense, despite being an unprecedented and unexplored worldwide situation, there have been some attempts to call into the research frame to study the possible neurocognitive sequels of COVID-19 pandemic. However, to our knowledge, there are not any studies investigating the impact of lockdown on neurocognitive symptoms in psychiatric patients. Only a few researchers are investigating the effects of lockdown and isolation on neurocognitive performance and functionality in the neurological population (such as Alzheimer disease, dementia or stroke) (Hantke and Gould, 2020;

Mcloughlin et al., 2020). The present study is focused on whether neurocognitive symptoms self-reported in psychiatric patients could have been affected by the lockdown, either indirectly (due to the increase or the presence of psychopathological symptoms and/or other variables) or as a direct consequence of the characteristics of the isolation situation. The analysis of neurocognitive symptoms during lockdown situation is important not only for describing the prevalence of cognitive complaints deficits reported but also for detecting factors that could be associated with neurocognitive performance and also to design early interventions to mitigate the negative effects.

The aim of the Barcelona Resllience Survey for Mental Health COVID-19 (BRIS-MHC) study was to detect the psychological effects of the lockdown in individuals with a psychiatric diagnosis comparing with the general population. The present study consists in a sub-analysis of the BRIS-MHC focused on the data of self-reported neurocognitive deficits. The aim of this study is to analyze the prevalence of self-reported neurocognitive symptoms during lockdown in the psychiatric population and to describe the variables that are associated with their presence.

2. Methods

The results of the present study belongs to the BRIS-MHC project which received ethical approval from the Hospital Clínic of Barcelona Ethics Committee (approval number: protocol HCB/2020/0530) according with the Declaration of Helsinki. Further information about BRIS-MHC project and survey are described in Solé et al., (2020). Summarized, we created an online and self-applied survey of 15 minutes approximately to assess the impact of lockdown concerning many variables of mental health in both patients and community controls. The survey was delivered in a period in which in Spain, although there was not a complete lockdown, there were severe mobility restrictions to essential activities (employment, medical care, sports and buying food) and during a restricting schedule.

2.1. Measures

Our original survey BRIS-MHC collected data on many variables but for the present study we only selected the more relevant ones related to cognition. The sociodemographic data collected were: age, gender, educational level and current work status. Participants were also asked to rate the frequency performance (*yes* or *no*) of several behavioral strategies to manage distress during lockdown, that is, coping strategies including healthy habits. In addition to diagnosis and duration of illness we also asked for the need of admission to the mental health service or visit from the psychiatric emergency during the lockdown or suicide attempts. We also included several items to assess changes during lockdown in terms of psychopathological symptoms such as depressive and anxiety symptomatology, sleep quality, psychotic-like experiences, and substance use (alcohol and cannabis). The presence of symptoms related to COVID-19 with or without diagnosis was also assessed. Trauma experiences during lockdown were assessed firstly asking for "experience of unpleasant event during lockdown" and if participants responded affirmatively further questions based on the Post-traumatic Stress Disorder Symptom Severity Scale-Revised (EGS-R) (Echeburúa et al., 2016) were administered. Cognitive reserve was also measured and calculated through a proxy based on maximum educational level achieved and leisure activities. The items and scales used to assess all constructs are described in detail in Solé et al., 2020. We describe briefly the main measures including in the present study:

a) Depressive and anxiety symptoms were assessed using items inspired in the Patient Health Questionnaire (PHQ-9) (Kroenke et al., 2001) and Generalized Anxiety Disorder (GAD-7) (Spitzer et al., 2006) questionnaire respectively, which scores reach from "0" (not at all) to "3" (nearly every day).
b) Psychotic-like experiences were assessed through nine items based in the Community Assessment Psychic Experiences-42 scale (CAPE-42) (Fonseca-Pedrero et al., 2012) to assess positive or negative dimensions.
c) Coping strategies were measured by asking about the performance of the following behaviors using a dichotomous scale ("yes" or "no") (i.e.: following a routine, maintaining a healthy or balanced diet, drinking water to hydrate, use of entertainment resources like hobbies, talking with relatives or friends, reading news about COVID-19 frequently, practicing physical exercise and taking part in relaxing activities).
d) For assessing cognition, a total of five items of self-reported subjective complaints tackling the main cognitive domains were created: attention, immediate memory, learning, executive function (planning), and processing speed. We selected "ecological" items that represent cognitive deficits with impact in daily functioning. One item corresponded to each cognitive domain. The items were inspired in the COBRA (Cognitive Complaints in Bipolar Disorder Rating Assessment) (Rosa et al., 2013) which is an self-applied scale highly recommended, reliable and validated to assess cognitive complaints in psychiatric population. We asked if during the lockdown the participant had experienced any of these cognitive deficits.

The items for assessing neurocognitive complaints were the following:

Since the lockdown began:

a) Attention: *"Do you find it hard to concentrate on certain activities for a period of time (20-30 min) such as reading the newspaper or watching television?"*
b) Processing speed: *"Have you performed activities slower than usual?"*
c) Memory: *"Have you had problems with remembering events that happened recently (i.e. something you read, a conversation, etc.)?"*
d) Learning: *Have you had difficulties in memorizing or learning new things (i.e. the shopping list, phone number, addresses, etc.)?"*
e) Executive function (planning): *"Have you had difficulties in planning and organizing daily activities (for example, cooking, shopping, trips, etc.)?"*

A Likert scale of four options (never (0), several days (1), more than half the days (2) and nearly every day (3)) was used for its quantification. Subsequently, we created a criterion to determine the presence or absence of subjective neurocognitive complaints as follows; in each cognitive domain: an answer below two points, that is, *no days or some days*, was classified as intact cognitive function or mild cognitive impairment. Consequently, a score greater or equal than two points was considered as a moderate and severe cognitive impairment. The same criterion was followed for all cognitive domains.

2.2. Participants

Participants were included from the online anonymous survey system of Hospital Clinic of Barcelona through a multiple step procedure: a) e-mail invitation to patients visited at the Mental Healthcare of the Hospital Clinic of Barcelona, b) dissemination of the

link through social media and other advertisements c) involvement of national associations of stakeholders (e.g., associations of users/caregiver). Thus, the sample was recruited by different non-probability sampling methods (convenience sampling, voluntary sampling and snowball procedure). The survey included one item asking them whether they had a psychiatric disorder, and if so, which psychiatric disorder they had. Finally, for the present analysis we included patients with different psychiatric diagnostic (schizophrenia, bipolar disorder, schizoaffective, psychotic disorder, major depressive disorder, anxiety and others psychiatric disorders) who answered the survey during the lockdown period. Within this group, the sample was divided between intact cognitive function/mild cognitive impairment (CI-) and moderate/severe cognitive impairment (CI+).

2.3. Statistical analysis

We divided the sample creating a dichotomous variable of overall Cognitive Impairment, taking into account all cognitive domains and following the same criterion: an answer of yes with a score of two or more in at least one cognitive domain was considered as a moderate/ severe cognitive impairment (CI+); below that score was considered intact cognitive function / mild cognitive impairment (CI-).

The descriptive analysis was performed by calculating the means and frequencies of variables. We used Chi-squared and Student's T-tests to detect socio-demographic differences between both groups. For binary variables, we applied the Yates correction when the expected count of the crosstab was less than five in one cell or more. Effect sizes for each variable were also calculated.

