Resumen en inglés de la tesis TEORÍA DE LA MENTE Y DESARROLLO DE SÍNTOMAS PSICÓTICOS EN EL TRASTORNO BIPOLAR

Abstract:

BACKGROUND: Development of psychotic symptoms in bipolar disorder is frequent, particularly in the manic phases, when they are present in more than half cases. Delusions (paranoid, megalomaniac, ruin, hypochondriacal, referential and bizarre) and auditory hallucinations (reviewed in Goodwin & Jamison, 1990) are the predominant psychotic symptoms. This appearance of psychotic symptoms is associated with a higher rate of family history of other psychotic disorders (Potash *et al*, 2001), higher comorbidity (Strakowski *et al*, 1995), worse clinical outcome (Coryell *et al*, 1990) and worse psychosocial adjustment. Some other studies have suggested that the development of psychotic symptoms could be associated with an early age at onset (Strober, 1996) and alterations in the brain structure (Reite *et al*, 1999). Despite the above, there is a lack of specific vulnerability markers to predict the development of psychotic symptoms in the course of bipolar disorder.

The relationship between Theory of Mind (ToM) and the development of psychosis has been increasingly debated in the last decade. ToM is defined as the *cognitive ability to infere mental states to oneself and to others*, in terms of thought, emotion and intention (Premack & Woodruff, 1978; Baron-Cohen, 1985). Frith (1992) proposed that a ToM abnormality could underlie the development of psychotic symptoms in schizophrenia, leading to a great volume of publications in that respect (see reviews Brüne, 2005; Harrington, 2005). The association between ToM deficit and negative symptoms (Frith & Corcoran, 1996; Langdon *et al*, 1997; Mazza *et al,* 2001) and disorganization symptoms (Sarfati *et al*, 1997; Sarfati &

Hardy-Bayle, 1999), has been shown, whereas the association with paranoid symptomatology seems to be more controversial (Corcoran *et al*, 1995; Pickup & Frith, 2001; Randall *et al*, 2003; Harrington, 2005). A supplementary line for debate has been whether a ToM deficit is a *state* marker (Pousa *et al,* 2006) or a *trait* marker *(*Janssen *et al, 2003)* in relation to psychosis.

There is a paucity of studies about ToM in bipolar disorder. Some affective patients were included as control group in schizophrenia studies (Frith & Corcoran, 1996; Drury *et al*., 1998; Sarfati *et al*, 1999; Fletcher *et al*., 1995; Mazza *et al.,* 2001), but these samples were small and heterogeneous. Kerr *et al*. (2003) found ToM deficit in 20 manic patients and 13 depressed patients versus the control group. Inoue *et al* (2004) studied 50 bipolar patients in clinical remission and 50 healthy control subjects, and detected a ToM deficit in the bipolar group. More recent studies (Olley et al, 2005; Bora et al, 2005) have confirmed a ToM deficit in euthymic bipolar patients associated to other cognitive deficits, mainly in executive function, but a relation to psychotic symptoms has not been assessed. After studying performance in a hinting task in 15 schizophrenic, 15 affective and 15 control patients, Marjoram *et al* (2005) found that a ToM deficit was related with the presence of delusions and hallucinations, regardless of the disorder.

The primary objective of this study is to evaluate ToM performance in euthymic bipolar patients and assess whether that relates to a previous history of psychotic symptoms. A secondary objective is to analyze the possible influence of other cognitive functions on ToM performance.

METHODS: Seventy-five euthymic bipolar I patients (42 with a history of psychotic symptoms [BP+] and 33 without a history of psychotic symptoms [BP-]) were recruited at two Mental Health Centers (Alcalá de Henares and Torrejón de Ardoz, Madrid) and at the Lithium Clinic of the Ramón y Cajal University Hospital (Madrid). Patients included in the study met the RDC criteria (Research Diagnostic Criteria, Spitzer *et al* 1978) for the diagnosis of bipolar I disorder, carried out

through the standardized interview Schedule for Affective Disorders and Schizophrenia (SADS, Spitzer *et al* 1978). Patients were required to have a history of at least 3 major affective episodes, according to the life history of the SADS interview. The current euthymic state was controlled by a score ≤ 7 on the Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960) and a score ≤ 7 in the Young Mania Rating Scale (YMRS; Young *et al*, 1978).

