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Neuropsychological and brain functional changes across the different phases of Schizoaffective Disorder

Alteraciones neuropsicológicas y neurofuncionales en las distintas fases del Trastorno Esquizoafectivo

Tesis presentada por:

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Para la obtención del grado de doctor por la Universidad Autónoma de Barcelona (U.A.B.)

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declaran y confirman que han supervisado la Tesis Doctoral titulada:

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Presentada por Mercè Madre Rull para optar al grado de

Doctor en Psiquiatría y Psicología Clínica

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Firmas,

Dr. Benedikt L. Amann	**Dra. Edith Pomarol-Clotet**	**Dr. Mercè Madre Rull**

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”The cases which are not classifiable are unfortunately very frequent.
We have to live with a sort of disorder to whom the criteria applied by us
are not sufficient enough to differentiate reliable in all cases
between Schizophrenia and Manic-Depressive Insanity.
And there are also many overlaps in this area”
Kraepelin E. Die Erscheinungsformen des Irreseins.
Z Gesamt Neurol Psychiatrie 1920; 62:1–29**.**

“Do schizoaffective disorders exist at all?
The question is very old; the answer is not very new.
In the last 100 years disorders in-between constitute a nosological nuisance,
but a clinical reality”
Andreas Marneros, 2006

ÍNDICE

ABREVIATURAS

APA = American Psychiatric Association

BADS = Behavioural Assessment of the Dysexecutive Syndrome

BOLD = Blood-Oxygenation-Level-Dependent

CGI = Clinical Global Impression

CI = Coeficiente Intelectual

CT = Computed Tomography

DLPFC = Dorsolateral prefrontal cortex

d' = theory index of sensitivity

DMN = Default Mode Network

DTI = Diffusion tensor imaging

DSM = Diagnostic and Statistical Manual for Mental Disorders

EPI = echo-planar imaging

FEAT= FMRI Expert Analysis Tool software

fMRI = Functional Magnetic Resonance Imaging

FSL = FMRIB Software Library

GAF = Global Assessment of Functioning scale

GE = General Electrics

GLM = General Linear Model

HAMD = Hamilton Rating Scale for Depression scale

ICA = Independent Components Analysis

ICD = International Classification of Diseases

IQ = Intelligence Quotient

MNI = Montreal Neurological Institute

MPFC = Medial prefrontal cortex

MRI = Magnetic Resonance Imaging

PET = Positron Emission Tomography

PANSS = Positive and Negative Syndrome Scale

RDC = Research Diagnostic Criteria

ROI = Region of Interest

SD = Standard deviation

SPM = Statistical Parametric Mapping software

TAP = Test de acentuación de palabras (Word Accentuation Test)

TE = Echo Time

TI = Inversion Time

TR = Repetition Time

VBM = Voxel-based Morphometry

YMRS = Young Mania Rating Scale

WAIS-III = Wechsler Adult Intelligence Scale, 3rd Ed.

WMS-III = Wechsler Memory Scale, 3rd Ed.

WHO = World Health Organization

PRÓLOGO

Esta tesis, presentada para obtener el grado académico de Doctor por la Universidad Autónoma de Barcelona (U.A.B.), es el resultado del trabajo realizado durante los años 2007-2015 en la Unidad de investigación del FIDMAG Hermanas Hospitalarias Research Foundation. Durante dicho periodo la doctorando ha obtenido el Diploma de Estudios Avanzados (DEA) cursando el doctorado de Psiquiatría del Departamento de Psiquiatría i Medicina Legal de la UAB.

Esta tesis se presenta por compendio de publicaciones y está formada por dos artículos publicados en revistas internacionales indexadas, en el ámbito de las neurociencias. A continuación se nombran otros artículos que han sido publicados o que se encuentran en proceso de publicación y que están relacionados con el tema de la presente tesis. Los resultados de estos estudios han sido también difundidos en diversos congresos nacionales e internacionales, en forma de pósteres y/o comunicaciones orales.