The *cognitive impairment* was considered as the primary outcome and thus the dependent variable. First, we performed univariate logistic regressions to detect variables statistically significantly contributing to cognitive impairment. Hereunder, the detected variables were introduced in the multiple logistic regression analyses. We fitted two multiple logistic regression models. The first model was composed of variables related to the presence of psychopathological symptoms during the lockdown. Thus, variables such as symptoms of depression, anxiety, sleep disorders, and the presence of negative and positive psychotic symptoms were considered. The second model was designed considering the coping strategies/ healthy habits that were carried out during the lockdown, specifically following a healthy and balanced diet, performing physical exercise, drinking water, maintaining hobbies, following a routine, doing relaxing activities, talking with friends, or relatives frequently, and reading or watching news about COVID-19 frequently. For both models, the presence of cognitive impairment was considered as the dependent variable. Variables related to psychopathological symptoms, on one side, and coping strategies/healthy habits, on the other side, were considered as the independent variables. The logistic regression multivariate was carried out for the two models using the backward Wald stepwise method. The odds ratio was calculated to measure the magnitude of the difference between both groups. The Hosmer-Lemeshow test was used to test the goodness of fit for logistic regression models. To compute the model performance and with an exploratory aim, we use ROC curve methodology. All analyses were conducted using the Statistical Package for the Social Sciences (SPSS) v23.0 and R version 4.0.3 (Vienna, Austria). Significance was set at $p<0.05$ (two tailed) for all analyses.

3. Results

3.1. Sociodemographic and clinical characteristics of CI- and CI+ groups

A total of 198 patients who answered the questionnaire completely were included in this study. Of those, 117 (59.1%) patients were classified in CI- and 81 (40.9%) with CI+. Table 1 shows all the socio-demographic and clinical characteristics of the psychiatric sample divided into two subgroups: intact/mild cognitive impairment and moderate/severe cognitive impairment. No significant differences were found in gender, age, educational level or current work status between both subgroups.

Clinical variables related with mental disease were analyzed and no differences between both groups were detected in terms of psychiatric admissions, suicidal attempts ($p = 0.13$) and chronicity ($p = 0.56$). A small percentage of patients in both groups increase the alcohol consumption (12.8% of CI- *vs* 16% of CI+, $p = 0.46$) as well as cannabis consumption (0.9% of CI- *vs* 3.7% of CI+, $p = 0.38$) but without significant differences between both groups. A higher proportion of patients (32 (40.5%)) in the CI+ group experienced unpleasant events during lockdown (*vs* 19.8% of CI-) with significant differences between both groups ($p = 0.002$). Cognitive reserve was also assessed and no differences between both groups were found ($t = -1.48$; $p = 0.053$). In our sample, three patients (1.5%) were confirmed cases of COVID-19, of those all were classified in the CI+ group. Twenty-two (11.3%) patients were suspected cases without diagnosis of COVID-19 and with mild symptoms, of those 12 (54.5%) were classified in CI+ group. No significant association was found between both groups and COVID-19 confirmed disease ($X^2 = 4.44$; $p = 0.07$).

Regarding psychopathological symptoms, the group of CI+ showed higher significant values of depressive symptoms ($p < 0.001$), anxiety symptoms ($p < 0.001$), positive psychotic-like experiences ($p < 0.001$), negative psychotic-like experiences ($p < 0.001$) and also a higher prevalence of sleep disturbances ($p = 0.008$). Table 2 shows the mean and the standard deviation of these values.

3.2. Cognitive domains

Within our whole sample, concerning cognitive domains, processing speed was the cognitive domain most affected; fifty-six patients (28%) indicated difficulties in this domain, 14% in more than a half of the day. Forty-three patients (21.3%) reported impairment in attention, whereas 8.4% indicated attention difficulties nearly every day. Forty patients (20%) indicated learning impairment and 8% reported difficulties nearly every day. Twenty-eight patients (14%) reported difficulties in immediate memory, of those 8.5% referenced memory problems nearly every day. Finally, planning as a measured of executive function was the cognitive domain least affected referred by patients, with twenty-four patients affected (11.9%), of those 6.5% patients indicated planning problems nearly every day. Finally, 66% of patients reported cognitive difficulties in more than one domain. If we take into account the number of affected cognitive domains, 35% of patients reported difficulties in one

Table 1 Sociodemographic and clinical characteristics.

Socio-demographic variables	Cognitive status Intact or Mild (CI-) ($n = 117$) n (%) /M (SD)	 Moderate or Severe (CI+) ($n = 81$) n (%) /M (SD)	X^2 or t, (p-value)
Age	47.34 (12.62)	44.78 (14.38)	1.27 (0.20)
Sex (female)	70 (60.9%)	51 (66.2%)	0.57 (0.45)
Educational level			5.89 (0.53)
Primary/elementals	2 (1.7%)	7 (8.6%)	
High school or medium	44 (37.9%)	33 (40.7%)	
University or higher	70 (60.3%)	41 (50.6%)	
Current work status			2.14 (0.71)
Employed (workplace)	17 (14.7%)	15 (19.2%)	
Tele-working	24 (20.7%)	14 (17.9%)	
Not working (temporary employment force adjustment, unemployed, dismissal, retired)	47 (40.5%)	27 (34.6%)	
Disability, sick leave	25 (21.6%)	21 (26.9%)	
Student	3 (2.6%)	1 (1.3%)	
Lockdown and COVID-19 related variables			
COVID-19 disease with positive test	0	3 (3.8%)	4.44 (0.07)
Unpleasant events during lockdown (yes)	23 (19.8%)	32 (40.5%)	9.92 (0.002)*
Psychiatric and clinical variables			
Psychiatric diagnosis			13.55 (0.000)*
Anxiety and depressive disorders	18 (15.4%)	30 (37%)	
Bipolar Disorder/Schizophrenia/Psychotic Disorder	96 (82.1%)	46 (56.8%)	
Duration of psychiatric illness			0.343 (0.56)
$\leq$ 10 years	37 (39.4%)	19 (34.5%)	
>10 years	57 (60.6%)	36 (65.5%)	
Medication leave (yes)	1 (1.1%)	7 (13%)	7.31 (0.007)*
Visit to psychiatric emergency (yes)	4 (3.5%)	0	1.37 (2.41)
Psychiatric admission (yes)	2 (1.7%)	1 (1.3%)	0.00 (1.00)
Suicide attempt (yes)	0	3 (3.8%)	2.54 (0.133)
Alcohol consumption (more)	15 (12.8%)	13 (16%)	1.57 (0.46)
Cannabis consumption (more)	1 (0.9%)	3 (3.7%)	0.79 (0.38)

CI-= Intact cognitive function and mild cognitive impairment group: CI+= Moderate and severe cognitive impairment group; M= Mean; SD= Standard Deviation

or less cognitive domain, 12.1% in two domains, 15.3% in three domains, 14.7% in four domains and, finally, a 22.1% of patients indicate difficulties in five cognitive domains.

3.3. Differences in cognitive performance according to psychiatric diagnoses

We split the psychiatric sample into anxiety/major depressive disorder and Bipolar disorder/Schizophrenia and related disorders and we found differences between both groups in overall cognitive impairment ($p = 0.000$; Cramer's $V = 0.27$) and in the following cognitive domains: attention ($p = 0.045$; Cramer's $V = 0.14$), memory ($p = 0.035$; Cramer's $V = 0.15$), planning ($p = 0.003$; Cramer's $V = 0.21$) and processing speed ($p = 0.003$, Cramer's $V = 0.22$). The Bipolar Disorder/Schizophrenia and related disorders group showed more impairment in all cognitive domains except in planning ability, whereas a higher prevalence of impairment was found in the anxiety/major depressive disorder group (52.4% vs 47.6%, respectively).

