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Cognitive Impairment and Risk of Depressive Episodes from a Bipolar Spectrum Perspective: A Case-Control Study in Older Adults during the COVID-19 Lockdown

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Abstract: Background: A wide range of conditions, including mixed depressive symptoms, hyperactivity, cognitive impairment (CI) might be expressions of Bipolar Spectrum Disorder (BSD) according to the neo-Kraepelinian perspective, even in advanced age. CI, which has a high prevalence in the elderly population, when it occurs in comorbidity with depression further hinders therapy response and functional ability. The present study aims to explore risk factors associated with CI in elderly individuals experiencing a depressive episode during lockdown a period marked by significant stressors and rhythm disruption. **Methods:** A case-control study analyzed data from a previous RCT (secondary analyses) on elderly individuals living at home, assessing depressive symptoms, cognitive performance, hyperactivity, and hypertension before (T0) and during lockdown (T1). **Results:** Participants with lower pre-pandemic cognitive performance were more prone to lockdown depression compared to those with higher baseline function ($F = 6.074$; $p = 0.016$). Among those experiencing lockdown depression without prior depression, those with low cognitive performance were more prevalent than the control group without depression (OR = 11.8; $p = 0.015$). **Conclusion:** This study highlights a potentially vulnerable subgroup within the elderly population that requires targeted interventions and support during stressful events. Future research should explore the underlying mechanisms linking cognitive decline and depression in older adults, particularly those with a possible bipolar spectrum predisposition.

Keywords: bipolar spectrum disorder; depressive disorder; cognitive impairment; advances technologies laboratory; elderly; social and biological rhythms

1. Introduction

The relationship between depression and cognitive impairment (CI) is complex and has primarily been studied in dementia field [1,2]. There are various perspectives that study this relationship. On one side, there is the concept of "pseudodementia," where depression may be considered a prodrome for the expression of Alzheimer's disease in

older adults [1,3]. From the perspective of vascular dementia, this temporal sequence can be reversed. In this case, CI caused by vascular microlesions can be a harbinger of severe depression, which, in turn, paves the path to slow progression towards decompensation with dementia and comorbid depression [4–6]. Beyond the different forms of dementia and the interpretative perspectives of depression like risk factor, there are other several common risk factors. For example, hypertension is a common risk factor for cardiovascular disease and dementia (including Alzheimer's dementia) [7,8].

Mild Cognitive Impairment (MCI) delineates a transitional stage between the typical CI associated with normal aging and the early stages of dementia [9,10]. It is now recognized that MCI and Major Depressive Disorder (MDD) are frequent co-occurring conditions in older adults [11,12]. CI is generally acknowledged as a factor contributing to poor response to therapy, and cognitive dysfunction mediates functional disability in patients with MDD [13]. Indeed, CI can persist even in remission of mood symptoms [11]. The co-occurrence of MCI is also frequent in bipolar disorders (BD) [14], and specifically, the decline in executive function measures has been found to be associated with the duration of illness [15]. Clinical and epidemiological studies commonly utilize screening tools for diagnosing depressive episodes, which may identify individuals with a current episode, without providing a lifetime diagnosis of MDD or BD [16,17].

However, the neo-Kraepelinian concept of the bipolar spectrum disorder (BSD) [18,19] expands beyond the confines of BD classification by the American Psychiatric Association (APA) [20]. This perspective includes various mood disorders associated with CI and MCI in older adults, such as MDD or MDD with mixed symptoms, as well as conditions characterized by hyperactivity without apparent mood episodes, which could progress into full-blown disorders even in advanced age [21–23]. According to this neo-Kraepelinian viewpoint, individuals with CI or MCI and frequent mood lability (without diagnosis), designated as type VI in BSD [24], may represent late-onset BSD or depressive episodes [24]. Stressful conditions exert a significant impact on elderly individuals, who are vulnerable to CI [25]. Furthermore, stressful conditions serve as potent triggers for numerous psychiatric disorders, particularly depressive disorders, BD and the BSD [26–29].

