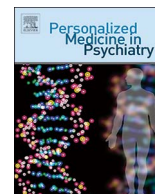




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Does gender influence cognitive function in non-psychotic depression?

Daniela Caldirola^{a,*}, Erika Sangiorgio^a, Alice Riva^a, Massimiliano Grassi^a, Alessandra Alciati^a, Chiara Scialò^a, Giampaolo Perna^{a,b,c}^a Department of Clinical Neurosciences, Hermanas Hospitalarias, Villa San Benedetto Menni Hospital, FoRiPsi, 22032 Albese con Cassano, Como, Italy^b Research Institute of Mental Health and Neuroscience and Department of Psychiatry and Neuropsychology, Faculty of Health, Medicine and Life Sciences, University of Maastricht, 6200 Maastricht, The Netherlands^c Department of Psychiatry and Behavioral Sciences, Leonard Miller School of Medicine, Miami University, 33136-1015 Miami, USA

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ABSTRACT

Cognitive impairment is a core feature of major depressive disorder (MDD). Although sex differences in several aspects of MDD have been established, previous findings are insufficient in determining whether sex differences exist in cognitive function. We investigated this topic in 130 medicated inpatients with current MDD without psychotic features (DSM-5 criteria) who were hospitalized to attend a 4-week psychiatric rehabilitation program. All variables analyzed were obtained from the patients' electronic medical records and recorded during hospitalization in accordance with standardized procedures. We considered clinical and neuropsychological variables collected within the first 3 days of hospital admission before any pharmacological modification and the beginning of the rehabilitation program. The standardized neuropsychological battery assessed verbal memory (Babcock Story Recall Test), language fluency (phonemic/semantic fluency test), verbal working memory (Digit Span backward), and psychomotor speed (Trail Making Test, Part A). As a whole, our sample significantly underperformed in comparison to Italian normative samples in all neuropsychological measures except for psychomotor speed. Controlling for potential confounding effects (illness severity/current smoking/medications), a general linear model revealed that compared with men, women significantly underperformed in all tests except for phonemic fluency. Our preliminary results indicate that women with non-psychotic MDD may be more susceptible than men to the detrimental cognitive effects of depression at least for some cognitive variables. If confirmed, this finding suggests that sex-dependent cognitive differences should be considered when tailoring therapeutic interventions in MDD.

Introduction

Major depressive disorder (MDD) [1] is a common mental illness that affects more than 300 million people worldwide [2], and it is one of the leading causes of the global burden of disability and disease [3].

Although a diagnosis of depression is mainly based on affective symptoms, growing evidence points to cognitive impairment as a core feature of MDD. Impaired ability to think, concentrate, or make even minor decisions is included in the current Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), diagnostic criteria of MDD [1]. Neuropsychological assessments have shown that compared with healthy controls (HCs), individuals who currently have depression have broad impairment in multiple cognitive domains, including language, memory, attention, psychomotor speed, visuospatial abilities, and executive function (e.g., working memory, inhibition, shifting, and planning) [4–6]. Some findings in older individuals with

depression have suggested an association between the severity of cognitive impairment and worse treatment outcomes [7].

Even after remission of acute depressive episodes, some cognitive impairments in memory, attention, speed of processing information, and executive function can persist [4,5,8–10] and may contribute to poor functional outcomes [11,12] and/or an increase in the relapse rate [13].

Moreover, bidirectional connections have been found between depression and Alzheimer's disease (AD)/other dementias [14,15], including the finding that a history of depression, particularly in late life, may confer an increased risk for later development of various types of dementia [16–18].

Although a number of studies have observed sex differences in multiple clinical aspects of MDD, the impact of gender on cognitive functioning has received little attention.

It has been established that women have higher rates of lifetime

* Corresponding author at: Department of Clinical Neurosciences, Hermanas Hospitalarias, Villa San Benedetto Menni Hospital, FoRiPsi, via Roma 16, 22032 Albese con Cassano, Como, Italy.

E-mail address: caldiroladaniela@gmail.com (D. Caldirola).

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MDD than men (22.1% and 14.4%, respectively) [19]; an earlier age at onset [20]; longer, more severe, and recurrent depressive episodes; and a greater risk for suicide attempts [21,22]. Conversely, only a few studies have compared the cognitive performance of women and men with MDD, providing mixed results, probably because of the heterogeneity of the samples and neuropsychological measures that were utilized. A small sample of older women with late-onset (LO) severe depression without psychotic symptoms and receiving psychotropic medications exhibited greater impairment in attention and verbal components of cognitive inhibition than healthy women, but did not differ from older men with LO depression [23]. No significant sex differences in emotional working memory were found in a small sample of drug-free patients with mild–moderate depression [24]. Women and men with non-psychotic MDD not taking medications did not exhibit behavioral differences in autobiographical memory recall, whereas they differed in regional hemodynamic activity during the task [25]. Finally, data derived from a very small subgroup of a multicenter, population-based case-control study indicated that compared with both men with depressive psychosis and healthy women, women with an ICD-10 diagnosis of depressive psychosis underperform in verbal/visual learning and memory, attention, processing speed, language, visual-spatial abilities, working memory, and executive function. Conversely, there were no significant differences in cognitive performance between men with depression and healthy men [26]. To date, findings are insufficient to draw conclusions on this issue.