3.4. Factors associated with cognitive impairment

First, the presence of psychopathological variables was considered as risk factors of cognitive impairment. The CI + group presented higher values in all these variables in comparison with CI- (see Table 2), with large effect sizes. Particularly, differences between both groups (CI - and CI+) were found in depressive symptoms (OR = 1.51, 95% IC = 1.34-1.70; $p < 0.001$), anxiety symptoms (OR = 1.53; 95% IC = 1.33-1.78; $p < 0.001$), in negative psychotic-like experiences (OR = 1.78; 95% IC = 1.42-2.23; $p < 0.001$), positive psychotic-like experiences (OR = 1.62; 95% IC = 1.34-1.96; $p < 0.001$) and finally in sleep disturbances (OR = 2.71; 95% IC = 1.27-5.79; $p = 0.01$) where the CI+ group presented higher percentages (84% *vs* 65.9%). Notably, the CI + group displayed higher values in all these variables in comparison with CI-. Related to coping strategies, healthy and regular habits, the univariate analysis reported significant differences between both groups also in many variables included in favor of CI- group. Thus, to perform physical exercise during lockdown (78.3% *vs* 57%;

Table 2 Results of the univariate analysis.

Psychopathological symptoms	Intact or Mild (CI-) ($n = 117$) n (%) /M (SD)	Moderate or severe (CI+) ($n = 80$) n (%) /M (SD)	X^2 or t (*p*-value)	OR	*p*-value
Depressive symptoms	4.36 (3.38)	11.39 (5.07)	-11.51 (<0.001)	1.51 (1.34-1.70)	<0.001*
Anxiety symptoms	3.29 (2.28)	6.27 (3.05)	-7.53 (<0.001)	1.53 (1.33-1.78)	<0.001*
Positive symptoms	0.99 (1.40)	2.51 (2.22)	-5.88 (<0.001)	1.62 (1.34-1.96)	<0.001*
Negative symptoms	1.00 (1.17)	2.48 (2.14)	-6.23 (<0.001)	1.78 (1.42-2.23)	<0.001*
Sleep disorder (yes)	58 (65.9%)	63 (84%)	6.92 (0.008)	2.71 (1.27-5.79)	0.01*
Coping strategies and healthy habits					
Routine (yes)	90 (77.6%)	47 (59.5%)	7.36 (0.007)	0.42 (0.23-0.79)	<0.001*
Physical exercise (yes)	90 (78.3%)	45 (57%)	10.03 (0.002)	0.37 (0.20-0.69)	0.002*
Healthy diet (yes)	99 (84.6%)	57 (73.1%)	3.89 (0.048)	0.49 (0.24-1.03)	0.051*
Hobbies (yes)	98 (84.5%)	58 (72.5%)	4.18 (0.041)	0.48 (0.24-0.98)	0.043*
Relaxing activities (yes)	98 (86%)	55 (68.8%)	8.36 (0.004)	0.36 (0.18-0.73)	0.005*
Drink water (yes)	109 (93.2%)	68 (86.1%)	2.71 (0.100)	0.45 (0.14-1.19)	0.107
Talk with friends or relatives frequently (yes)	114 (97.4%)	77 (97.5%)	0.000 (1.000)	0.98 (0.16-6.05)	0.99
News about COVID-19 frequently (yes)	76 (65%)	50 (62.5%)	0.12 (0.724)	0.90 (0.50-1.62)	0.72

M= Mean; SD= Standard Deviation; OR=Odds Ratio.

OR = 0.42; 95% IC = 0.20-0.69; $p = 0.001$), to follow a routine (77.6% *vs* 59.5%; OR = 0.42, 95% IC = 0.23-0.79; $p < 0.001$); to maintain a healthy diet (84.6% *vs* 73.1%; OR = 0.49; 95% IC = 0.24-1.03; $p = 0.051$), to do hobbies (84.5% *vs* 72.5%; OR = 0.48; 95% IC = 0.24-0.98; $p = 0.043$) and to perform relaxing activities (86% *vs* 68.8%; OR = 0.36; 95% IC = 0.18-0.73; $p = 0.005$) were more prevalent in the CI- group indicating that maintaining these behaviors could be considered as protective factors against the presence of self-reported neurocognitive symptoms. In contrast, the behavior of drinking water for maintaining hydrated (93.2% *vs* 86.1%; OR = 0.45; 95% IC = 0.14-1.19; $p = 0.107$), talking with friends or relatives (97.4% *vs* 97.5%; OR = 0.98; 95% IC = 0.16-6.05; $p = 0.99$) and watching the news about COVID-19 (65% *vs* 62.5%; OR = 0.90; OR = 0.50-1.62; $p = 0.72$) seemed not to be associated.

Secondly, two multiple logistic regression analyses were carried out introducing the statistically significant variables in the previous univariate analysis, one considering psychopathological variables as risk factors and another one with the coping strategies/healthy habits as protective factors. The results of this analysis are shown in Table 3. For the first model, after entering the psychopathological variables (depression, anxiety, sleep disorders and the presence of negative and positive psychotic like experiences) in step 4 the presence of depressive symptoms (OR = 1.42; 95% IC = 1.24-1.63; $p < 0.001$) and negative psychotic-like experiences (OR = 1.45; 95% IC = 1.03-2.04; $p = 0.04$) were both risk factors of cognitive impairment, indicating that the group with the greatest neurocognitive symptoms had a higher rate of depressive and negative symptoms. Fig. 1 represents the adjusted probability of those significant variables. The second model composed of coping strategies and healthy habits, in step 1 to perform physical activity (OR = 0.45; 95% IC = 0.23-0.87; $p = 0.02$), relaxing activities (OR = 0.46; 95% IC = 0.22-0.98; $p = 0.04$) and following a routine (OR = 0.52; 95% IC = 0.26-1.01; $p = 0.09$) were the variables that better explain that model. In this case, the prevalence of patients who had performed these behaviors was higher in the intact and mild group, indicating that to carry out this kind of activities could be a protective factor against cognitive impairment. Fig. 2 shows the adjusted probability prediction for cognitive impairment of the three last significant variables from the coping strategies and health habits model.

However, as an additional exploratory analysis in order to clarify which factors were contributing higher to cognitive performance, we pooled all variables (psychopathological symptoms and coping strategies) in a unique model and we found that in step 9 the variables of depressive symptoms (OR = 1.39; 95% IC = 1.21-1.59; $p < 0.001$) and negative psychotic-like symptoms (OR = 1.49; 95% IC = 1.04-2.14; $p = 0.05$) were the variables that better explained the differences between both groups, showing therefore the same results as model 1.

Finally, the results of the ROC curve showed an area under the curve (AUC) of 0.895 for the first model and 0.65 for the second model, indicating good adjustment of both models but a slightly better for the first one (see Fig. 3).The model resulting from the analysis of all variables showed the same ROC curve than the first model since the significant variables were the same.

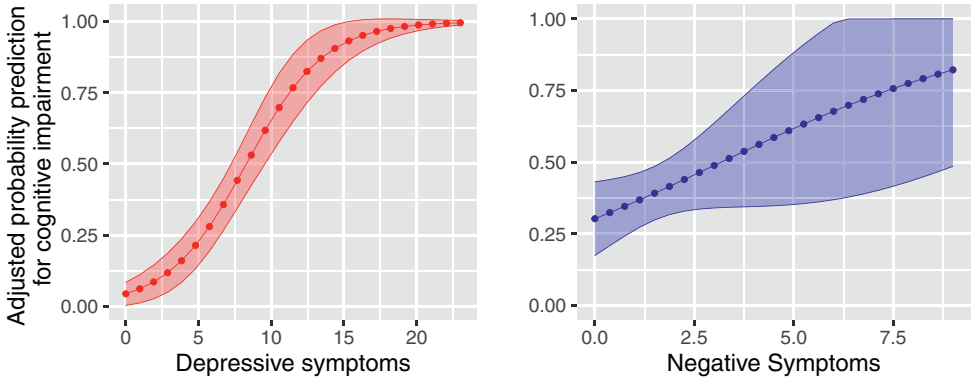


Fig. 1 Adjusted probability prediction for cognitive impairment of psychopathological symptoms model.