The COVID-19 pandemic has profoundly affected people due to the fear of contagion, the loss of loved ones and relatives, and the economic problems it has induced, resulting in an increase in mood disorders in several communities [30–33] and particularly, in specific samples of population more vulnerable or more exposed to risks during the pandemic [34,35]. A further element of risk introduced by the pandemic has been the implementation of lockdowns and the subsequent alteration of personal and social rhythms, which are closely related with biorhythms. Rhythms dysregulation exposes elderly individuals to the risk of CI [36]. Moreover, the lockdown measures could also impact mood disorders. Studies have found that in countries with more stringent lockdown measures, such as Italy, the incidence of depressive episodes in individuals with BD was higher compared to countries with less stringent lockdown measures, such as Tunisia [37]. On the other hand, numerous studies have emphasized that activities aimed at maintaining or restoring the regularity of biological and social rhythms during the pandemic can be important protective factors in terms of mental health [38–40].

The objective of the present study is to examine the preceding risk factors associated with CI and in a group of elderly individuals during the lockdown, a stressful condition, compared to relative controls. The sample experiencing a depressive episode, hypertension and, in contrast to the depressive episode, a high vitality and level of energy measured via the Short Form Health Survey-12 items (SF-12) [41], this last aspect may be an indicator of hyperactivity in line with the BSD perspective hypothesis.

The case-control design was established within cohort of elderly individuals initiated a year earlier at the conclusion of a randomized controlled trial (RCT), with their final evaluation coincidentally occurring during the lockdown implemented due to the COVID-19 pandemic [42,43].

2. Materials and Methods

2.1. Design and Study Sample

A case-control over a cohort study (secondary analyses) was carried out on elderly sample people previously recruited for a RCT on exercise [42] and then followed for one year. The present sample also included individuals selected for the RCT but not included in the study due to oversubscription in the randomization, and they remained on a waiting list for a possible future trial. As detailed previously [42], inclusion criteria were individuals aged ≥65 years, regardless of sex, living at home, and who had to pass a medical evaluation to participate in non-competitive physical activity. Exclusion criteria were age <65 years, presence of health conditions unsuitable for moderate physical activity, BMI > 35, history of psychosis and/or mania, and presence of brain disease. Our sample consists of 15 cases and 78 controls. Among the cases, 11 were females and 4 were males, while among the controls, 39 were females and 39 were males ($p = 0.098$). The average age of the cases was 73.46 ± 4.26, whereas the controls had an average age of 72.41 ± 4.88 ($p = 0.439$). All individuals were assessed for depressive symptoms at cohort entry (T0) in April 2019 and 48 weeks later, in April 2020 (T1), during lockdown. Cognitive performance was evaluated at T0, along with the assessment of hyperactivity and the presence of hypertension. To assess the association between mild cognitive impairment as a potential antecedent of depressive episodes, the entire cohort was divided into individuals with depressive episodes at the end of the evaluation at T1 (during lockdown) and individuals without depressive episodes at T1.

2.2. Instruments

The Patient Health Questionnaire-9 (PHQ9) [44], is a rating self-administered scale, adopted in the Italian version [44,45], used to identify Depressive Episodes. The nine items of the tools refer to the core symptoms of the Depressive Episode according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria. According to the international cut-off, people with a PHQ9 score >4 are considered to have a Depressive Episode of at least mild severity [44].

The cognitive performance of each probands was measured with the Addenbrooke's Cognitive Examination (ACE), a cognitive test that needs about 15 min for the administration; ACE evaluates specifically five cognitive areas: memory, attention/orientation, language, verbal fluency, visual-spatial skills [46].

The mini–mental state examination (MMSE) a 30-point tool commonly used in research and clinical settings was also adopted as ad adjunctive tool for detecting the cognitive impairment [47]. MMSE, well-known, as tool to measures and screened cognitive impairment it is also used to measure the cognitive performance and to follow the changes of cognitive impairment over time [47]. In this study the correction of the score by age was adopted [48,49].

Question 10 of the Short Form Health Survey-12 items (SF-12) questionnaire [41] "How long in the last 4 weeks did you feel full of energy" was considered as a measure of possible hyperactivity refers to a level of physical or mental activity that is significantly higher than average [50]. Answer 6 = always (on the Likert scale) was considered indicative of possible hyperactivity.

The presence of arterial hypertension was measured based on the medical evaluation at T0 into the RCT.

