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## Trait or state? A longitudinal neuropsychological evaluation and fMRI study in schizoaffective disorder

Merce Madre<sup>a,b,e</sup>, Joaquim Radua<sup>a,c,d</sup>, Ramon Landin-Romero<sup>a</sup>, Silvia Alonso-Lana<sup>a</sup>, Raimond Salvador<sup>a,c</sup>, Francesco Panicali<sup>a</sup>, Edith Pomarol-Clotet<sup>a,c</sup>, Benedikt L. Amann<sup>a,c,\*</sup>

<sup>a</sup> FIDMAG Research Foundation Germanes Hospitalàries Barcelona, Barcelona, Spain

<sup>b</sup> Departament de Psiquiatria i Medicina Legal, Doctorat de Psiquiatria i Psicologia Clínica, Universitat Autònoma de Barcelona, Barcelona, Spain

<sup>c</sup> CIBERSAM, Madrid, Spain

<sup>d</sup> Department of Psychosis Studies, Institute of Psychiatry, King's College London, London, UK

<sup>e</sup> Division of Psychiatry, University College of London, London, UK

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### ABSTRACT

Schizoaffective patients can have neurocognitive deficits and default mode network dysfunction while being acutely ill. It remains unclear to what extent these abnormalities persist when they go into clinical remission. Memory and executive function were tested in 22 acutely ill schizoaffective patients; they also underwent fMRI scanning during performance of the n-back working memory test. The same measures were obtained after they had been in remission for  $\geq 2$  months. Twenty-two matched healthy individuals were also examined. In clinical remission, schizomanic patients showed an improvement of memory but not of executive function, while schizodepressive patients did not change in either domain. All schizoaffective patients in clinical remission showed memory and executive impairment compared to the controls. On fMRI, acutely ill schizomanic patients had reversible frontal hypo-activation when compared to clinical remission, while activation patterns in ill and remitted schizodepressive patients were similar. The whole group of schizoaffective patients in clinical remission showed a failure of de-activation in the medial frontal gyrus compared to the healthy controls. There was evidence for memory improvement and state dependent changes in activation in schizomanic patients across relapse and remission. Medial frontal failure of de-activation in remitted schizoaffective patients, which probably reflects default mode network dysfunction, appears to be a state independent feature of the illness.

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### 1. Introduction

Since the first description of schizoaffective disorder in 1933 (Kasanin, 1933), its nosological status has been debated repeatedly (Pope et al., 1980; Marneros, 2003; Heckers, 2009; Jager et al., 2011). This uncertainty remains until today, with DSM-V considering removing it as a separate category and instead adding mood symptoms as a dimension to schizophrenia and schizophreniform disorder. However, the category was ultimately maintained; it was felt that there was not enough neurobiological data to support this motion (Allin et al., 2010; Cosgrove and Suppes, 2013).

From a neuropsychological point of view, cognitive impairment, mainly attention and memory deficits and executive dysfunction, is well documented in patients with schizoaffective disorder (e.g. Torrent et al., 2007; Bora et al., 2009; Studentkowski et al., 2010; Amann et al., 2012). Conversely, there exists less functional neuroimaging data: Our

group recently published results of 32 acutely ill schizoaffective patients who, using a working memory task, activated prefrontal, parietal and temporal regions significantly less than healthy subjects (Madre et al., 2013). They also showed failure of de-activation in the medial frontal cortex which was more pronounced in the schizodepressed than in the schizomanic group. The finding of failure of deactivation was interpreted as evidence of dysfunction in the so-called default mode network, a series of interconnected brain regions which are metabolically active at rest but whose activity diminishes while the brain performs a wide range of cognitive tasks (Gusnard and Raichle, 2001; Raichle et al., 2001). Similar failure of de-activation during cognitive task performance has also been found in schizophrenia (Pomarol-Clotet et al., 2008; Whitfield-Gabrieli et al., 2009; Milanovic et al., 2011; Salgado-Pineda et al., 2011; Schneider et al., 2011) and bipolar disorder (Allin et al., 2010; Fernandez-Corcuera et al., 2013; Pomarol-Clotet et al., 2012).