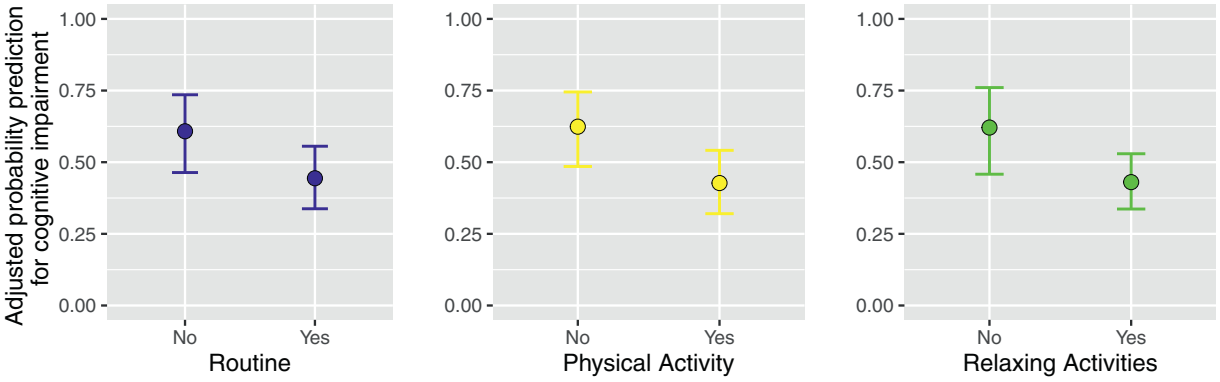


Fig. 2 Adjusted probability prediction for cognitive impairment of coping strategies and healthy habits model.

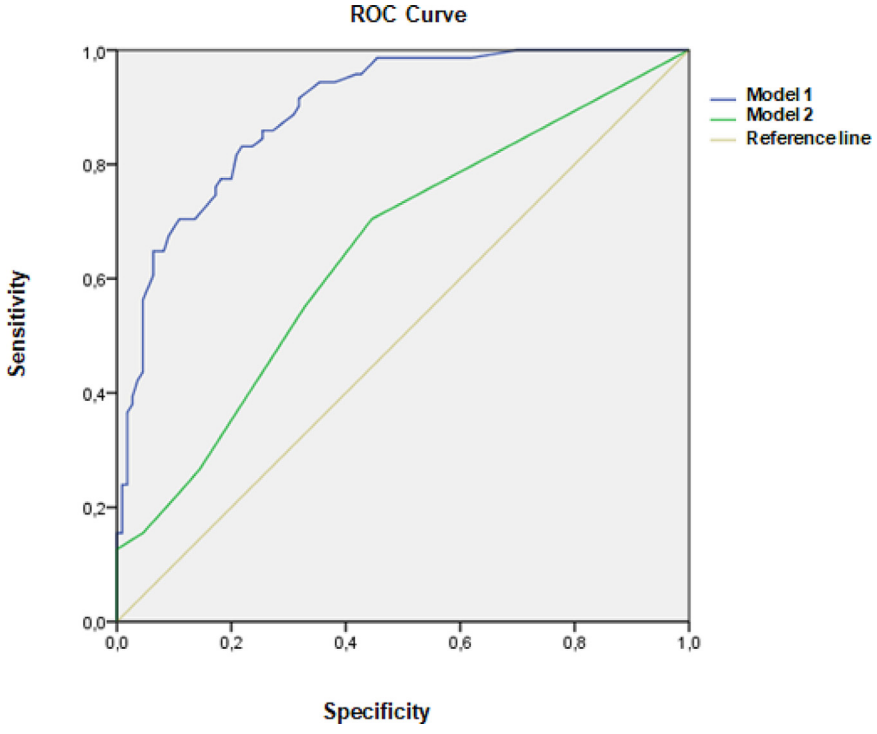


Fig. 3 ROC curve of the two logistic regression models.

Table 3 Results of the multiple logistic regression models.

Model 1. Psychopathological symptoms				Model 2. Coping strategies and healthy habits			
	OR (95% CI)	*p*-value	ROC (CI)		OR (95% CI)	*p*-value	ROC (CI)
Depressive symptoms	1.42 (1.24-1.63)	<0.001*	0.90	Physical activity	0.45 (0.23-0.87)	0.02*	0.65
Negative symptoms	1.45 (1.03-2.04)	0.04*	(0.85-	Relaxing activities	0.46 (0.22-0.98)	0.04*	(0.57-
Constant	0.03	<0.001*	0.94)	Routine	0.52 (0.26-1.01)	0.09*	0.73)
				Constant	3.20	0.01*	

CI= Confidence Interval; OR=Odds Ratio; ROC= Receiver Operating Characteristics

4. Discussion

The current global pandemic crisis caused by COVID-19 has given rise to a particular scenario. On one hand, lockdown and mobility restrictions imposed by the government led to significant social isolation and a decrease in daily activities. On the other hand, the health crisis and the increase in the number of infected people and deaths caused a feeling of insecurity and exceptional situation not previously experienced. Both can lead to the appearance or increase of symptoms of anxiety, stress, sleep problems and depression (Hao et al., 2020; Kujawa et al., 2020) in the general population. In this sense, the psychiatric population is especially vulnerable to experiencing these feelings and symptoms derived from an extraordinary situation like this (Kontoangelos et al., 2020). It is also well reported that psychiatric patients have large rates of cognitive impairment in many cognitive domains (Torres et al., 2007). To our knowledge, this is the first study that assesses the prevalence of self-reported neurocognitive symptoms during lockdown in a psychiatric population and detects risk and protective factors associated with self-reported cognitive performance. In general terms, our results show that almost half of patients with some psychiatric diagnosis reported moderate subjective cognitive complaints during lockdown (40.9% CI + vs 59.09% of CI-).

In the present study, depressive and negative psychotic symptoms were the most associated with moderate and severe cognitive complaints. The high prevalence of psychopathological symptoms found would be in line with previous reports that indicate an increase in the severity of psychiatric symptoms during lockdown in the psychiatric population (Vieta et al., 2020; Vindegaard and Benros, 2020). In our sample, the mean depressive symptoms in the CI + group was significantly higher, fulfilling the criteria for moderate depression (Kroenke et al., 2001). In addition, the association detected between depressive symptoms and cognitive performance is consistent with the previous results found in the literature. Likewise, the presence of depressive symptoms is frequently associated with poorer cognitive performance (Bora et al., 2013; Rock et al., 2014) not only in the acute episode (Serra-Blasco et al., 2019) but also in euthymia or during the remission period (Hasselbalch et al., 2011). It is important to consider that we are assessing subjective and self-reported neurocognitive complaints and patients with unipolar depression tend to overestimate their cognitive difficulties, indicating greater severity of cognitive deficits than those verified in the objective neuropsychological assessment (Lahr et al., 2007; Serra-Blasco et al., 2019). This could indicate that, in our sample, there could be a bias due to these patients reporting more cognitive deficits and therefore there may be an over-representation of patients with symptoms of depression in the CI + group. Negative psychotic symptoms are also associated with poorer cognitive performance (de Gracia Dominguez et al., 2009; Leanza et al., 2018). However, it is difficult to distinguish negative psychotic symptoms from depressive symptoms, and there may be an overlap (Strauss and Cohen, 2017), since there are two domains that share some symptoms such as anergy, apathy and social isolation (An der Heiden et al., 2016). In our study, the value of negative psychotic-like experiences was obtained through an adaptation of the CAPE-42 scale (Fonseca-Pedrero et al., 2012) where we only included three items *(Do you ever feel that your feelings are lacking in intensity?; Do you ever feel that you are neglecting your appearance or personal hygiene?; Do you ever feel that you have no interest to be with other people?),* which although they are classified as negative symptoms by the scale, they can also represent depressive symptoms. In addition, in our sample lower percentage was made up of patients with a diagnosis of psychotic disorder (n= 31) compared with bipolar disorder (n= 111); this over-representation of patients with bipolar disorder could had produced a bias in that construct representing higher values of depressive symptoms.