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PÓSTERES Y COMUNICACIONES ORALES

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Disfunción ejecutiva y deterioro de la memoria en el Tr. Esquizoafectivo: una comparación con el Tr. Bipolar, Esquizofrenia y controles

Amann B, Gomar J, Ortíz J, Amann B, Gomar J, Ortíz J, Mckenna P, R Salvador, Sarró S, Madre M, Ladín R, Goikolea JM, Pomarol-Clotet E.

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"Brain function abnormality in schizoaffective disorder: an fMRI study". *Comunicación oral. Curso Actualizaciones Clínicas en Psiquiatría. Marzo 2013, Hospital de Sant Rafael, Barcelona.*

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ABSTRACT

Neuropsychological and brain functional changes across the different phases of Schizoaffective Disorder

The term schizoaffective psychosis was introduced by Kasanin in 1933 to describe the apparent occurrence of patients who did not fit into the category of either schizophrenia or manic-depressive psychosis. Ever since, its nosology has been a matter of controversy and studies have been scarce dedicated to shed light into the neurobiology of this disorder.

The present thesis aimed to add insight to the literature of neurobiological underpinnings of schizoaffective disorder, taking into account also longitudinal aspects of the disease. Specifically, the thesis reports two fMRI studies which examined a sample of patients meeting both RDC and DSM-IV criteria for schizoaffective disorder, bipolar type. This patient sample was compared with age, sex and premorbid-IQ matched healthy controls. All subjects underwent at least one fMRI scan, during performance of the n-back working memory test. Additionally, memory and executive functioning were assessed. Linear models were used to obtain maps of activations and de-activations in the groups.

The first study was a cross-sectional study evaluating patterns of brain activation and de-activation in acute schizomanic or schizodepressive schizoaffective patients. Compared to controls, the schizoaffective patients showed a reduced activation in the DLPFC and also a failure of de-activation in the medial frontal cortex. This latter area corresponds to the anterior node of the DMN.

In the second study the same patients were reassessed after at least two months of clinical remission. The subgroup of schizomanic patients were found to show a reversible frontal hypoactivation during n-back performance when compared to clinical remission, while no changes in the brain response to the task were seen in schizodepressive patients in comparison to clinical remission. The whole group of schizoaffective patients in clinical remission showed a failure of de-activation in the medial frontal cortex compared to the healthy controls. The cognitive assessment in the second study showed that schizomanic patients improved in memory but not in executive functioning from active illness to remission, while schizodepressive patients did not show changes in either domain. All schizoaffective patients in clinical remission continued to show memory and executive impairment compared to the controls.

Overall, the present thesis suggests that DLPFC hypoactivation is a state feature of schizoaffective disorder. This finding aligns it with schizophrenia but also with bipolar disorder, where reduced DLPFC activity has also been described. Failure of de-activation, and by extension DMN dysfunction, appeared across all different phases of the disorder, as a trait feature of the illness. DMN dysfunction has also been described in a range of psychiatric disorders, including schizophrenia and bipolar disorder. Cognitive impairment was a further finding of this thesis. There was some evidence of memory improvement in euthymic schizomanic patients, but this was partial and the patients still showed deficits in remission, in particular executive dysfunction.

RESUMEN

Alteraciones neuropsicológicas y neurofuncionales en las distintas fases del Trastorno Esquizoafectivo

El término esquizoafectivo fue introducido por J. Kasanin en 1933, para describir a un grupo de pacientes que no encajaban ni con el diagnóstico de esquizofrenia ni en el de las psicosis maníaco-depresivas. La nosología del trastorno esquizoafectivo siempre ha sido un tema controvertido y se han llevado a cabo pocos estudios que hayan sido útiles para clarificarla.

El objetivo de la presente tesis es estudiar las bases neurobiológicas de esta enfermedad, evaluando las alteraciones que aparecen tanto en las fases de descompensación como los cambios a nivel longitudinal. Este trabajo está compuesto por dos estudios que usan la resonancia magnética funcional para examinan a un grupo de pacientes con trastorno esquizoafectivo, tipo bipolar, diagnosticados según los criterios RDC y DSM-IV. Los pacientes fueron comparados con un grupo de sujetos sanos, apareados por edad, sexo y CI pre-mórbido. A todos los sujetos se les realizó al menos un escáner, mientras realizaban una tarea de memoria de trabajo 'N-back'. Paralelamente, se realizó un estudio neuropsicológico, evaluando la memoria y función ejecutiva. Se obtuvieron los mapas de activación y desactivación cerebral mediante un modelo lineal general y se realizó un análisis longitudinal de medidas repetidas.

