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Research paper

Manual motor speed dysfunction as a neurocognitive endophenotype in euthymic bipolar disorder patients and their healthy relatives. Evidence from a 5-year follow-up study

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ABSTRACT

Background: Few studies have examined Manual Motor Speed (MMS) in bipolar disorder (BD). The aim of this longitudinal, family study was to explore whether dysfunctional MMS represents a neurocognitive endophenotype of BD.

Methods: A sample of 291 subjects, including 131 BD patients, 77 healthy first-degree relatives (BD-Rel), and 83 genetically-unrelated healthy controls (HC), was assessed with the Finger-Tapping Test (FTT) on three occasions over a 5-year period. Dependence of FTT on participants´ age was removed by means of a lineal model of HC samples, while correcting simultaneously the time and learning effect. Differences between groups were evaluated with an ANOVA test.

Results: The patients' performance was significantly worse than that of HC over time ($p \leq 0.006$), and these deficits remained when non-euthymic BD patients (n=9) were excluded from analysis. Some significant differences between BD patients and BD-Rel ($p \leq 0.037$) and between BD-Rel and HC ($p \leq 0.033$) were found, but they tended to disappear as time progressed ($p \geq 0.057$). Performance of the BD-Rel group was intermediate to that of BD and HC. Most sociodemographic and clinical variables did not affect these results in patients. ($p \geq 0.1$). However, treatment with carbamazepine and benzodiazepines may exert a iatrogenic effect on MMS performance ($p \leq 0.006$).

Limitations: Only right-handed subjects were included in this study. Substantial attrition over time was detected.

Conclusions: There were significant differences between the patients´ MMS performance and that of healthy relatives and controls, regardless of most clinical and sociodemographic variables. Dysfunctional MMS could be considered an endophenotype of BD. Further studies are needed to rule out possible iatrogenic effects of some psychopharmacological treatments.

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1. Introduction

There has been increasing interest in the neurobiological processes underlying bipolar disorder (BD), such as mechanisms associated with mood fluctuations, its core symptoms, neurocognitive deficits and the effects of the disease on interpersonal and psychosocial functioning (Bortolato et al., 2015; Porter et al., 2015; Lolich et al., 2015). Several approaches have been used to identify the endophenotypic profile associated with BD, including genetic, neurocognitive, physiological, and neuroimaging methods (Hasler et al., 2006;; Scott et al., 2010; Lövdahl et al., 2014; Kim et al., 2015; Sarıçiçek et al., 2015). There is growing interest in identifying neurocognitive endophenotypes associated with BD, since cognition is a major predictor of patients' functional outcomes (Tabarés-Seisdedos et al., 2008; Depp et al., 2012). The most suitable candidates include verbal memory and learning, attention / concentration, and executive functions such as cognitive flexibility, verbal fluency, and working memory (Balanzá-Martínez et al., 2008; Bora et al., 2009; Glahn et al., 2010). Motor functions in general, and manual motor speed (MMS) in particular, are among the least studied domains (Balanzá-Martínez et al., 2008). According to a meta-analysis of functional neuroimaging studies, the entire neural network subserving different finger tapping tasks include the primary sensorimotor cortex, the supplementary motor area, the basal ganglia, and the cerebellum (Witt et al., 2008). Moreover, finger tapping is impaired by damage to brain regions such as dorsal premotor and prefrontal areas (Calautti et al., 2010), and the cerebellum (Molinari et al., 2007). In addition, fine motor skills such as finger tapping are considered complex motor skills requiring higher cognitive demand (Best, 2010). Indeed, their relationship with higher-order executive cognition is thought to be mediated by the co-activation of the prefrontal cortex and the cerebellum (van der Fels et al., 2015). The finger tapping test therefore can be considered an useful quantitative tool for the assessment of motor system.