Coping strategies are those that are carried out, internally or externally, to cope with a stressful or traumatic situation, and are aimed at restoring balance and reducing stress (Folkman and Lazarus, 1988). In our study, although a higher percentage of patients (70.3-80%) performed this type of activities during lockdown, such as following a routine, doing physical activity, carrying out a balanced and healthy diet, doing hobbies as well as relaxing activities, significant differences between both groups according to cognitive severity (CI + and CI-) were detected. More importantly, among patients who implemented these strategies, the highest percentage (62.8-66.7%) corresponded to the intact and mild cognitive impairment group, demonstrating that performing these coping-oriented activities during confinement may protect against subjective cognitive complaints. In the present study, several coping strategies were considered protective factors of cognitive impairment and, specifically, physical activity, performing relaxing activities and following a routine were more associated with less cognitive impairment. In this sense, performing this kind of activities could promote a healthy and active lifestyle and it could favored good brain functioning, protecting against cognitive decline (Christie et al., 2017; Clare et al., 2017). In particular, physical activity has great benefits on cognitive performance (Kurebayashi and Otaki, 2017) in vari-

ous cognitive functions such as executive function or memory (Etnier et al., 2006; Josefsson et al., 2012), enhancing brain function through changes at the systemic, cellular, and molecular levels (Di Liegro et al., 2019; Kramer and Erickson, 2007; Loprinzi et al., 2013). Positive benefits of moderate physical exercise on mental health and well-being have also been shown (Simpson and Katsanis, 2020) reducing stress, anxiety and depressive symptoms (Mikkelsen et al., 2017; Peluso & Guerra de Andrade, 2005). Performing physical exercise could decrease the risk of depressive relapse in bipolar disorder (BD) and improve well-being, promoting changes in the brain that include decrease of inflammation, neural growth and release of endorphins. It is also a way to reduce stress, and improve memory and sleep regulation (Reinares et al., 2020). In our previous results from the present project we found that patients, in addition to having higher values of depressive and anxiety symptoms compared with community controls, also exhibited less rates of performance in these kind of activities (i.e. following a routine, talk to relatives or friends, do physical exercise, to maintain a healthy and balanced diet, and pursue hobbies) (Solé et al., 2020). On the contrary, those psychiatric patients that had pursued hobbies were found to report higher rates of resilience in the face of the lockdown situation (Verdolini et al., 2021). Overall, all these activities, might indirectly help reducing psychopathological symptoms and improve or maintain cognitive performance. Specific recommendations to BD have been proposed to manage the risk generated by lockdown, considering some modifiable strategies such as balance diet, maintaining physical exercise and to perform relaxing activities as a main target (Hernández-Gómez et al., 2021). Emerging digital technologies have been proposed as a suitable tool for the monitoring of behavior changes in psychiatric patients (Jagesar et al., 2021). In one study assessing the effects of the crisis caused by COVID-19 on mental health, it was found that the use of coping strategies were related to less index of post-traumatic stress, depression, and insomnia symptoms (Guo et al., 2020). Our results are also congruent with a previous report (Fullana et al., 2020) indicating that some coping styles such as following a healthy diet and not reading news about COVID-19 very often were associated with low levels of anxiety. Following a routine, taking the opportunity to pursue hobbies and staying outdoors were also associated with lower levels of depression in the general population. Summarizing, these coping styles could be included under the umbrella of "modifiable" strategies that are carried out in a conscious and active way in order to mitigate the negative effects of a “traumatic” situation and improve mental health globally (Sim et al., 2010). However, the relation between better cognitive functioning and the use of coping strategies could also indicate a higher facility of the preserved group to implement these kind of activities, thus, not really reflecting protective factors.

However, when both psychopathological symptoms and coping strategies were considered all together to assess which were the ones most associated with cognitive performance, we found that only those related to psychopathological symptoms (depressive and negative symptoms) resulted to be significant. This demonstrates that, in the present study, these variables were more associated with self-reported neurocognitive symptoms than the coping strategies. Indeed, from a clinical point of view, treating psychopathological symptoms represents the first step of an integrated treatment strategy that should be also accompany by psychosocial and psychoeducational interventions. Notably, as an intervention strategy, after the treatment of the acute symptomatology, these activities are considered a potentially modifiable strategies, cost-effectiveness that, in addition to improving the cognitive reserve, they could benefit the cognitive functioning as well as quality of life.

It is important to highlight that this study assesses cognitive deficits through self-reported subjective cognitive complaints. Although there are studies that report a correlation between subjective cognitive complaints and objectified neuropsychological performance (Jensen et al., 2015; Tourjman et al., 2019), an inverse relationship has also been found (Martínez-Arán et al., 2005), with a tendency to overestimate deficits in those with better cognitive performance in mood disorders (Miskowiak et al., 2012; Svendsen et al., 2012).

5. Limitations

The present study is not exempt of limitations. First, we cannot determine whether cognitive complaints were present prior to lockdown, so we cannot assure the magnitude of this change. Furthermore, we obtained the information from a self-applied scale assessing subjective cognitive complaints, thus, the information cannot be contrasted with an objective neuropsychological assessment. Furthermore, although they were inspired in the COBRA scale, the five items for assessing cognitive symptoms was not validated. In that way, it is important to consider that those are descriptive items, which represent only screening measures. Besides, due to the lack of validated computerized instruments, we had to adapt paper and pencil instruments to online surveys which are not validated in that form. Our sample of psychiatric patients had an over-representation of BD, so our data could not be fully extrapolated to the whole psychiatric population. The cross-sectional design of the study precludes us from drawing causal conclusions. Further longitudinal studies would be necessary to better understand the nature of the relationship between cognitive functioning and the use of coping strategies.Finally, the psychiatric diagnosis and the clinical characteristics were also self-reported.

6. Future considerations

It will be critical to design psychological intervention programs to relieve the effects of lockdown, on the one hand, and the indirect effects of the pandemic, on the other, focusing on improving psychiatric symptoms, cognitive deficits and providing tools to improve resilience and enhance protective factors (Vinkers et al., 2020). Further studies will be also needed to investigate the relationship between subjects with COVID-19 diagnosis, including the different forms of manifestation and symptoms spectrum, and the effects on neurocognitive performance through a comprehensive neuropsychological assessment.

Overall, our results highlight that psychopathological variables are risk factors for perceived subjective cognitive performance in the psychiatric population during lockdown caused by the COVID-19 pandemic, while the performance of coping strategies and healthy habits would be protective factors against cognitive dysfunction. These results have a clinical implication in daily clinical practice, highlighting the need to design therapeutic interventions not only focused in the treatment of acute psychiatric symptomatology but also to include the enhancement of coping strategies and provide our patients with tools to cope with this stressful pandemic situation that seems to stay for a long time.

Contributors

CT, BS, NV, SA, LM and EV conceived the study and the survey, with substantial contributions from the other authors. Extraction, analysis, or interpretation of data: LM, BS, NV, SA, CT and EV. Statistical analysis: LM and BS. Literature search and wrote de first draft: LM, BS, CT, NV and SA. All authors substantially participated in the final manuscript, which was reviewed, revised and approved by all authors.