2.3. Data Analysis Section

The data were analyzed using the SPSS software (version 23). Differences in the mean scores of ACE-R and MMSE at T0 between the two groups—those with depressive episodes at T1 and those without—were assessed using one-way ANOVA. A subsequent analysis was conducted by further dividing the group of individuals with a depressive episode at T1 into those who had depression at T0 and those who did not. Due to the small sample size, cognitive performance homogeneity was assessed using non-parametric analysis, measuring the frequency of individuals below the average and one standard deviation of

the scores in the overall sample. These frequencies were then compared between the two subgroups of individuals with depression at T1 and the group without depression at T1. A similar analysis was conducted to assess homogeneity by age. Fisher's exact test was used to directly compare nominal variables such as sex, response 6 on the SF-12 scale, and the presence of arterial hypertension. Statistical significance was set at $p < 0.05$

2.4. Ethical Aspect

The study was conducted in adherence to the Declaration of Helsinki. The Ethics Committee of the University Hospital of Cagliari reviewed and approved the study on 25 October 2018 (PG/2018/15546). Written informed consent was requested and obtained from each participant before their involvement in the study.

3. Results

At T1 (during lockdown), 15 individuals were identified as suffering from a depressive episode (16.12%), of which 73.3% were females compared to 50% in the 78 controls Chi-square = 2.757 (1df) $p = 0.098$ OR = 2.7 (CI95% 0.8–9.3), the mean age in cases was 73.46 ± 4.26 compared to 72.41 ± 4.88 in the controls (ANOVA F = 0.605, 1, 91 df, $p = 0.439$). Table 1 also shows the difference between cases and controls (groups distinguished on the basis of the presence of a depressive episode at T1) in cognitive performance at T0. The case group achieved an ACE-R score of 85.5 ± 6.18 versus 89.8 ± 6.19 in controls (ANOVA 1, 91 df F = 6.074, 1, 91 df, $p = 0.016$), an MMSE score of 26.4 ± 1.6 versus 27.4 ± 1.8 in controls (ANOVA F = 4.012, 1, 91 df, $p = 0.049$).

Table 1. Study sample and differences in cognitive performance in cases and controls.

	Cases (D + T1)	**Controls (D−T1)**	**ANOVA**	**Total**
N	15 (16.12%)	78 (73.88%)		93
Female	11/15 73.3%	39/78 50%	Chi-square = 2.757 (1 df) $p = 0.098$ OR = 2.7 (CI95% 0.8–9.3)	50
Age	73.46 ± 4.26	72.41 ± 4.88	F = 0.605 (1, 91 df) $p = 0.439$	72.58 ± 4.78
ACE-R T0	85.5 ± 6.18	89.8 ± 6.19	F = 6.074 (1, 91 df) $p = 0.016$	89.1 ± 6.19
MMSE T0	26.4 ± 1.6	27.4 ± 1.8	F = 4.012 (1, 91 df) $p = 0.049$	27.2 ± 1.9

In Table 2 is carried out a comparison in the subgroups of people with depression at T1 subdivided based on having already depression at T0 using the group of people without depression at T0 and T1 (N = 78) as pivot. The individuals with a score of ACE-R above mean-1standard deviation of the overall distribution are more frequent in the group without depression at t0 (50% vs. 8.82% in the pivotal group, Fisher Exact test $p = 0.015$; OR 11.8; CI95% 1.9–71.9) as well as individuals with a score of MMSE correct by age above mean and 1standard deviation of the overall distribution (50% vs. 1.14% in the pivotal group, Fisher Exact test $p = 0.049$; OR 6.1; CI95% 1.1–34.1). The two parameters relating to cognitive performance show no differences in the comparison between the group that was already depressed at T0 and the control group. None of the other parameters considered show statistically significant differences in the two groups compared to the comparison group (sex, age, frequency of people with hyperactivity, presence of arterial hypertension). The results presented in this study have not been adjusted for multiple testing. This should be taken into consideration when interpreting the statistical significance of our findings.

Table 2. Comparison of Subgroups of Individuals with Depression at T1, Subdivided Based on Prior Depressive Episodes at T0.

