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Sex-related variation of neurocognitive functioning in bipolar disorder: Focus on visual memory and associative learning

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ABSTRACT

Bipolar disorder (BD) is associated with cognitive deficits in attention, verbal memory and executive functions. However, only few studies have examined sex effects on cognition despite their clinical relevance. Given that visual memory/ learning has been understudied the aim of our study was to investigate sex-related variation in cognition (executive functions and visual memory/ learning) in BD. Cognitive performance of 60 bipolar-I patients and 30 healthy controls was evaluated by using CANTAB battery tasks targeting spatial memory (SRM), paired associative learning (PAL) and executive functions. We fitted a multivariate analysis of covariance (MANCOVA), followed by task-specific ANCOVAs. A significant diagnosis by sex interaction effect was detected (MANCOVA); specifically, diagnosis-specific sex effects were found for SRM and PAL, as healthy males outperformed healthy females but this pattern was attenuated in BD patients. Patients' clinicodemographic characteristics, current psychopathology or medication status did not differ across sexes and were, therefore, unlikely to explain detected sex effects. Our study is one of few studies to assess sex-related variation in cognition in BD and the first to record a diagnosis-specific sex effect for two tasks of visuo-spatial memory/ learning, indicating that sex-related variation in healthy subjects is disrupted in BD.

1. Introduction

By now, a large number of studies have investigated neuropsychological performance in bipolar disorder (BD). Their results indicate impairments primarily in the areas of sustained attention, executive function and verbal or non-verbal memory both in the active phases of the disease and in euthymia (Bortolato et al., 2015; Cullen et al., 2016; Goodwin et al., 2008; Quraishi and Frangou, 2002). Neuropsychological deficits are related to non-adherence to medication and contribute to worse long-term functional outcomes such as poor quality of life and psychosocial disability (Dickerson et al., 2004).

The study of memory is central to BD mainly because of the localization of memory processes in the hippocampus which is also a region that is closely related to mood regulation and the pathophysiology of BD with several lines of evidence demonstrating structural and functional hippocampal abnormalities in bipolar patients (Bearden et al., 2008; Chepenik et al., 2012; Frazier et al., 2005; Frey et al., 2007; Otten and Meeter, 2015). A large number of studies have detected memory deficits in BD mainly in verbal memory assessments whereas non-verbal memory has been relatively less investigated in BD (Arts et al., 2008; Bora et al., 2009; Quraishi and Frangou, 2002). For instance, in the Arts et al. (2008) meta-analysis, 98 BD patients were compared to 89 controls on visual memory tasks while 414 BD patients and 427 controls were compared on several verbal memory tasks. Visual memory has been examined mainly with the Rey–Osterrieth figure task in small sample size studies wherein small and medium effect size differences were detected between BD patients and controls for visuoconstruction and delayed visual recall, respectively (Altshuler et al., 2004; Deckersbach et al., 2004; Ferrier et al., 1999; van Gorp et al., 1998). However, given the lateralization of memory functions in relation to stimulus type (with left and right hemisphere structures including left/ right hippocampus involved in verbal and visual stimuli memory processing, respectively) (Banks et al., 2012; Kelley et al., 1998), the study of non-verbal mnemonic processes is relevant in BD. Moreover, deficits in executive functions have been reported in several studies in euthymic bipolar patients. In particular, impairments in working memory, attentional set shifting, inhibitory control and verbal fluency represent the most replicated findings in euthymia (Bourne et al., 2013; Torres

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et al., 2007).

The identification of factors affecting neurocognitive functioning in BD has received much attention with research focusing mainly on clinical and neurobiological factors. Although sex is a plausible predictor of neurocognition, suggested by sexual dimorphism in normal brain structures, as well as sex-related differences in neurocognition in healthy participants and in schizophrenic patients (Andreano and Cahill, 2009; Torniainen et al., 2011; Zanelli et al., 2013), only few studies have specifically assessed sex-related differences in neurocognitive functioning in BD (Barrett et al., 2008; Bucker et al., 2014; Carrus et al., 2010; Gogos et al., 2010; Vaskinn et al., 2011). This relative paucity of studies is notable especially in the light of sex's well documented effect on clinical profile and course of BD (Arnold, 2003; Diflorio and Jones, 2010). In fact, several studies show that women are more likely than men to experience mixed mania, a higher number of depressive episodes, rapid cycling and seasonal types of the disorder as well as Bipolar Disorder type II; on the other hand, men are more prone to experience more manic episodes, have an earlier age of onset and worse psychosocial outcome than women with BD (Arnold, 2003; Diflorio and Jones, 2010; Kennedy et al., 2005).

Therefore, the aim of the current study was to investigate potential diagnosis-specific sex effects on neurocognitive functioning (executive functions and visual memory, including visual associative learning) in BD.