Complementarily, 48 healthy subjects with no previous personal psychiatric history were selected. Control subjects were recruited among the patients' companions at a primary healthcare visit, being matched with the group of patients by age, sex and educational level. MINI (*Mini-International Neuropsychiatric Interview, 1999)* was used to exclude psychiatric comorbidity.

The Theory of Mind Advanced Test by F. Happé (1999) was used in the version translated and adapted by E. Pousa (2003). Theory of minds stories include double meanings, errors, persuasions and deceptions (two examples of each), and the questions require an inference on the thoughts, emotions and intentions of the stories' main characters. Asarnov's Test was used to assess sustained attention and the Wisconsin Card Sort Test (WCST; Heaton, 1981) was used to assess executive function. This test measures the ability to adequately use information to solve problems, designing a strategy of action.

Statistical data analysis and the computerized quality control of the analyses were performed by the Statistical Package for Social Sciences, or SPSS, (Norusis 1995, version 14.0). The significance level for all hypothesis contrast tests was set at 0.05. The normal distribution for each variable was examined via the Kolmogorov-Smirnov test. Student's t-test and ANOVA were used for continuous variables with normal distribution. Non-parametric tests (Mann-Whitney U test and Kruskal Wallis test) were used for variables without normal distributions in the studied population. After the ANOVA or Kruskal-Wallis analyses across 3 groups, either Student's t-test or Mann-Whitney U test were applied between each pair of groups for mean values comparison, performing multiple *post hoc* comparisons, and later applying the

Bonferroni correction. Chi square test was used for the contrast of qualitative variables hypotheses. A multiple linear regression analysis was performed to avoid a possible confusion effect of other variables.

RESULTS: Mean age was 47.6 years (SD 13.1), and no significant differences among the study groups were observed (ANOVA; $p = 0.264$). The two bipolar groups (BP+ and BP-) did not differ in age, educational level, age at onset, years of evolution, number of affective episodes, number of hospitalizations or number of psychotropic agents administered. Mean age of the overall bipolar group was 48.2 (SD 11.7), and the mean time duration of the illness was 20.5 (SD 11.7) years. Mean age at onset was 27.9 years (SD 10.6). The mean number of mania (4.6, SD 3.7) and depressive (4.3, SD 3.3) relapses was similar. The mean number of hospitalizations in the whole bipolar group was 2.5 (SD 2.9), although 18 patients had never been admitted.

Scores were significantly different across the 3 groups in Happé's ToM test (Kruskal Wallis; $p = 0.035$). Both BP+ (Mann-Whitney; $p = 0.041$) and BP- (Mann-Whitney; $p = 0.014$) groups showed a significantly lower score than the control group. The differences across these 3 groups in the *physical* sham stories of Happé's test were also significant (Kruskal Wallis; $p = 0.022$), such that the BP+ (Mann-Whitney; $p = 0.013$) and BP – (Mann-Whitney; $p = 0.0274$) groups got worse scores than the control group.

Scores showed significant differences in this variable (ASARNOV) across the 3 groups (ANOVA; $p < 0.001$). The sustained attention performances in BP+ (19.9) and BP- (20.2) groups were similar (Student t; $p = 0.855$). The results from both BP+ (Student t; $p= 0.002$) and BP- (student t; $p = 0.003$) groups were lower than the control group (23.5).

Scores in the WCST were significantly different across the 3 groups in terms of the number of categories completed (Kruskal-Wallis; $p = 0.001$). These differences indicated a lower mean of completed categories by BP- group (4.5) versus the control group (5.0) (Mann-Whitney; $p = 0.00$) and the BP+ group (4.9) (Mann-Whitney; $p = 0.015$). The mean values of categories completed in BP+ and control groups were similar (Mann-Whitney; $p= 0.135$). The same difference pattern was seen in the number of correct answers (Kruskal-Wallis; $p = 0.000$), and in the mean number of random errors (Kruskal-Wallis; $p = 0.054$).