Role of the funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

Dr. Bernardo has been a consultant for, received grant/research support and honoraria from, and been on the speakers/advisory board of AB-Biotics, Adamed, Angelini, Casen Recordati, Janssen-Cilag, Menarini, Roviand Takeda. Dr. García-Rizo has received honoraria/travel support from Janssen-Cilag, Lundbeck and Ferrer, and the PI20/00661 project, integrated into the State Plan of Scientific and Technical Research and Innovation 2013–2016 and co-financed by the ISCIII-General Evaluation Branch and the European Regional Development Fund (FEDER). Dr. Martínez-Aran has received funding for research projects and/or honoraria as a consultant or speaker for the following companies and institutions (work unrelated to the topic of this manuscript): Otsuka, Pfizer, AstraZeneca, Bristol-Myers Squibb, Lundbeck, the Spanish Ministry of Economy and Competitiveness and Instituto de Salud Carlos III. Dr. Vieta has received grants and served as consultant, advisor or CME speaker unrelated to this work for the following entities: AB-Biotics, Abbott, Allergan, Angelini, Dainippon Sumitomo Pharma, Ferrer, GH Research, Gedeon Richter, Janssen, Lundbeck, Otsuka, Sage, Sanofi-Aventis, Sunovion, and Takeda. The other authors do not declare any conflict of interest related to this manuscript.

Acknowledgements

The authors would like to thank the support of the Spanish Ministry of Science and Innovation; the CIBER of Mental Health (CIBERSAM); the Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement (2017 SGR 1365; 2017 SGR 1355) and the CERCA Programme / Generalitat de Catalunya. Dr. Carla Torrent is funded by the Spanish Ministry of Economy and Competitiveness, ISCIII, through a 'Miguel Servet' postdoctoral contract (CPI14/00175) and the Miguel Servet II (CPII19/00018). The study has been supported by a BITRECS project conceded to NV. BITRECS project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No. 754550 and from "La Caixa" Foundation (ID 100010434), under the agreement LCF/PR/GN18/50310006. This work has also been supported by the projects SLT006/17/00357 and SLT006/17/00345 in the "Pla estrategic de Recerca i Innovacio en Salut 2016-2020" (Health Department) CERCA (Programme/Generalitat de Catalunya). JR was supported by the Spanish Ministry of Science, Innovation, and Universities / Economy and Competitiveness / Instituto de Salud Carlos III (CPII19/00009, PI19/00394), co-financed by ERDF Funds from the European Commission ("A Way of Making Europe"). MB is also grateful for the support of the Institut de Neurociències, Universitat de Barcelona.

References

Almeria, M., Cejudo, J.C., Sotoca, J., Deus, J., Krupinski, J., 2020. Cognitive profile following COVID-19 infection: clinical predictors leading to neuropsychological impairment. Brain Behav. Immun. – Heal. 9, 100163. doi:10.1016/j.bbih.2020.100163.

Alonso-Lana, S., Marquié, M., Ruiz, A., Boada, M., 2020. Cognitive and neuropsychiatric manifestations of COVID-19 and effects on elderly individuals with dementia. Front. Aging Neurosci. doi:10.3389/fnagi.2020.588872.

Alonso, J., Vilagut, G., Mortier, P., Ferrer, M., Alayo, I., Aragón-Peña, A., Aragonès, E., Campos, M., Cura-González, I.D., Emparanza, J.I., Espuga, M., Forjaz, M.J., González-Pinto, A., Haro, J.M., López-Fresneña, N., Salázar, A.D.M., de, Molina, J.D., Ortí-Lucas, R.M., Parellada, M., Pelayo-Terán, J.M., Pérez-Zapata, A., Pijoan, J.I., Plana, N., Puig, M.T., Rius, C., Rodríguez-Blázquez, C., Sanz, F., Serra, C., Kessler, R.C., Bruffaerts, R., Vieta, E., Pérez-Solà, V., 2021. Mental health impact of the first wave of COVID-19 pandemic on Spanish healthcare workers: a large cross-sectional survey. Rev. Psiquiatr. Salud Ment. doi:10.1016/j.rpsm.2020.12.001.

An der Heiden, W., Leber, A., Häfner, H., 2016. Negative symptoms and their association with depressive symptoms in the long-term course of schizophrenia. Eur. Arch. Psychiatry Clin. Neurosci. 266, 387–396. doi:10.1007/s00406-016-0697-2.

Bora, E., Harrison, B.J., Yücel, M., Pantelis, C., 2013. Cognitive impairment in euthymic major depressive disorder: a meta-analysis. Psychol. Med. doi:10.1017/S0033291712002085.

Brooks, S.K., Webster, R.K., Smith, L.E., Woodland, L., Wessely, S., Greenberg, N., Rubin, G.J., 2020. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. Lancet 395, 912–920. doi:10.1016/S0140-6736(20)30460-8.

Christie, G.J., Hamilton, T., Manor, B.D., Farb, N.A.S., Farzan, F., Sixsmith, A., Temprado, J.J., Moreno, S., 2017. Do lifestyle activities protect against cognitive decline in aging? A review. Front. Aging Neurosci. doi:10.3389/fnagi.2017.00381.

Clare, L., Wu, Y.T., Teale, J.C., MacLeod, C., Matthews, F., Brayne, C., Woods, B., 2017. Potentially modifiable lifestyle factors, cognitive reserve, and cognitive function in later life: a cross-sectional study. PLoS Med. 14. doi:10.1371/journal.pmed.1002259.

Cothran, T.P., Kellman, S., Singh, S., Beck, J.S., Powell, K.J., Bolton, C.J., Tam, J.W., 2020. A brewing storm: the neuropsychological sequelae of hyperinflammation due to COVID-19. J. Clean. Prod. 88, 957–958. doi:10.1016/j.bbi.2020.06.008.

de Gracia Dominguez, M., Viechtbauer, W., Simons, C.J.P., van Os, J., Krabbendam, L., 2009. Are psychotic psychopathology and neurocognition orthogonal? A systematic review of their associations. Psychol. Bull. 135, 157–171. doi:10.1037/a0014415.

Di Liegro, C.M., Schiera, G., Proia, P., Di Liegro, I., 2019. Physical activity and brain health. Genes doi:10.3390/genes10090720.

Echeburúa, E., Amor, P.J., Sarasua, B., Zubizarreta, I., Holgado-Tello, F.P., Muñoz, J.M., 2016. Escala de gravedad de síntomas revisada (EGS-R) del trastorno de estrés postraumático según el DSM-5: Propiedades psicométricas. Ter. Psicol. 34, 111–128. doi:10.4067/S0718-48082016000200004.

Etnier, J.L., Nowell, P.M., Landers, D.M., Sibley, B.A., 2006. A meta-regression to examine the relationship between aerobic fitness and cognitive performance. Brain Res. Rev. doi:10.1016/j.brainresrev.2006.01.002.

Folkman, S., Lazarus, R.S., 1988. Coping as a mediator of emotion. J. Pers. Soc. Psychol. 54, 466–475. doi:10.1037/0022-3514.54.3.466.

Fonseca-Pedrero, E., Paino, M., Lemos-Giráldez, S., Muñiz, J., 2012. Validation of the community assessment psychic experiences -42 (CAPE-42) in Spanish college students and patients with psychosis. Actas Esp. Psiquiatr. 40, 169–176.

Fullana, M.A., Hidalgo-Mazzei, D., Vieta, E., Radua, J., 2020. Coping behaviors associated with decreased anxiety and depressive symptoms during the COVID-19 pandemic and lockdown. J. Affect. Disord. doi:10.1016/j.jad.2020.06.027.

Ganguli, M., Du, Y., Dodge, H.H., Ratcliff, G.G., Chang, C.C.H., 2006. Depressive symptoms and cognitive decline in late life: a prospective epidemiological study. Arch. Gen. Psychiatry 63, 153–160. doi:10.1001/archpsyc.63.2.153.

Gómez-Ramiro, M., Fico, G., Anmella, G., Vázquez, M., Saguè-Vilavella, M., Hidalgo-Mazzei, D., Pacchiarotti, I., Garriga, M., Murru, A., Parellada, E., Vieta, E., 2021. Changing trends in psychiatric emergency service admissions during the COVID-19 outbreak: report from a worldwide epicentre. J. Affect. Disord. 282, 26–32. doi:10.1016/j.jad.2020.12.057.

