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Research report

Neuropsychological performance in melancholic, atypical and undifferentiated major depression during depressed and remitted states: a prospective longitudinal study

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ABSTRACT

Background: Considerable evidence has demonstrated that melancholic and atypical major depression have distinct biological correlates relative to undifferentiated major depression, but few studies have specifically delineated neuropsychological performance for them.
Method: In a six-week prospective longitudinal study, we simultaneously compared neuropsychological performance among melancholic depression ($n=142$), atypical depression ($n=76$), undifferentiated major depression ($n=91$), and healthy controls ($n=200$) during a major depressive episode and a clinically remitted state, respectively. We administered neuropsychological tests assessing processing speed, attention, shifting, planning, verbal fluency, visual spatial memory, and verbal working memory to all participants.
Results: During the depressive state, the three subtypes displayed extensive cognitive impairment, except for attention, when compared with the healthy controls. Melancholic depression significantly differed from atypical depression in processing speed and verbal fluency. In the remitted state, the three subtypes recovered their visual spatial memory and verbal working memory functions to the healthy control level. The recovery of the other domains (processing speed, set shifting, planning, and verbal fluency), however, was different across the subtypes. No predictive relationship existed between neuropsychological performance and the treatment outcome.
Limitations: The drop-out rate in the six-week longitudinal study was relatively high.
Conclusion: Our data provide preliminary evidence that during depressed states the three major depressive subtypes display similar cognitive deficits in some domains but differ in such domains as processing speed and verbal fluency. The recovery of the cognitive deficits following clinical remission from depression may be associated with subtypes of major depressive disorder.

1. Introduction

Major depressive disorder (MDD) is a heterogeneous disorder. In the current Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition (DSM-IV-TR), a category of major depressive episode (MDE) includes different depressive syndromes, such as melancholic and atypical types. While melancholic depression falls into the MDD realm, many authors have argued that it represents a distinct mood

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disorder from MDD (Parker et al., 2010a, 2010b). They suggest such a classification mainly on the basis of its distinct biological correlates [e.g. adrenocorticotropin, hypercortisolemia, and characterized sleep disturbance] (Armitage, 2007; Cizza, et al., 2012, Lamers et al., 2013; Rush et al., 1997), preferential treatment response (Brown, 2007; Petrides et al., 2001), and its clinical features (Parker et al., 2013).

Initially contrasted with melancholic depression, atypical depression as a DSM-IV-TR-defined subtype distinguishes itself by a more favorable response to monoamine oxidase inhibitors (MAOIs) than tricyclic antidepressants (TCAs) treatment (Pae et al., 2009; Quitkin et al., 1988). Furthermore, many clinical studies have demonstrated that atypical depression differs from melancholic depression in having a younger age of onset, less severe and fewer episodes, having a longer duration of an episode, being over-represented among females, and having more co-morbidities with anxiety and substance abuse (Gili et al., 2012; Posternak and Zimmerman, 2002; Stewart et al., 2010). Some authors have also suggested biological discriminating markers, including cortisol levels (Anisman et al., 1999; Lamers et al., 2013), inflammatory markers [e.g., interleukin-6] (Lamers et al., 2013), and hemispheric asymmetry (Bruder et al., 1989) for atypical, melancholic, and undifferentiated depression (which is defined as having neither melancholic nor atypical features).

Considering the special positions of melancholic and atypical depression in nosology as well as the clinical and biological differences across them, it is important to delineate cognitive function (e.g., attention and executive function) for each of them rather than intuitively treating them the same, either as undifferentiated depression or as having no differences within MDD. The data of the neuropsychological performance of MDD, largely generated from studies of mixed samples without subtyping, suggest that MDD patients display a wide range of cognitive deficits during depressive episodes but in remitted states, have shown both non-impairment and impairment results for attention, processing speed, and executive function; the last is perhaps the most controversial (Gallagher et al., 2007; Hasselbalch et al., 2011; Snyder, 2013). One main contributing factor may be the "contaminated" samples (mixed samples without subtyping), because several studies comparing neuropsychological performance in melancholic with non-melancholic depression show that they differ in attention (Quinn et al., 2012), processing speed, visual working memory (Austin et al., 1999), set shifting (Austin et al., 1999; Michopoulos et al., 2008), semantic fluency (Naismith et al., 2003), and response selection (Rogers et al., 2004). In addition, it is worth noting that many studies using only a small number of neuropsychological measures of executive function may create a task impurity problem (Snyder, 2013). For instance, a low score on a single executive task such as the color-word Stroop task may not be due to impaired executive function but to non-executive abilities such as visual processing (Miyake et al., 2001).

