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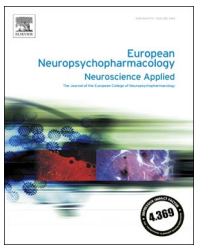

Cognitive predictors of illness course at 12 months after first-episode of depression

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Abstract
Major Depressive Disorder (MDD) entails cognitive dysfunction in many cognitive domains, but it is still uncertain whether such deficits are present in the early stages. The purpose of the study is to determine the cognitive performance in first episode depression (FED) exploring the presence of different cognitive profiles, and the role of cognition in FED at baseline and long-term. Ninety subjects (18–50 years) were included, 50 patients with a FED and 40 healthy controls. Participants were assessed with a neuropsychological battery, covering language, attention, verbal memory, processing speed and executive domains. Neuropsychological group comparisons were performed with MANOVAs. A hierarchical cluster analysis was run to identify clusters of patients with similar neuropsychological performance. Two generalized linear models were built to predict baseline HDRS-17 and changes at 12 months. Patients performed significantly worse than healthy controls in language, attention/working memory, verbal memory, processing speed and executive functioning, with moderate to large effect sizes (0.5 - 1). Two clusters were found: cognitively preserved patients (n=37) and cognitively impaired patients (n=13). Large effect sizes of cognitive impairment in FED were observed between the two cognitive clusters (preserved and impaired). Depressive symptoms at baseline were predicted by verbal memory (p=0.003), while 12-month changes were predicted by

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executive function (p=0.041) and language (p=0.037). Cognitive performance predicted depressive symptoms at baseline and at follow-up, pointing to the usefulness of cognitive assessment even at the commencement of the illness.

1. Introduction

Cognitive dysfunction is considered a central characteristic of Major Depressive Disorder, MDD (Bortolato et al., 2015). Diminished ability to think or to concentrate or to make decisions is part of the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) for MDD. Currently, there is sufficient scientific evidence that proves the existence of cognitive impairment not only in the acute phase of the disease, but even in periods of remission of clinical symptoms (Rock et al., 2014). Cognitive dysfunction has been correlated with poorer occupational and psychosocial functioning, as well as with an increased risk of relapse (Evans et al., 2014; Hammar and Ardal, 2009). Despite it is well accepted that MDD entails cognitive dysfunction in attention, processing speed, memory and executive function, there is a lack of agreement on the specificity or the degree of such cognitive deficits.

Among the factors related with the inconsistencies in cognitive impairment, the mixture of patients included in previous studies could be the most relevant one, given that cognitive deficits may depend on the stage of the illness and on different depression trajectories (Hammar and Ardal, 2009), making it difficult to ascertain whether cognitive symptoms arise together with the rest of depressive symptoms. Therefore, a more adequate approach to disentangle this issue is to investigate cognitive functioning in a homogeneous sample with similar illness burden as for instance patients with a first episode of depression (FED). The scarce literature of cognitive functioning in FED shows that cognitive impairment are already observable in early stages of MDD (Ahern and Semkovska, 2017; Lee et al., 2012). But again, there still exists some controversy upon the degree of impairment, given that the majority of these studies base their conclusions on group differences, considering that patients would have a unique neuropsychological profile (i.e., averaging neurocognitive performance of all patients). Therefore, it might be necessary to define subgroups of patients taking into account their cognitive characteristics, as some patients could present cognitive deficits while others could not.

Yet, current literature on cognitive dysfunction in FED has not provided any evidence on the usefulness of assessing cognition at the commencement of the illness. Although nowadays research findings point towards a holistic perspective of major depressive symptomatology (i.e., including the core depressive symptoms and the cognitive ones), we are far from seeing that cognitive evaluation will help clinicians and psychotherapists when treating patients. Previous works have already determine that cognitive symptoms, in particular executive dysfunction, can remain beyond the acute episode (Ahern and Semkovska, 2017), as well as they can represent vulnerability factors for further relapses (Lee et al., 2012). Therefore, cognitive performance may be used as a predictive factor of long-term clinical manifestations, but no studies have been carried out on this regard.

The aims of this study were to determine the cognitive performance of patients with a first episode depression in order to explore the presence of different cognitive profiles; and to investigate whether cognitive deficits at illness onset could predict baseline clinical profile and follow-up clinical outcomes. The first hypothesis is that there will be different levels of cognitive impairment in the group of FED patients. The second hypothesis is that cognitive performance together with other known factors will be predictive of initial and future depressive symptoms.

2. Experimental procedures

2.1. Participants

Ninety subjects aged between 18 and 50 years were included in the present study, 50 patients fulfilling criteria for a first episode of depression (FED; DSM-IV-TR criteria) and 40 healthy controls. FED patients were recruited from the emergency psychiatric services of the Hospital Sant Pau in Barcelona and Hospital Parc Taulí in Sabadell, and healthy controls, from the community. Patients were antidepressant treatment-naïve or had taken antidepressants for less than two weeks prior of the study inclusion. Treatment regimens were homogeneous for all patients and included a Selective Serotonin Reuptake Inhibitor -SSRI- (mainly escitalopram 20 mg/day or citalopram 40 mg/day, and in five cases fluoxetine) plus benzodiazepines if needed. Depressive symptoms were evaluated using the 17-item Hamilton Depression Rating Scale (HDRS-17; Hamilton, 1960; Bobes et al., 2003) at the beginning of the study and twelve months after. Patients were required to have a total score $\geq$14 on the HDRS-17 for inclusion. Exclusion criteria for all participants were axis I comorbidity according DSM-IV-TR, significant physical or neurological illnesses or intelligence quotient (IQ) <80. Lifetime psychiatric diagnoses and first-degree relatives with psychiatric diagnoses were exclusion criteria for healthy controls. The study was approved by the Research Ethics Board of Hospital de Sant Pau and permission was obtained from the Ethics Committee of Hospital

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