Guo, J., Feng, X.L., Wang, X.H., van IJzendoorn, M.H., 2020. Coping with COVID-19: exposure to covid-19 and negative impact on livelihood predict elevated mental health problems in Chinese adults. Int. J. Environ. Res. Public Health 17, 1–18. doi:10.3390/ijerph17113857.

Hantke, N.C., Gould, C., 2020. Examining older adult cognitive status in the time of COVID-19. J. Am. Geriatr. Soc. 68, 1387–1389. doi:10.1111/jgs.16514.

Hao, F., Tan, W., Jiang, L., Zhang, L., Zhao, X., Zou, Y., Hu, Y., Luo, X., Jiang, X., McIntyre, R.S., Tran, B., Sun, J., Zhang, Z., Ho, R., Ho, C., Tam, W., 2020. Do psychiatric patients experience more psychiatric symptoms during COVID-19 pandemic and lockdown? A case-control study with service and research implications for immunopsychiatry. Brain. Behav. Immun. 87, 100–106. doi:10.1016/j.bbi.2020.04.069.

Hasselbalch, B.J., Knorr, U., Kessing, L.V., 2011. Cognitive impairment in the remitted state of unipolar depressive disorder: a systematic review. J. Affect. Disord. doi:10.1016/j.jad.2010.11.011.

Heneka, M.T., Golenbock, D., Latz, E., Morgan, D., Brown, R., 2020. Immediate and long-term consequences of COVID-19 infections for the development of neurological disease. Alzheimers Res. Ther. 12, 69. doi:10.1186/s13195-020-00640-3.

Hernández-Gómez, A., Andrade-González, N., Lahera, G., Vieta, E., 2021. Recommendations for the care of patients with bipolar disorder during the COVID-19 pandemic. J. Affect. Disord. doi:10.1016/j.jad.2020.09.105.

Huang, M., Huang, Y., Yu, L., Hu, J., Chen, J., Jin, P., Xu, W., Wei, N., Hu, S., Qi, H., Xu, Y., 2016. Relationship between negative symptoms and neurocognitive functions in adolescent and adult patients with first-episode schizophrenia. BMC Psychiatry 16. doi:10.1186/s12888-016-1052-x.

Jagesar, R.R., Roozen, M.C., van der Heijden, I., Ikani, N., Tyborowska, A., Penninx, B.W.J.H., Ruhe, H.G., Sommer, I.E.C., Kas, M.J., Vorstman, J.A.S., 2021. Digital phenotyping and the COVID-19 pandemic: capturing behavioral change in patients with psychiatric disorders. Eur. Neuropsychopharmacol. 42, 115–120. doi:10.1016/j.euroneuro.2020.11.012.

Jensen, J.H., Støttrup, M.M., Nayberg, E., Knorr, U., Ullum, H., Purdon, S.E., Kessing, L.V., Miskowiak, K.W., 2015. Optimising screening for cognitive dysfunction in bipolar disorder: validation and evaluation of objective and subjective tools. J. Affect. Disord. 187, 10–19. doi:10.1016/j.jad.2015.07.039.

Josefsson, M., De Luna, X., Pudas, S., Nilsson, L.G., Nyberg, L., 2012. Genetic and lifestyle predictors of 15-year longitudinal change in episodic memory. J. Am. Geriatr. Soc. 60, 2308–2312. doi:10.1111/jgs.12000.

Kontoangelos, K., Economou, M., Papageorgiou, C., 2020. Mental health effects of COVID-19 pandemia: a review of clinical and psychological traits. Psychiatry Investig. 17, 491–505. doi:10.30773/pi.2020.0161.

Kramer, A.F., Erickson, K.I., 2007. Capitalizing on cortical plasticity: influence of physical activity on cognition and brain function. Trends Cognit. Sci. doi:10.1016/j.tics.2007.06.009.

Kroenke, K., Spitzer, R., Williams, J., 2001. The PHQ-9: validity of a brief depression severity measure. J. Gen. Intern. Med. 16. doi:10.1046/J.1525-1497.2001.016009606.X.

Kujawa, A., Green, H., Compas, B.E., Dickey, L., Pegg, S., 2020. Exposure to COVID-19 pandemic stress: associations with depression and anxiety in emerging adults in the United States. Depress. Anxiety 23109. doi:10.1002/da.23109.

Kurebayashi, Y., Otaki, J., 2017. Correlations between physical activity and neurocognitive domain functions in patients with schizophrenia: a cross-sectional study. BMC Psychiatry 17. doi:10.1186/s12888-016-1176-z.

Lahr, D., Beblo, T., Hartje, W., 2007. Cognitive performance and subjective complaints before and after remission of major depression. Cognit. Neuropsychiatry 12, 25–45. doi:10.1080/13546800600714791.

Leanza, L., Egloff, L., Studerus, E., Andreou, C., Heitz, U., Ittig, S., Beck, K., Uttinger, M., Riecher-Rössler, A., 2018. The relationship between negative symptoms and cognitive functioning in patients at clinical high risk for psychosis. Psychiatry Res. 268, 21–27. doi:10.1016/j.psychres.2018.06.047.

Loprinzi, P.D., Herod, S.M., Cardinal, B.J., Noakes, T.D., 2013. Physical activity and the brain: a review of this dynamic, bi-directional relationship. Brain Res. doi:10.1016/j.brainres.2013.10.004.

Martínez-Arán, A., Vieta, E., Colom, F., Torrent, C., Reinares, M., Goikolea, J.M., Benabarre, A., Comes, M., Sánchez-Moreno, J., 2005. Do cognitive complaints in euthymic bipolar patients reflect objective cognitive impairment? Psychother. Psychosom. 74, 295–302. doi:10.1159/000086320.

Mcloughlin, B.C., Miles, A., Webb, T.E., Knopp, P., Eyres, C., Fabbri, A., Humphries, F., Davis, D., 2020. Functional and cognitive outcomes after COVID-19 delirium. Eur. Geriatr. Med. doi:10.1007/s41999-020-00353-8.

Mikkelsen, K., Stojanovska, L., Polenakovic, M., Bosevski, M., Apostolopoulos, V., 2017. Exercise and mental health. Maturitas doi:10.1016/j.maturitas.2017.09.003.

Millan, M.J., Agid, Y., Brüne, M., Bullmore, E.T., Carter, C.S., Clayton, N.S., Connor, R., Davis, S., Deakin, B., Derubeis, R.J., Dubois, B., Geyer, M.A., Goodwin, G.M., Gorwood, P., Jay, T.M., Joëls, M., Mansuy, I.M., Meyer-Lindenberg, A., Murphy, D., Rolls, E., Saletu, B., Spedding, M., Sweeney, J., Whittington, M., Young, L.J., 2012. Cognitive dysfunction in psychiatric disor-

ders: characteristics, causes and the quest for improved therapy. Nat. Rev. Drug Discov. doi:10.1038/nrd3628.

Miskowiak, K., Johnsen, S., Sattler, S., Nielsen, S., Kunalan, K., Rungby, J., Lapperre, T., Porsberg, C., 2021. Cognitive impairments four months after COVID-19 hospital discharge: pattern, severity and association with illness variables. Eur. Neuropsychopharmacol. 46, 39–48. doi:10.1016/J.EURONEURO.2021.03.019.

Miskowiak, K., Vinberg, M., Christensen, E.M., Kessing, L.V., 2012. Is there a difference in subjective experience of cognitive function in patients with unipolar disorder versus bipolar disorder? Nord. J. Psychiatry 66, 389–395. doi:10.3109/08039488.2012.658862.