Given the clinical and treatment implications of cognitive impairment in MDD, differences in cognitive function of affected individuals based on their gender are worthy of investigation. In case of sex-dependent differences in patterns and/or severity of cognitive impairment, they should be considered to tailor therapeutic interventions aimed at improving cognitive function and affective symptoms. The aim of the present study was to explore the influence of gender on cognitive function in a sample of inpatients with current MDD without psychotic features.

Material and methods

Participants

One hundred and thirty inpatients with MDD (DSM-5 criteria) [1] (106 women and 24 men) were recruited over 36 months from consecutive admissions to Villa San Benedetto Menni Hospital (Albese con Cassano, Como, Italy) to attend a 4-week psychiatric rehabilitation program. We included inpatients aged 18–75 years suffering from a current depressive episode without psychotic features, whereas the exclusion criteria included other current Axis I disorders (DSM-5 criteria) [1], suspected or diagnosed mental retardation (IQ < 70), lifetime neurologic disease/trauma or drug or alcohol abuse/dependence (DSM-5 criteria), electroconvulsive therapy in the preceding 6 months, hypothyroidism/hyperthyroidism or any clinical conditions that might influence the validity of neuropsychological assessment, or relevant modification of pharmacologic treatment (addition or discontinuation of medications) in the 4 weeks preceding hospitalization. Psychiatric diagnoses were determined by experienced psychiatrists via a clinical interview according to the DSM-5 criteria [1]. At the time of testing, all patients were undergoing treatment involving antidepressants [selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), or other antidepressants], 74 (56%) patients were undergoing antipsychotic augmentation (typical or atypical), 25 (19%) patients were undergoing mood stabilizer augmentation (lithium, carbamazepine, pregabalin, lamotrigine, oxcarbazepine), and 96 (74%) patients were administered benzodiazepines. All participants voluntarily provided written informed consent after a detailed explanation of the entire procedure. This study was performed in accordance with the Declaration of Helsinki and approved by the Inter-Company Ethics Committee of Como,

Lecco, and Sondrio.

Procedures and measures

All variables analyzed in this study were obtained from the patients' electronic medical records (EMRs). Each EMR included historical and clinical variables that clinicians collected during the hospitalization in accordance with standard procedures that are part of the usual clinical practice at Villa San Benedetto Hospital. All variables were collected within the first 3 days of hospital admission, before any pharmacological modification and the beginning of the rehabilitation program.

Psychiatric assessment

Senior psychiatrists collected sociodemographic/clinical information and patients' psychiatric histories through patient interviews and, when appropriate, from relatives or via patients' medical records. The severity of a patient's clinical condition was measured by the psychiatrist-rated 7-point Clinical Global Impression Scale-Severity (CGI-S) [27], ranging from 1 (normal) to 7 (among the most severely ill patients).

Neuropsychological assessment

Trained psychologists administered the following standardized neuropsychological battery, lasting for approximately half an hour. The results were expressed as both scores adjusted for age and education and equivalent scores (see "Statistical analysis"). Articles providing Italian normative data for the tests we administered (see below) did not show sex differences in performance.

Babcock story recall test

This task is a verbal memory measure in which the psychologist reads a short story and the participant is asked to recall it immediately and again after a 10-min period. The outcome measure is the number of elements recalled (range 0–52), corrected for age and education; the higher the score, the better the performance [28].

Phonemic fluency test

This task is a language fluency measure in which participants are asked to recall as many words as possible using three different letters (phonemic cues) given one at a time, with a maximum time of 60 s for each letter. The outcome is the total number of recalled words; the higher the score, the better the performance [29].

Semantic fluency test

This task is a language fluency measure where participants are asked to recall as many words as possible using three different categories (semantic cues) given one at a time, with a maximum time of 60 s for each category. The outcome is the total number of recalled words; the higher the score, the better the performance [29].

Digit Span backward

This task is a verbal working memory span measure in which participants are asked to repeat a sequence of numbers in the reverse order. The sequence to repeat becomes progressively longer and the test continues until the participant becomes unable to continue. The outcome is the number of digits correctly repeated (range 2–8); the higher the score, the better the performance [30].

Trail Making Test, Part A (TMT-A)

This task is a psychomotor speed measure where participants are asked to quickly connect numbered dots from 1 to 25 in the ascending order. The outcome measure is the time taken to complete the task; the lower the score, the better the performance [31].

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