	People D− at T1 (Controls)	**People D− at T0 and D+ at T1 (Cases)**	**Fisher Exact Test OR (CI 95%)**	**People D− at T0 and D+ at T1 (Cases)**	**Fisher Exact Test OR (CI 95%)**
Female	39/78 (50%)	4/6 (66.6%)	$p = 0.904$ 2 (0.5–8.6)	7/9 (77.7)	$p = 0.109$ 3.5 (0.7–17.9)
Individuals over age of Mean-1sd of the overall sample	15 (19.7)	1 (16.6%)	$p = 0.731$ 0.8 (0.1–7.7)	2 (22.2%)	$p = 0.560$ 1.2 (0.2–6.3)
Individuals above Mean-1sd of the overall distribution of ACE-R	6 (8.82%)	3 (50%)	$p = 0.015$ 11.8 (1.9–71.9)	2 (22.2%)	$p = 0.421$ 3.4 (0.6–20.0)
Individuals above Mean-1sd of the overall distribution of MMSE correct	11 (14.1%)	3 (50%)	$p = 0.49$ 6.1 (1.1–34.1)	6.1 (1.1–34.1)	$p = 0.966$ 3.0 (0.6–14.0)
Hyperactivity at SF12 item 10 (answer 6)	9 (11.8%)	1 (16.7%)	$p = 0.544$ 1.5 (0.2–14.6)	0 (0)	$p = 0.278$ NC
Hypertension	33 (42.3%)	4 (66.6%)	$p = 0.232$ 2.7 (0.5–15.8)	4 (44.4%)	$p = 0.586$ 2.7 (0.3–4.4)

NC: Not Classified; D−: without depression; D+: with depression.

4. Discussion

This study benefitted from a longitudinal design, assessing participants' cognitive function one year before the pandemic and again for serendipity during lockdown in a particular condition of stress and modification of individual and social rhythms. Despite the limitations of a small sample size and unplanned secondary analyses, the findings point to an interest potential link between pre-existing cognitive decline and the development of depression during the lockdown.

Participants with lower cognitive performance measured pre-pandemic could be more likely to experience depression during lockdown compared to those with higher baseline cognitive function.

Following stratification of the lockdown-depressed sample by their prior depressive status (i.e., depressed vs. non-depressed one year earlier), despite the further loss of power of the study, an interesting pattern could emerge. Within the subgroup without pre-existing depression (but developing depression during lockdown), individuals with a low cognitive performance (one standard deviation below the mean) measured one year earlier (at the time without a depressive episode) were more frequent compared to the control group without depression.

This difference was suggested by both independent instruments (ACE-R and MMSE). The group of people with depression at the end of the observation but already with a depressive episode one year earlier did not present a different frequency of individuals with cognitive performance lower than one standard deviation below the mean compared to the control group without depression at the end of the follow up.

Although none of the other parameters considered showed differences in the two groups of people with a depressive episode during the lockdown (groups distinct based on whether they had a depressive episode a year before) in comparison with those who were not depressed, some elements are still worth highlighting. First of all, the fact that 1/3 of the sample with depression during the lockdown but without depression a year before, at the first assessment, answered question 10 of the SF-12 questionnaire "How long in the last 4 weeks did you feel full of energy" with the answer "always". Although it does not present a statistically significant difference compared to the frequency in people who are not depressed a year later, it could still suggest that at least those people possess those personality characteristics of basic hyperactivity intercurrent with depressive episodes which identified that set of conditions typical of the BSD and already reported as

associated with the risk of CI or MCI in old age, called bipolar type number six according classifications [18,24]. This would also explain the fact that specifically in that group a lower cognitive performance was identified as independent of the depressive state at the time of the evaluation. The low power of the study prevents considerations regarding variables that do not present a difference.

The verification of the presence of hypertension was due to the possibility that a difference in cognitive performance could be due to vascular deficit (vascular depression) [51–53] which however is not in contradiction with the hypothesis of conditions falling within the BSD.

The hypothesis that at least some of the old adults who fell into depression during the lockdown had a typical profile of the BSD could be also in line with the demonstrated increased risk of depressive episodes among people with BD in relation to the rigid lockdown and the consequent modification of rhythms social and biological [37,54–57].