Moreno, C., Wykes, T., Galderisi, S., Nordentoft, M., Crossley, N., Jones, N., Cannon, M., Correll, C.U., Byrne, L., Carr, S., Chen, E.Y.H., Gorwood, P., Johnson, S., Kärkkäinen, H., Krystal, J.H., Lee, J., Lieberman, J., López-Jaramillo, C., Männikkö, M., Phillips, M.R., Uchida, H., Vieta, E., Vita, A., Arango, C., 2020. How mental health care should change as a consequence of the COVID-19 pandemic. Lancet Psychiatry doi:10.1016/S2215-0366(20)30307-2.

Mortier, P., Vilagut, G., Ferrer, M., Serra, C., Dios Molina, J., López-Fresneña, N., Puig, T., Pelayo-Terán, J.M., Pijoan, J.I., Emparanza, J.I., Espuga, M., Plana, N., González-Pinto, A., Ortí-Lucas, R.M., Salázar, A.M., Rius, C., Aragonès, E., Cura-González, I., Aragón-Peña, A., Campos, M., Parellada, M., Pérez-Zapata, A., Forjaz, M.J., Sanz, F., Haro, J.M., Vieta, E., Pérez-Solà, V., Kessler, R.C., Bruffaerts, R., Alonso, J., 2021. Thirty-day suicidal thoughts and behaviors among hospital workers during the first wave of the Spain COVID-19 outbreak. Depress. Anxiety. doi:10.1002/da.23129.

Peluso, M.A.M., Guerra de Andrade, L.H.S., 2005. Physical activity and mental health: the association between exercise and mood. Clinics doi:10.1590/S1807-59322005000100012.

Reinares, M., Martínez-Arán, A., Vieta, E., 2020. Psychotherapy Bipolar Disorders Integrative Approach | Mental health, Psychiatry and Clinical Psychology |. Cambridge University Press. Cambridge University Press.

Rock, P.L., Roiser, J.P., Riedel, W.J., Blackwell, A.D., 2014. Cognitive impairment in depression: a systematic review and meta-analysis. Psychol. Med. doi:10.1017/S0033291713002535.

Rosa, A.R., Mercadé, C., Sánchez-Moreno, J., Solé, B., Bonnin, Mar, Del, C., Torrent, C., Grande, I., Sugranyes, G., Popovic, D., Salamero, M., Kapczinski, F., Vieta, E., Martinez-Aran, A., 2013. Validity and reliability of a rating scale on subjective cognitive deficits in bipolar disorder (COBRA). J. Affect. Disord. 150, 29-36. doi:10.1016/j.jad.2013.02.022.

Salari, N., Hosseinian-Far, A., Jalali, R., Vaisi-Raygani, A., Rasoulpoor, Shna, Mohammadi, M., Rasoulpoor, Shabnam, Khaledi-Paveh, B., 2020. Prevalence of stress, anxiety, depression among the general population during the COVID-19 pandemic: a systematic review and meta-analysis. Glob. Health 16, 57. doi:10.1186/s12992-020-00589-w.

Serra-Blasco, M., Torres, I.J., Vicent-Gil, M., Goldberg, X., Navarra-Ventura, G., Aguilar, E., Via, E., Portella, M.J., Figuereo, I., Palao, D., Lam, R.W., Cardoner, N., 2019. Discrepancy between objective and subjective cognition in major depressive disorder. Eur. Neuropsychopharmacol. 29, 46–56. doi:10.1016/j.euroneuro.2018.11.1104.

Sim, K., Huak Chan, Y., Chong, P.N., Chua, H.C., Wen Soon, S., 2010. Psychosocial and coping responses within the community health care setting towards a national outbreak of an infectious disease. J. Psychosom. Res. 68, 195–202. doi:10.1016/j.jpsychores.2009.04.004.

Simpson, R.J., Katsanis, E., 2020. The immunological case for staying active during the COVID-19 pandemic. Brain. Behav. Immun. doi:10.1016/j.bbi.2020.04.041.

Solé, B., Verdolini, N., Amoretti, S., Montejo, L., Rosa, A., Hogg, B., Garcia-Rizo, C., Mezquida, G., Bernardo, M., Martinez-Aran, A., Vieta, E., Torrent, C., 2020. Effects of the COVID-19 pandemic and lockdown in Spain: comparison between community controls and patients with a psychiatric disorder. Preliminary results from the BRIS-MHC STUDY. J. Affect. Disord. 281. doi:10.1016/j.jad.2020.11.099.

Spitzer, R.L., Kroenke, K., Williams, J.B.W., Löwe, B., 2006. A brief measure for assessing generalized anxiety disorder: The GAD-7. Arch. Intern. Med. 166, 1092–1097. doi:10.1001/archinte.166.10.1092.

Strauss, G.P., Cohen, A.S., 2017. A transdiagnostic review of negative symptom phenomenology and etiology. Schizophr. Bull. doi:10.1093/schbul/sbx066.

Svendsen, A.M., Kessing, L.V., Munkholm, K., Vinberg, M., Miskowiak, K.W., 2012. Is there an association between subjective and objective measures of cognitive function in patients with affective disorders? Nord. J. Psychiatry 66, 248–253. doi:10.3109/08039488.2011.626870.

Talreja, B., Kataria, L., Shah, S., 2013. Cognitive function in schizophrenia and its association with socio-demographics factors. Ind. Psychiatry J. 22, 47. doi:10.4103/0972-6748.123619.

Torres, I.J., Boudreau, V.G., Yatham, L.N., 2007. Neuropsychological functioning in euthymic bipolar disorder: a meta-analysis. Acta Psychiatr. Scand. 116, 17–26. doi:10.1111/j.1600-0447.2007.01055.x.

Tourjman, S.V., Juster, R.P., Purdon, S., Stip, E., Kouassi, E., Potvin, S., 2019. The screen for cognitive impairment in psychiatry (SCIP) is associated with disease severity and cognitive complaints in major depression. Int. J. Psychiatry Clin. Pract. 23, 49–56. doi:10.1080/13651501.2018.1450512.

Varatharaj, A., Thomas, N., Ellul, M.A., Davies, N.W.S., Pollak, T.A., Tenorio, E.L., Sultan, M., Easton, A., Breen, G., Zandi, M., Coles, J.P., Manji, H., Al-Shahi Salman, R., Menon, D.K., Nicholson, T.R., Benjamin, L.A., Carson, A., Smith, C., Turner, M.R., Solomon, T., Kneen, R., Pett, S.L., Galea, I., Thomas, R.H., Michael, B.D.CoroNerve Study Group, 2020. Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. Lancet Psychiatry doi:10.1016/S2215-0366(20)30287-X.

Verdolini, N., Amoretti, S., Montejo, L., García-Rizo, C., Hogg, B., Mezquida, G., Rabelo-da-Ponte, F.D., Vallespir, C., Radua, J., Martinez-Aran, A., Pacchiarotti, I., Rosa, A.R., Bernardo, M., Vieta, E., Torrent, C., Solé, B., 2021. Resilience and mental health during the COVID-19 pandemic. J. Affect. Disord. doi:10.1016/J.JAD.2021.01.055.

Vieta, E., Pérez, V., Arango, C., 2020. Psychiatry in the aftermath of COVID-19. Rev. Psiquiatr. Salud Ment. 13, 105. doi:10.1016/J.RPSM.2020.04.004.

Vindegaard, N., Benros, M.E., 2020. COVID-19 pandemic and mental health consequences: Systematic review of the current evidence. Brain. Behav. Immun. doi:10.1016/j.bbi.2020.05.048.

Vinkers, C.H., van Amelsvoort, T., Bisson, J.I., Branchi, I., Cryan, J.F., Domschke, K., Howes, O.D., Manchia, M., Pinto, L., de Quervain, D., Schmidt, M.V, van der Wee, N.J.A., 2020. Stress resilience during the coronavirus pandemic. Eur. Neuropsychopharmacol. 35, 12–16. doi:10.1016/j.euroneuro.2020.05.003.