A question that has not yet been addressed in the literature is whether and to what extent neuropsychological and functional imaging changes seen in schizoaffective disorder persist into remission or in other words: Are detected abnormalities a state or trait phenomenon of the disease? This is pertinent to the relationship of the disorder to schizophrenia and bipolar disorder, since neuropsychological deficits

\* Corresponding author at: FIDMAG Research Foundation, CIBERSAM, Dr. Antoni Pujadas 38, 08830 Sant Boi de Llobregat, Spain. Tel.: +34 936529999; fax: +34 936400268.

E-mail address: [benedikt.amann@gmail.com](mailto:benedikt.amann@gmail.com) (B.L. Amann).

in the former disorder are widely considered to be static and unchanging, whereas those in bipolar disorder are presumed to resolve with clinical remission (e.g. Murray et al., 2004), even if the phenomenon of euthymic cognitive impairment indicates that this is not complete in all cases (e.g. Martinez-Aran et al., 2004; Robinson et al., 2006). Similarly, while functional imaging changes in schizophrenia are usually considered to be persistent, studies comparing patients in different phases of bipolar disorder, together with a small number of longitudinal studies, clearly point to changes between phases of illness and euthymia (Chen et al., 2010; Lim et al., 2013).

The present study was undertaken to examine the neuropsychological and functional neuroimaging features of schizoaffective disorder from a longitudinal perspective. We used a sample that contained roughly equal numbers of schizomanic and schizodepressive patients. Participants were studied when they were ill, and again when they were in clinical remission. We hypothesized that brain function, measured with cognitive tests and fMRI, differed in the two states.

## 2. Methods

### 2.1. Participants

The patient sample consisted of 22 patients with schizoaffective disorder, bipolar type and were part of the sample of a previously published study of our group (Madre et al., 2013). They all met Research Diagnostic Criteria (RDC) (Spitzer et al., 1978) for schizoaffective disorder, based on a psychiatrist interview and the review of case-notes. We used these criteria because they are the most detailed of all available criteria for schizoaffective disorder. They posit that patients show schizophrenic symptoms and also affective symptoms meeting criteria for a full affective syndrome, similar to those required for depression and mania/hypomania in DSM-IV and ICD-10.

Exclusion criteria included age younger than 18 or older than 65 years, IQ < 70, left-handedness, history of neurological disease or brain trauma, and alcohol/substance abuse within 12 months prior to participation. Patients were also excluded if they developed a physical comorbidity during the follow-up phase.

A schizomanic episode was defined as follows: Young Mania Rating Scale (YMRS) scores >18 and Hamilton Rating Scale for Depression (HRSD) scores <8; patients in a schizodepressive episode had a HRSD score >18 and YMRS score <8. Psychotic symptoms were required to be also present in both acute phases, defined on the basis of the following Positive and Negative Symptom Scale (PANSS) items (Kay et al., 1987): P1 ≥ 4, or P3 ≥ 4, or P5 ≥ 5, or P6 ≥ 6 or PG9 ≥ 5. To be considered in clinical remission, patients were required to be in clinical remission during at least 2 months follow-up after the acute episode, defined as scores in HRSD <8, YMRS scores <8 and PANSS items P1, P3, P5, P6 and PG9 ≤ 2. For comparisons of the PANSS between the acute phase and clinical remission, the total PANSS score, the PANSS positive, PANSS negative and PANSS general psychopathology scores were described separately.

Patients had to have a premorbid IQ in the normal range, as estimated using the Word Accentuation Test (Test de Acentuación de Palabras, TAP) (Del Ser et al., 1997; Gomar et al., 2011), which requires pronunciation of Spanish words whose accents were removed. Current IQ was measured using four subtests of the Wechsler Adult Intelligence Scale III (WAIS-III) (vocabulary, similarities, block design, and matrix reasoning).