The covariables included in the maximum model (executive function, administration of "mood stabilizer + antipsychotic" and "mood stabilizer") did not modify differences by group ($p < 0.020$; $p < 0.015$ and $p < 0.020$, respectively), and the coefficient (B) modification was minimal, such that they were therefore extracted from the model step by step. On the contrary, the exclusion of sustained attention substantially modified the group effect (coeff (B) 1.138 versus 1.585), so it could not be removed from the model. From this analysis it may be concluded that Sustained Attention is a confusion factor in the differences found in the ToM according to the group (BP+, BP- and control).

Discussion: Results revealed a ToM deficit in this sample of euthymic bipolar patients versus healthy volunteers, corroborating findings from previous studies (Inoue, 2004; Olley *et al*, 2005; Bora *et al*, 2005). Our study adds several methodological advantages such as a larger sample size, diagnostic homogeneity and more restrictive euthymia criteria. In addition, we assessed the relationship of this deficit with a previous history of psychotic symptoms, with the purpose of testing the metarepresentational deficit-based model of psychosis (Frith, 1992).

Comparing results by group pairs it was concluded that there were differences in bipolar patients with respect to the control group, without differences between the two groups of bipolar patients (BP+ and BP-). That leads us to think that a ToM deficit -assessed by means of the advanced Happé's test- is not associated with a

previous history of psychosis and, therefore, it can be concluded that *is not a vulnerability marker of psychos*is. Other studies comprising patients with schizophrenia have concluded that ToM is defectual in psychotic episodes but it becomes normal upon remission (Corcoran *et al*, 1995; Drury *et al*, 1998; Pickup & Frith, 2001). Additionally, except for the studies by Herold *et al* (2002) and Janssen *et al* (2003), recent ToM evaluations in schizophrenic patients in a remission phase showed results equivalent to those of the healthy population (Pousa *et al*, 2006). All that supports the idea that ToM deficit in psychosis is *state – dependent*, inherent to the psychotic state, instead of a permanent developmental dysfunction, similar to autism. In other words, when patients are delusional, they lose ToM ability but it is later recovered at the base level in remission. Since ToM deficit was similar in euthymic bipolar patients with and without a history of psychotic symptoms, our results are consistent with the conception of ToM as a *state* marker, not a *trait* marker, of psychosis. Nevertheless, ToM deficit appeared associated with the bipolar disorder itself.

Multiple factors could be involved in the ToM deficit in euthymic bipolar patients. The most likely explanation is that this deficit could be only a part of a global cognitive impairment. Our results revealed that ToM deficit is accompanied by an equivalent deficit in control stories and physical stories of the Happé instrument, and by a significant deficit in sustained attention and executive function, which is consistent with the previously reported data (Clark *et al*, 2002; Quraishi & Frangou, 2002; Bora *et al*, 2005). All this indicates that *ToM deficit in euthymic bipolar patients appears in the context of a general cognitive deficit.* The cognitive function that appeared most involved in ToM differences was sustained attention, and not executive functions as other studies suggest (Russell *et al*, 1999). On the other hand, there were no differences in cognitive performance between the groups *with* and *without* history of psychotic symptoms. This is in agreement with other studies (Goldberg *et al*, 1993) that refute the hypothesis of a subset of psychotic bipolar patients with a specific cognitive deficit. Along this line a recent study (Selva *et al*, 2006) has shown that performance in attention, verbal memory, verbal fluency

and executive functions is similar in patients with and without history of psychotic symptoms.

These findings of ToM deficit in euthymic bipolar patients open the way for a line of research about the cognitive mechanisms underlying the psychosocial disadjustment that these patients present. As suggested by Roncone *et al* (2002), mentalization skills could be more decisive for keeping a job or a social network than other neurocognitive variables. Designing rehabilitation programs focused on social cognition may favourably influence the quality of life of the bipolar patients