Executive functioning in schizophrenia spectrum disorder patients and their unaffected siblings: A ten-year follow-up study

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ABSTRACT

Executive dysfunction represents a core deficit that is associated with schizophrenia spectrum disorders (SSDs). However, the longitudinal course of executive deficits in SSDs is still controversial.

The aim of this study was to examine the executive performance of 34 SSD patients in relation to 34 of their unaffected siblings over a period of 10 years. Both groups completed psychopathological and executive assessments. Thirteen healthy controls were assessed using the same instruments.

At baseline, the SSD patients differed significantly from siblings and controls in their performance on the Trail Making Test-B (TMT-B) and the number of categories in which they succeeded in the Wisconsin Card Sorting Test (WCST). They also differed significantly from the controls in the total number of errors in the WCST. The siblings did not differ in executive functioning from the controls over the follow-up. Longitudinally, the patients demonstrated significant improvement only for the TMT-B. However, only 14.71% of the patients showed reliable and clinically significant improvements for the TMT-B, and 8.82% made more errors on the WCST at the follow-up evaluation. Less than 3% of the patients showed either improved or worse results on the remaining measures of the WCST. A stabilisation pattern for the WCST was observed in the three groups.

The patients performed worse than their siblings and controls on both executive tests. Some patients exhibited significant improvements in the TMT-B over time, but this improvement was reliable and clinically significant for less than 15% of the sample. Thus, we conclude that the patients exhibited stable impairments over time in the executive functions assessed.

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1. Introduction

Patients with schizophrenia spectrum disorders (SSDs) show marked cognitive impairments in most clinical neuropsychological tests and very few preserved domains of cognitive performance (Gold et al., 2009). Executive function, attention and memory are the most severely affected cognitive functions in SSD patients (Goldberg et al., 2003). Between 27% and 46% of schizophrenia patients exhibit patterns of selective executive dysfunction and between 54% and 90% have at least one executive deficit (Johnson-Selfridge and Zalewski, 2001; Chan et al., 2006a). Executive deficits have a substantial impact on functional outcomes (Semkovska et al., 2004; Altshuler et al., 2007; Bowie et al., 2008) and are closely related to chronicity (Greenwood et al., 2008). In recent years, social cognition has drawn researchers' interest due to its relationship with functional outcomes (Fett et al., 2011).

Similar to other cognitive impairments, executive dysfunction in SSDs represents a core deficit that is present long before the onset of symptoms (Cannon et al., 2006; Wozniak et al., 2008). Moreover, it has been shown that first-degree unaffected relatives show executive impairment profiles that are, although attenuated, similar to those of their affected relatives (Cannon et al., 2000; Harvey et al., 2010; Schulze et al., 2011).

Although there is agreement regarding the prevalence and functional relevance of executive impairment, controversial findings have been reported concerning the course of these deficits in SSD patients. Although significant age-related declines in abstraction functions have been reported among schizophrenia patients (Fucetola et al., 2000), most studies suggest that these initial impairments are stable (Rund, 1998; Heaton et al., 2001; Townsend and Norman, 2004; Mur et al., 2008; Wozniak et al., 2008) or might even improve over time (Gold et al., 1999; Hoff et al., 2005). Longitudinal studies have reported improvement (Sweeney et al., 1991; Gold et al., 1999; Townsend et al., 2002) or no significant change over time (Hoff et al., 1992; Censits et al., 1997) on the Wisconsin Card Sorting Test (WCST). Similar results were found in other patient populations with psychosis, including euthymic bipolar patients, for whom executive functioning and processing speed were reported as the only two cognitive domains that were impaired over a period of two years (Mur et al., 2008).

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The aim of the current study was to examine the executive function performance of a group of SSD patients relative to their unaffected siblings and a group of healthy controls over a period of 10 years. Our main goals were to examine the change over time in the executive performance of patients compared to their unaffected siblings and to determine the magnitude of the change and its clinical significance relative to a healthy control group.

We hypothesised that there would be a discrepancy between patients and their unaffected relatives regarding executive impairment, whereby patients would show an initial impairment that would remain stable over time and their unaffected siblings would show a similar trajectory to that of the healthy controls.

2. Methods

2.1. Sample

The initial sample population included 89 nuclear families. Between 1999 and 2001, 89 patients who were affected by DSM-IV SSDs (APA, 1994) were recruited from consecutive admissions to the Psychiatric Unit of Virgen del Camino Hospital in Pamplona, Spain; the admissions were due to psychotic exacerbations. We subjected the patients' parents and one healthy sibling (sample described elsewhere, (Rosa et al., 2004)) to a comprehensive evaluation that included psychopathological, motor, and neuropsychological assessments.