2. Method

2.1. Subjects

Sixty bipolar patients were consecutively recruited in the study from the 2nd Department of Psychiatry of Athens University Medical School at Attikon General Hospital during the period May 2008–November 2009. All patients had a Bipolar Disorder type I diagnosis according to the DSM-IV criteria (American Psychiatric Association, 2000) and they were either attending the outpatient clinic ($N = 30$) or were admitted to the psychiatric inpatient unit ($N = 30$). Outpatients were all euthymic (HAMD and YMRS scores ≤ 10), whereas inpatients were assessed close to their discharge after having responded to treatment while being at least partially remitted. Patients were excluded if they had a serious neurological or medical condition as well as a history of substance or alcohol misuse in the past 6 months or an eating disorder diagnosis.

Thirty healthy controls were also included in the study. Healthy controls were recruited in the hospital and were either members of the staff or caregivers of patients admitted in other medical departments. All subjects did not suffer from any major mental disorder (depression, schizophrenia, bipolar disorder). Exclusion criteria for controls were the same as for the patients. Every participant signed an informed consent form following detailed description of the study. The study was approved by the Ethics Committee of Attikon General Hospital.

2.2. Clinical assessment

Current and lifetime diagnostic status of patients was confirmed with the Mini International Neuropsychiatric Interview (Sheehan et al., 1998). Presence of dementia was excluded by the administration of the Mini Mental State Examination questionnaire (Folstein et al., 1975). Clinical assessment and symptom evaluation took place on the same day of cognitive testing via administration of the 17-item Hamilton depression rating scale (HAMD-17) (Hamilton, 1960) and Young mania rating scale (YMRS) (Young et al., 1978). Information about patients' psychiatric history (age at onset (defined as the age when subjects first experienced an episode of either polarity), duration of illness, number and type of previous episodes and history of psychotic symptoms) and current treatment was collected from the patients, primary caregivers and medical records.

Control subjects were assessed by a brief clinical interview based on the MINI, including items on demographic data, personal history, any present complaints, psychiatric and medical history, past and current medical or psychiatric therapies, and a brief mental state examination (overall behavior, psychomotor activity, speech, mood, thought content and form, perception, cognition and judgment).

2.3. Neuropsychological assessment

Patients were administered a series of tests from the Cambridge neuropsychological test automated battery (CANTAB) which is a computer-administrated set of tasks developed to assess specific components of cognition, especially those associated with frontal and medial temporal regions of the brain (Robbins et al., 1994). The tasks were given by the same qualified psychiatrist and in the same order to all participants.

2.3.1. Visuo-spatial memory and learning assessment

Spatial recognition memory (SRM). This memory task assesses the ability to remember the spatial location of visual stimuli. Five squares are presented in sequence at different locations on the screen, and then subjects are presented a pair of squares and asked to identify which is at a location where a square was previously presented. Percentage of correct responses is recorded.

Paired associates learning (PAL). This visuospatial learning task assesses the ability to learn associations between specific visual patterns and their location on the screen. Designs are presented in boxes on the screen in a randomized order. The designs are then presented sequentially in the center of the screen and subjects are instructed to indicate the box in which each design was initially presented. The task involves sequential stages of increasing difficulty. The total number of errors adjusted for the number of stages successfully completed ("total errors adjusted") is recorded.

2.3.2. Executive function assessment

Intradimensional/Extradimensional attentional set shifting (ID/ED). This test involves sequential stages of increasing difficulty and was designed to examine component executive function processes (rule discovery and reversal) evaluated in aggregate by the Wisconsin Card Sorting Test (WCST). It assesses the ability to maintain attention to different examples within a stimulus dimension and the ability to shift attention to a previously irrelevant stimulus dimension. The number of errors committed (adjusted for the number of stages successfully completed) are recorded.

Stockings of Cambridge (SOC). This executive function task investigates the ability of planning and problem solving. It is a modified version of the well known Tower of London task and requires subjects to rearrange colored balls in vertical columns to match a desired final arrangement in a specified minimum number of moves. Subjects are told to plan their sequence of moves before starting to move the balls shown on the monitor. The "total problems solved in minimum moves" variable is recorded as the basic measure of the subject's planning ability.

2.4. Statistical analysis

Statistical analyses were carried out with SPSS version 22.0. The normality of the distribution of all variables was evaluated with the Shapiro–Wilk test. For the investigated variables that were not normally distributed, medians and interquartile ranges were used in descriptives. Statistical significance was set at 0.05.

Comparison between males and females within patient and control groups on neuropsychological measures was performed with Mann Whitney or student's t test as appropriate. To explore sex effects, a multivariate analysis of covariance (MANCOVA) with all neuropsychological measures was performed using sex and diagnosis