Endophenotypes should be associated with the disease within a population, be state-independent, be heritable, and co-segregate with the disease within families (Gottesman and Gould, 2003). Accordingly, including a group of relatives is key to identify such neurocognitive endophenotypes. In a systematic review, we (Balanzá-Martínez et al., 2008) found only two family studies which had evaluated motor functioning in BD. First-degree relatives of BD patients had spared motor skills assessed with the Purdue Pegboard test, whereas high-risk offspring of BD patients performed worse than the offspring of healthy subjects in the Grooved Pegboard test (McDonough-Ryan et al., 2002). According to a subsequent cross-sectional report, BD patients and their healthy relatives had several neuropsychological deficits, including motor function measured by the Finger Tapping, Grip Strength and Grooved Pegboard tests, with relatives showing an intermediate performance (Frantom et al., 2008). The aforementioned studies provided inconsistent findings, and only Frantom et al. assessed MMS. Our group (Salazar-Fraile et al., 2009) has previously shown that specific and stable neurocognitive deficits in patients with schizophrenia and BD may be associated with slow MMS, which points to it as an endophenotype of both conditions.

The assessment of state-independence of a neurocognitive endophenotype (e.g. it is present regardless of whether or not the disease is active) may be performed with cross-sectional studies during euthymia or with longitudinal designs (Vieta, 2014). Follow-up, prospective neuropsychological studies of BD patients are scarce and report inconsistent results regarding the stability of neurocognitive deficits (for recent reviews, see Lim et al., 2013; Samamé et al., 2014). However, patients' motor performance has not been meta-analysed due to the low number of available studies (Samamé et al., 2014). Moreover, to our knowledge, no longitudinal study examining relatives of BD patients has been published. Therefore, a study combining a family and longitudinal designs might help to move the field forward.

The purpose of the present follow-up, family study was to examine the suitability of MMS as a bipolar endophenotype. Our hypothesis is that, if both BD patients, regardless of their clinical condition or medication, and their healthy first-degree relatives show a dysfunction in MMS that remains stable over time, it may constitute an endophenotype of BD.

2. Methods

2.1. Study design

The present study is part of an ongoing, larger neurocognitive investigation of severe mental disorders carried out by the CIBERSAM-G24/ TMAP- UV in Valencia, Spain. In this follow-up study, neurocognitive, clinical and functional data of psychiatric patients, their unaffected first-degree relatives and genetically-unrelated healthy volunteers are simultaneously assessed three times over a 5-year period (Tabarés-Seisdedos et al., 2008; Salazar-Fraile et al., 2009; Selva-Vera et al., 2010).

2.2. Participants

The sample of this study is composed of 291 adult participants, including 131 BD patients, 77 of their healthy first-degree relatives (parents, siblings and offspring; BD-Rel) and 83 volunteers with no personal and family psychiatric history, which constitute healthy controls (HC). BD and BD-Rel were recruited from three mental health centers in the metropolitan area of Valencia (Spain), and HC were recruited by word of mouth in the same areas of residence. BD was diagnosed by experienced psychiatrists according to the DSM-IV-TR criteria (American Psychiatric Association, 2000), and all patients were confirmed to be clinically stable at the time of evaluation. HC were of similar ages and years of education. The following exclusion criteria were applied: BD-Rel should not be suffering from severe mental illness; patients should not have any substance use disorder, an IQ below 70, head trauma, motor dysfunctions and neurological or medical conditions that might hinder the performance of the tests. After explaining the study procedures to the participants, they signed an informed consent form approved by the Ethics Committee of the University Clinical Hospital of Valencia. Left-handed people were excluded from the analysis, as they were a very small minority and, due to the test characteristics, their inclusion might have distorted the results.

2.3. Assessments

2.3.1. Sociodemographic and clinical assessment

The second assessment (T2) took place an average of one year after the first assessment (T1), whereas the third assessment (T3) took place an average of 5 years after T1. Sociodemographic data were collected at each time point (T1, T2, T3): sex, age, living status, occupational status, and years of education. For patients, the following clinical data were collected: age of onset, family history of mental illness, type and number of psychopharmacological treatment (comparison of “on and off” patients), and adherence to treatment. In order to assess mood state over the course of the study, the variable “euthymia” based on the scores or the Young Mania Rating Scale (YMRS) (Young et al., 1978; Colom et al., 2002) and the Hamilton Rating Scale for Depression (HRSD-17) (Hamilton, 1960; Ramos-Brieva and Cordero-Villafáfila, 1986) was entered in the analysis. Euthymic patients score is “1” when total YMRS score is less or equal than 6 and total HRSD-17 total score is less or equal than 8. Higher scores in one or both scales give a score “0” in the variable “euthymia”, meaning that a given patient is “not euthymic”.

2.3.2. Estimated Intelligence Quotient (IQ)

The estimated Intelligence Quotient (IQ) was calculated by means