En el primer estudio transversal, se examinaron los patrones de activación cerebral durante un episodio de descompensación, esquizomaníaco o esquizodepresivo. Los pacientes mostraron una hipoactivación del DLPFC, así como un déficit en desactivar la corteza frontal medial, comparado con los sujetos sanos. Esta última región corresponde al nodo anterior de la red neuronal por defecto o DMN.

En el segundo estudio, los mismos pacientes fueron revaluados tras alcanzar la remisión clínica, definida como un periodo de eutimia superior a dos meses. El subgrupo de pacientes esquizomaníacos mostró una hipoactivación frontal en la fase aguda que revirtió al alcanzar la eutimia. Por el contrario, en el subgrupo de pacientes esquizodepresivos no se observaron diferencias entre la fase aguda y la remisión clínica. Al comparar todos los pacientes esquizoafectivos en remisión clínica con los sujetos sanos, los pacientes mostraron un déficit en desactivar la corteza frontal medial, indicando una disfunción del DMN. En el segundo estudio también se evaluó la memoria y función ejecutiva. En ambas pruebas, todos los pacientes en remisión clínica mostraron un menor rendimiento en comparación al grupo de sujetos sanos. En el subgrupo de pacientes esquizomaníacos mejoró la memoria al alcanzar la remisión clínica, sin embargo, no hubo cambios en la función ejecutiva. Por el contrario, en el subgrupo de pacientes esquizodepresivos no se encontraron diferencias significativas entre la fase aguda de la enfermedad y la remisión clínica.

Globalmente, los resultados de la presente tesis sugieren que las fases agudas del trastorno esquizoafectivo se caracterizan por una hipoactivación del DLPFC. Esta alteración equipara el trastorno esquizoafectivo con la esquizofrenia y el trastorno bipolar, en los cuales la hipoactivación del DLPFC ha sido también descrita. Por otro lado, el fracaso en desactivar la corteza frontal medial, apareció tanto en la fase aguda como la fase de remisión clínica, independientemente del estado psicopatológico, sugiriendo una disfunción del DMN, como factor de rasgo intrínseco a la enfermedad. La disfunción del DMN ha sido previamente descrita en otras patologías psiquiátricas, entre las que se encuentran la esquizofrenia y el trastorno bipolar. Otro hallazgo de la presente tesis, son las alteraciones cognitivas en los pacientes esquizoafectivos, presentes tanto en las fases agudas, como en los periodos de eutimia. Únicamente se objetivó una mejora parcial en la memoria en el subgrupo de pacientes esquizomaníacos al alcanzar la eutimia.

INTRODUCTION

Nosology

A century ago, Emil Kraepelin made the distinction between dementia praecox, later to be called schizophrenia, and manic-depressive disorder, later to be referred to as bipolar disorder (Kraepelin, 1899). Although the distinction has held up well, some limitations have become evident concerning Kraepelin's requirement that patients with schizophrenia almost always develop deterioration, and patients with manic-depressive disorder have a good prognosis (Andreasen *et al.*, 2005, Mckenna, 2007). With respect to the latter issue, Kraepelin himself questioned in 1920 his own dichotomy concept: 'It is becoming increasingly obvious that we cannot satisfactorily distinguish these two diseases' (Kraepelin, 1920). Thirteen years later, the term schizoaffective psychosis was introduced by Kasanin (1933), to describe the apparent occurrence of patients who did not fit into the category of either schizophrenia or manic-depressive psychosis. He described nine patients with a good premorbid functioning, who developed acute psychoses, often in the setting of stress that showed a fluctuating mixture of psychotic and affective symptoms. The patients all recovered fully after a few months.