In contrast, several systematic reviews and surveys reported low frequencies of major depressive disorders in older adults during the COVID-19 pandemic and lockdown [58–60]. This finding appears to contradict the high risk observed in other age groups by other systematic reviews [30–33], which is likely due to the multiple risk factors associated with the pandemic. However, a systematic review attempted to identify the main risk factors associated with the onset of depression, anxiety, sleep disorders, post-traumatic stress disorder, and obsessive-compulsive disorder during COVID pandemic, pinpointing advanced age, among other relevant factors such as female gender, high level of education, and unmarried status, as one of the most significant [61]. In particular, this seems to be confirmed by prospective longitudinal epidemiological cohort studies and reviews specifically conducted within the European framework [62,63]. Furthermore, it should be noted that there could be notable differences between elderly individuals residing in densely populated urban areas and those in rural communities [64] during the lockdown. The risk exposure and the potential impact of the lockdown on developing this type of distress are likely to be higher, especially among particularly vulnerable groups [65] who experience conditions that considerably disrupt biorhythms [66,67] and who have multiple comorbidities, often common among the elderly population [53].

These findings highlight the need for increased awareness of the potential for serious health consequences, including death, and the importance of support for older adults [68,69], especially the sub-group at risk with specific characteristics.

4.1. Strengths of the Study

The strengths of our study are:

- there is an association between pre-existing mild cognitive impairment and increased risk of depression during the lockdown in older adults highlights interesting aspects;
- the study identifies a potentially vulnerable subgroup of the elderly population that requires targeted interventions and support during stressful events;
- this study underscores the need for further research on the mechanisms linking cognitive decline and depression in older adults, particularly those with a possible predisposition to BSD.

4.2. Limitations

The limitations of our study are:

- the small sample size limits the generalizability of the results;
- the use of secondary analyses reduces the robustness of the conclusions;
- due to the sample and analysis limitations, the results cannot be widely generalized to the entire elderly population.
- Using statistical analyses such as ANOVA in a case-control study can introduce potential biases. However, due to the inclusion of continuous variables, we found this type of statistical analysis to be more appropriate.

5. Conclusions

While the limitations of a small sample and secondary analyses restrict the generalizability of our findings, the observed association between pre-existing mild CI and increased risk of depression during lockdown in older adults highlight interesting aspects. A depressive episode in an older adult with pre-existing CI can itself be a manifestation of BSD. Despite a general trend suggesting low risk of depression in elderly populations throughout the pandemic, this study highlights a potentially vulnerable subgroup within the elderly population that requires targeted interventions and support during stressful events. Future research should explore the underlying mechanisms linking cognitive decline and depression in older adults, particularly those with a possible BSD predisposition. Older adults with pre-existing cognitive impairment (CI) are at an increased risk of depression during stressful events. Therefore, clinicians should prioritize these individuals for targeted mental health interventions and monitoring during such periods. Additionally, our study indicates the need to develop strategies for the early identification of older adults with mild CI, as they may be at a higher risk of depression. Providing timely psychological support and resources can help mitigate the impact of stressors such as lockdowns. Furthermore, routine cognitive and mental health assessments for the elderly should include evaluations for depressive symptoms, especially for those with known cognitive impairments. This integrated approach can aid in the early detection and management of depression. Therefore, policymakers should consider the vulnerability of older adults with mild CI in public health planning, particularly during emergencies like pandemics. Ensuring access to mental health services and community support can help protect this at-risk group. Training programs for healthcare professionals should include modules on recognizing the interplay between cognitive impairment and depression in older adults. Enhancing their ability to identify and manage these conditions can improve patient outcomes. Public health campaigns should raise awareness about the increased risk of depression in elderly individuals with cognitive impairments. Educating families and caregivers can foster supportive environments and encourage early intervention.

These implications underscore the importance of a proactive and comprehensive approach to mental health care in older adults, especially those with cognitive vulnerabilities, to improve their overall well-being and quality of life.

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Institutional Review Board Statement: The study is registered on ClinicalTrials.gov (NCT03858114). The Regional Ethical Committee has approved the study with reference number PG/2018/15546, approved 25 October 2018.

Informed Consent Statement: Informed consent was signed by each candidate.

Data Availability Statement: The datasets of this study will be not publicly available due to individual privacy rules.

Conflicts of Interest: The authors declare no conflict of interest.

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