For the present study, only the patients and their siblings were invited to participate in the second evaluation in 2009. The mean time between the two evaluations was 9 years and 6 months (range: 7–11 years). At the follow-up evaluations, the sample population consisted of 34 sibling pairs (38% of the initial sample). The reasons for participant discontinuation were as follows: the death of one sibling (8 pairs; 7 patients and 1 sibling); traumatic brain injury to the patient (1 pair); the patients moved or were unreachable (11 pairs); and one of the siblings declined to participate (35 pairs).

We also included a healthy control group comprising 26 volunteers (16 men and 10 women). Inclusion criteria for the control subjects were as follows: the absence of major psychiatric disorders, neurological illness or brain injury; the absence of drug or alcohol abuse disorders; the absence of first-degree relatives with major psychiatric illness; and the absence of any drug treatment. At the follow-up evaluation, the control group consisted of 13 subjects (9 men and 4 women). The reasons for participant discontinuation were as follows: 3 subjects declined to participate and 10 had moved or were unreachable. The mean time between the two evaluations was 13 years and 3 months (range: 13–15 years).

All subjects provided written informed consent for participation in the study, and the study was approved by the local ethics committee.

2.2. Procedures

2.2.1. Clinical assessments

The demographic and clinical variables were assessed according to the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al., 1992) at baseline and at the follow-up evaluations. The patients and their siblings underwent psychopathological assessments at both examinations to determine the presence of current or lifetime psychopathological symptoms.

Drug abuse by patients and their siblings was assessed using a structured interview that was based on an adaptation of the Composite International Diagnostic Interview (CIDI) (World Health Organisation, WHO, 1993). Consumption habits at baseline and at follow-up were determined using the available sources of information (participants, family, and charts). The ratings were classified from 0 (no consumption) to 5 (dependence).

The clinical assessments were carried out by an experienced psychiatrist who was blinded to the participants' cognitive status (VB). At baseline, the assessments were made during an index admission once the patients reached clinical stability. The siblings were also evaluated during the patient's admission. At follow-up, the patients were clinically stabilised for at least 6 months prior to the assessment, and both patients and siblings were evaluated during the same week.

2.2.2. Neuropsychological assessments

The participants were administered the following two executive tests: form B of the Trail Making Test (TMT-B) (Reitan and Wolfson, 1993), which assesses cognitive flexibility, and alternating and divided attention, and the computerised version of the Wisconsin Card Sorting Test (WCST-64) (Heaton et al., 1993), which assesses the cognitive flexibility, and the ability to form abstract concepts, to shift and maintain set, and to use feedback (Miyake et al., 2000). The TMT-B is scored according to the time required to draw lines connecting characters that are sequentially alternating between numbers (1–13) and letters (A–L) (e.g., 1–A–2–B). In the WCST, participants are instructed to sort a set of cards and match them with one of four cards presented on the computer on the basis of a target criterion (colour, shape, or number), but they are not told the criterion; they are only told whether their choice is wrong or right. After ten successful trials, the sorting criterion changes without notice, and the participants are required to adjust to the new sorting criterion and continue sorting the cards. The indices of test performance included the total number of categories, total number of errors, number of perseverative errors, conceptual level responses, and failure to maintain set.

An experienced neuropsychologist (AMS) who was blinded to clinical status assessed each participant (patients, siblings and controls).

2.3. Data analysis

To compare the demographic characteristics between groups, we applied the t-test and chi-squared test. A one-way ANOVA was performed to compare executive performance between patients, siblings, and controls at baseline and follow-up.

Repeated measures of the multivariate analysis of variance (MANOVA) were performed for each neuropsychological variable to assess time and group effects regarding executive performance. The testing occasion was the within-subjects factor (baseline and follow-up), and the group was the between-subjects factor (patients, siblings, and controls). A multivariate analysis of covariance (MANCOVA) was performed for each variable according to age, gender, drug abuse, and diagnosis to account for potential differences between groups.

To ensure that the study subjects in the later evaluations were representative of the initial cohort, we computed independent t-tests comparing the patients (n = 34), siblings (n = 34) and controls (n = 13) of the current study to those in the original sample who did not participate in the current study (55 patients and siblings and 26 controls) in terms of demographic and clinical variables.

The Reliable Change Index (RCI) was estimated to characterise changes in the executive tests. The RCI is a statistical tool that is used in many areas of medicine to help determine whether an individual's performance on a neuropsychological test has changed from a previous assessment of the same test. It evaluates whether a patient change is unlikely to be caused by a single measure of unreliability, such as measurement error or practice effect (Jacobson and Truax, 1991). It requires a matched, healthy control group to be reassessed using the same instruments within the same timeframe as the patient group.

In addition, we determined the clinically significant change (CSC), which represents the extent to which change over time is clinically meaningful. We calculated the cut-off point according to the C criterion of Evans et al. (1998). The control group allowed us to test whether the patients moved from a clinical distribution to a normative distribution over time. The cut-off point represents the