Currently, the existence of schizoaffective patients is recognized in the two major diagnostic systems, DSM-IV/-V and ICD-10 as a disorder characterized by simultaneous and/or alternating psychotic symptoms and affective mood episodes. However, eighty years after the term was introduced, the nosological status of schizoaffective disorder remains elusive and controversial. Several models for the nosological classification of schizoaffective disorder have been proposed as follows (see also figure 1):

I. Schizoaffective disorder is a variant of affective disorders (e.g. Pope *et al.*, 1980)

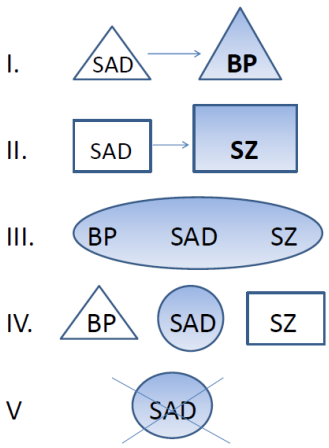
II. Schizoaffective disorder is a variant of schizophrenia (e.g. Welner *et al.*, 1977)

III. Schizoaffective disorder belongs to a continuum (e.g. Crow, 1986)

IV. Schizoaffective disorder is a third independent form of psychosis, besides schizophrenia and affective disorders (e.g. Procci, 1976)

V. Schizoaffective disorder does not exist (e.g. Lake and Hurwitz, 2006, Maier, 2006)

Figure 1: Nosological models of schizoaffective disorder (Amann, 2014).



Abbreviations: BP: bipolar disorder; SAD: schizoaffective disorder; SZ: schizophrenia.

At the centre of the debate is the question of the relationship and boundaries between affective and schizophrenic disorders. The categorical model proposes that schizophrenia and affective disorders are distinct and mutually exclusive illnesses and views schizoaffective disorder as either a form of schizophrenia (Lehman, 1975, Welner *et al.*, 1977), a form of affective disorder (Pope *et al.*, 1980), or an illness distinct from both schizophrenic and affective disorders, as argued by Procci (1976). On the other hand, the continuum or spectrum model defines a continuum of psychosis severity and considers

schizophrenia and affective disorders as opposite poles, with schizoaffective disorder midway between the two poles. The illness is viewed as a heterogeneous spectrum of patients, some of whom are more schizophrenic, and others more affective (Beck, 1967, Crow, 1986, Kendler *et al.*, 1995, Peralta and Cuesta, 2008).

Schizoaffective disorder has been also conceptualized aetiologically, specifically as the expression of genetic risk factors for both schizophrenia and bipolar disorder (Bertelsen and Gottesman, 1995, Craddock *et al.*, 2005). Finally, it has been provocatively questioned if schizoaffective disorder really exists at all. Maier (2006) suggested hereby that it may be more appropriate to broaden the concepts of schizophrenia and bipolar disorder and discard schizoaffective disorder. In this line, another group (Lake and Hurwitz, 2006) argued that schizoaffective disorder is a severe mood disorder with psychotic features and not a different or separate disease whereas it should be eliminated from the current diagnostic systems.

Epidemiology

The lifetime prevalence of schizoaffective disorder in the general population has been estimated to be between 0.3% (Perala *et al.*, 2007) and 1.1% (Scully *et al.*, 2004), in two studies that used DSM-IV and DSM-III-R criteria respectively. A review of various studies, based on DSM-III criteria, revealed also that the disorder appears to be more common in women than in men (Marneros *et al.*, 1990). However, the age of onset for women appears later than in men (Salokangas *et al.*, 2003). Schizoaffective bipolar subtype appears to predominate in younger patients, with depressive symptoms being more prevalent in females. In contrast, the depressive subtype appears to be more commonly reported in older patients (Malhi *et al.*, 2008).