By comparing neuropsychological performance across subtypes of MDD, it may help identify discriminating cognitive markers, therefore better classifying the subtypes in this disorder. Cognitive deficits may serve as an endophenotype for MDD (Christensen et al., 2006; Peterson and Weissman, 2011) and as a discriminator for unipolar and bipolar depression (Xu et al., 2012); in this regard, a cognitive profile may have the potential value to differentiate depressive subtypes that have exhibited distinct biological correlates. Moreover, patterns of activations in the brain regions underpinning cognitive function are distinct among atypical, melancholic, and undifferentiated depression (Fountoulakis et al., 2004), and further implying such a potential for serving as differentiating cognitive markers.

Given the above considerations, we thus aimed, both for the major depressive and clinically remitted states, to delineate neuropsychological performance on atypical, melancholic, and undifferentiated depression independently, with an emphasis on several aspects of executive function (e.g., shifting, planning, and verbal and visual working memory) using a comprehensive battery of neuropsychological instruments, as well as on further examining whether, or to what extent, specific domains could differentiate them. In addition, several studies found that such cognitive profiles as processing speed (Taylor et al., 2006), visual memory (Herrera-Guzman et al., 2008), and executive function (Douglas et al., 2011) might predict treatment outcome in MDD patients. The secondary aim then was to inspect the predictive value of neuropsychological performance for antidepressant treatment outcomes in MDD.

2. Method

2.1. Study settings and design

Guangzhou Psychiatric Hospital—China's oldest psychiatric hospital, established by Dr. J. G. Kerr in 1898 (Zhang and Ning, 2010), — launched a study entitled "The Clinical and Biological Characteristics and Optimizing treatment in bipolar depressive disorder (CBCOB)" from June 2007 to November 2010, with the main aims being to optimize treatments and functional outcomes for patients with MDD or bipolar disorders, as well as to improve the detection of bipolar disorders (especially bipolar II) in MDD patients in the context of clinical features and biological markers. In the project, the Guangzhou Psychiatric Hospital research team collaborated with The First Affiliated Hospital of Jinan University researchers, as noted elsewhere (Xu et al., 2012), and both hospitals were tertiary medical centers (e.g., national and university centers) from which all of the participants of the study were recruited. The project was approved by the institutional review board (IRB) of the Guangzhou Psychiatric Hospital and administrated at China clinical trial (ChiCTR-TNRC-10001112, http://www.chictr.org/).

The present data is derived from the foregoing study, which was a prospective, semi-naturalistic, and six-week open-label trial on MDD during a MDE, consisting of two phases. In Phase I, a one-to seven-day screening period, in-patients or out-patients receiving psychiatry services in the two specialist hospitals were referred to the study when diagnosed as MDD by their first contact psychiatrist. After obtaining written consent that was approved by the IRB of Guangzhou Psychiatric Hospital, one full-time research psychiatrist for the study conducted subsequent clinical interviews and applied the Chinese version of the Structured Clinical Interview for DSM-IV-TR Axis I Disorders Patient Edition (SCID-I/P) to confirm the diagnoses (First et al., 2002). Another senior psychiatrist of this study conducted an independent clinical interview. The inter-rater reliability for MDD between the two interviewers was excellent (kappa value > 0.95). Medical records including blood chemistry such as thyroid and sex hormones were collected. Therefore, we utilized all the information available and diagnosed the patients according to the combination of the consensus of the clinical impression, the SCID interview, and a review of medical records.

In Phase II, a six-week semi-naturalistic treatment, Dr. Dang Y. evaluated patients using broad clinical instruments each week. These were supplemented by scheduled clinical interviews performed by Dr. Xu G. As an additional quality control, a group of three senior psychiatrists assigned by the Guangzhou Psychiatric Hospital conducted random inspections at this stage. In brief, all of the patients in this study underwent systematic assessments, and their diagnoses were prospectively validated.

2.2. Sample and medication

The project recruited 353 patients with DSM-IV-TR-defined MDD, aged 18–60 years, of whom 309 agreed to take part in the