Patients received two cognitive assessments and were scanned on two occasions, during a schizoaffective episode (session A) and during clinical remission (session B). In most cases the first scan was while they were acutely ill and the second when they had recovered, but 2 of the 12 schizomanic patients and 1 of the 12 schizodepressive patients were first scanned in remission. Two patients were scanned in the schizomanic, the schizodepressive phase and in clinical remission.

The control sample consisted of 22 Spanish Caucasian healthy subjects. They were recruited via poster and web-based advertisement in the hospital and local community, and from staff in the research unit. They were selected to be age-, sex- and TAP-matched to the patients. All healthy subjects underwent a detailed diagnostic interview in which they were asked about personal or familiar history of mental illness and were excluded if they reported a personal or first-degree relative with a history of mental illness and/or treatment with psychotropic medication. They met the same exclusion criteria as the patients and were all right-handed. They underwent a single cognitive assessment.

Both groups were scanned twice, session A in the acute phase and B in clinical remission. The interval of the two sessions of healthy controls was similar to the interval of patients: mean length of time from the first to second scan  $570 \pm 583$  days in patients vs  $515 \pm 248$  days in healthy controls.

The study was approved by the local ethical committee and carried out in accordance with the Declaration of Helsinki. All participants gave written informed consent after having had the study explained to them.

### 2.2. Cognitive and neuropsychological assessment

Memory was assessed using four subtests of the Spanish version of the 3rd edition of the Wechsler Memory Scale [WMS-III (Wechsler, 1997; Pereña et al., 2004)]: verbal long-term memory (Logical Memory I), visual memory (Faces I), short-term memory (Digit Span) and working memory (Letter-Number Sequencing). Raw scores on these tests were converted into age-related scaled scores, and these a composite sum score was derived.

Executive function was tested using the Behavioural Assessment of the Dysexecutive Syndrome (BADS) (Wilson et al., 1996), which has been adapted for use in Spanish populations (Vargas et al., 2009). This is a battery of six tests examining different aspects of executive function: set-shifting (Rule Shift Cards), planning and problem solving (the Action Programme, Key Search and the Zoo Map Tests), cognitive estimation (the Temporal Judgement Test) and strategic allocation of resources (the Modified Six Elements Test). Scores on the individual tests can be combined to give an overall 'profile' score.

### 2.3. fMRI paradigm and acquisition

As stated before, in a previous publication of our group (Madre et al., 2013), we compared cross-sectional fMRI findings of acute schizomanic and schizodepressed patients with healthy controls. We used the same fMRI techniques as in the actual longitudinal study where patients underwent the second scan once they reached clinical remission for at least 8 weeks. The participants performed hereby a sequential-letter version of the n-back task (Gevins and Cutillo, 1993). Two levels of memory load (1-back and 2-back) were presented following a block design. Each block consisted of 24 capital letters that were changed every 2 s, and all blocks contained five repetitions (1-back and 2-back depending on the block) located randomly within the blocks. Individuals had to indicate letter repetitions by pressing a button. Four 1-back and four 2-back blocks were presented in an interleaved way, and between them an asterisk flashing with the same frequency as the letters (i.e. a baseline stimulus) was presented during 16 s. Letters were shown in green in 1-back blocks and in red in the 2-back blocks. All participants had previously conducted a training session outside the scanner.

N-back performance was measured using the signal detection theory index of sensitivity (Swets et al., 1978), which indicates a better ability to discriminate between targets and non-targets. Participants with negative values in this index (either in the 1-back or in 2-back versions of the task), which suggests that they were not performing the task, were excluded from the study.

Two hundred sixty-six scanning volumes were acquired from the same 1.5-T GE Signa scanner during this task using a gradient echo-

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