Psychopathological symptoms

The disorder is classified into two groups: schizoaffective disorder, bipolar type, also called 'schizoaffective disorder, manic type', when patients present with manic and depressive symptoms; or schizoaffective disorder, unipolar type, also called ´schizoaffective disorder, depressive type´, in cases that patients suffer from depressive symptoms only and do not present manic symptoms during the course of the illness. As stated before, schizoaffective disorder is characterised by both mood and psychotic symptomatology. During the course of the illness, patients may suffer from pure psychotic episodes, pure affective episodes (manic, depressive or mixed) or from concurrent affective and psychotic symptoms (schizomanic or schizodepressive episodes). However it should be noted that both DSM-IV/V and ICD-10 require that schizophrenic and affective symptoms overlap at some stage in time during the same episode.

Studies trying to distinguish schizoaffective disorder from schizophrenia and affective disorders on the basis of psychopathological symptoms are scarce and have had conflicting results. Some authors have argued that subtle differences in clinical symptoms may be useful to distinguish the disorders: Whaley (2002) reported that delusions at first presentation are more frequent among patients with schizophrenia and schizoaffective disorder than among patients with bipolar disorder and Shenton *et al.* (1987) found that hallucinations are more common among patients with schizophrenia than among those with schizoaffective or bipolar disorder. By contrast, other authors have observed no differences in the frequency of delusions and hallucinations between subjects with schizophrenia, schizoaffective disorder, psychotic mania and psychotic mixed mania, suggesting that positive symptoms may not be a useful construct to differentiate them (Benabarre *et al.*, 2001). Negative symptoms have shown more evidence of differences between diagnostic groups than positive symptoms. Negative symptomatology and level of insight have been found to better differentiate cross-sectionally affective states from

schizophrenia and schizoaffective disorder in two studies (Cuesta and Peralta, 1995, Kitamura and Suga, 1991). Another study by Pini *et al.* (2004), compared clinical symptoms among groups of patients with schizophrenia, schizoaffective disorder, psychotic mania and psychotic mixed mania. There were no differences in rates of specific types of delusions and hallucinations between groups; however negative symptoms and lack of insight were higher in schizoaffective and schizophrenic patients.

Diagnosis

The diagnostic concept of schizoaffective disorder has undergone significant changes since its first definition by Kasanin (1933). As noted, Kasanin described nine patients who developed acute psychosis in the setting of good premorbid functioning and who fully recovered after some months. Almost twenty years later schizoaffective psychosis was included for the first time as a subtype of schizophrenia in the 1st and then in the 2nd versions of the Diagnostic and Statistical Manual for Mental Disorders (DSM-I, DSM-II) and in the 8th and 9th versions of the International Classification of Diseases (ICD-8, ICD-9) published by the American Psychiatric Association (APA, 1952, 1968) and the World Health Organization (WHO, 1965, 1978), respectively. Neither of these systems was criterion-based, and so the diagnosis depended only on the clinicians' judgement that both significant schizophrenic and mood symptoms were present to a significant degree.

In 1978, with the introduction of the Research Diagnostic Criteria (RDC), schizoaffective disorder became for the first time a diagnosis with its own separate category (Spitzer *et al.*, 1978). The RDC also provided operational criteria for the disorder, as it did for schizophrenia and major affective disorders. These included the temporal co-occurrence of a full affective syndrome and at least one of a set of ´core schizophrenic symptoms´, such as bizarre delusions, first-rank symptoms, or nearly continuous

hallucinations. A distinction was made between a 'mainly schizophrenic' subtype, requiring persistence of psychosis for more than a week (or poor premorbid functioning) and a 'mainly affective' subtype without psychosis for more than a week (and good premorbid functioning). A summary of RDC criteria are shown in Table 1a and 1b.

The RDC served as a model for DSM-III (APA, 1980), which appeared two years later. In this, schizoaffective disorder was listed as a separate category of illness, distinct from both schizophrenia and affective disorder. However, unlike all other psychotic disorders, no specific operational criteria were provided for making the diagnosis. The following revision, the DSM-III-R (APA, 1987), continued to define schizoaffective disorder as distinct from schizophrenia and bipolar disorder, and introduced a set of criteria that have remained relatively unchanged until the present.

Since 1994 two sets of diagnostic criteria for schizoaffective disorder have been predominantly used: the DSM-IV/IV-R (APA, 1994, 2000) and the ICD-10 (WHO, 1994). However, the two classifications differ in number, quality and sequence of symptoms required. Both DSM-IV-R and ICD-10 require an uninterrupted period of illness during which there is either (i) a major depressive episode, (ii) a manic episode, or (iii) a mixed episode concurrent, plus (iv) symptoms that meet criterion A for schizophrenia. Additionally, DSM-IV-R specifies schizoaffective disorder as being of either a bipolar type, for those experiencing a current or previous manic/mixed syndrome, or a depressive type, for those with no current or previous manic/mixed syndrome. DSM-IV-R requires a two week period of prominent schizophrenic symptoms without the presence of affective symptoms, whereas ICD-10 uses a more heterogeneous definition and specifies simply that schizoaffective patients must meet the criteria for both schizophrenia and mood disorder within the same episode or concurrently for at least part of the episode. A summary of the DSM-IV-R criteria is shown in Table 2.

Table 1a: Research Diagnostic Criteria (RDC) for Schizoaffective Disorder: schizomanic episode (Spitzer *et al.*, 1978)

Criteria for schizoaffective mania (RDC)

(A through E, are required)

A. One or more distinct periods with predominantly elevated, expansive, or irritable mood. The elevated, expansive, or irritable mood must be relatively persistent and prominent during some part of the illness or occur frequently. It may alternate with depressive mood. If the disturbance in mood occurs only during periods of alcohol or drug intake or withdrawal from them, it should not be considered here.

B. If mood is elevated or expansive, at least three of the following symptoms must be definitely present to a significant degree, four if mood is only irritable.
   1. More active than usual –either socially, at work, at home, sexually or physically restless.
   2. More talkative than usual or feeling a pressure to keep on talking.
   3. Flight of ideas or subjective experience that thoughts are racing.
   4. Inflated self-esteem (grandiosity, which may be delusional).
   5. Decreased need for sleep
   6. Distractibility i.e. attention is too easily drawn to unimportant or irrelevant external stimuli.
   7. Excessive involvement in activities without recognising the high potential for painful consequences e.g., buying sprees, sexual indiscretions, foolish business investments, reckless driving.

C. At least one of the following symptoms suggestive of schizophrenia is present during the active phase of the illness.
   1. Delusions of being controlled (or influenced) or of thought broadcasting, insertion or withdrawal.
   2. Nonaffective hallucinations of any type throughout the day for several days or intermittently throughout a 1 week period.
   3. Auditory hallucinations in which either a voice keeps up a running commentary on the subject's behaviours or thoughts as they occur or two or more voices converse with each other.
   4. At some time during the illness had more than 1 week when he exhibited no prominent depressive or manic symptoms but had delusions or hallucinations.
   5. At some time during the illness had more than 1 week when he exhibited no prominent manic symptoms but had several instances of marked formal thought disorder, accompanied by either blunted or inappropriate affect, delusions or hallucinations of any type, or grossly disorganised behaviour.

D. Signs of the illness have lasted at least one week from the onset of the noticeable change in the patient's usual condition (current signs of the illness may not now meet criteria A, B or C and may be residual affective or residual schizophrenic symptoms only, such as mood disturbance, blunted or inappropriate affect, extreme social withdrawal, mild formal thought disorder, or unusual thoughts or perceptual experiences).

E. Affective syndrome overlaps temporally to some degree with the active period of schizophrenic-like symptoms (delusions, hallucinations, marked formal thought disorder, bizarre behaviour, etc).

Table 1b: Research Diagnostic Criteria (RDC) for Schizoaffective Disorder: schizodepressive episode (Spitzer *et al.*, 1978)

Criteria for schizoaffective depression (RDC)

(A through E, are required)

A. One or more distinct periods with dysphoric mood or pervasive loss of interest or pleasure. The disturbance is characterised by symptoms such as the following: depressed, sad, blue, hopeless, low, down in the dumps, "don't care anymore", or irritable. The disturbance must be a major part of the clinical picture during some part of the illness and relatively persistent or occur frequently. It may not necessarily be the most dominant symptom. It does not include momentary shifts from one dysphoric mood to another dysphoric mood, e.g., anxiety to depression to anger, such as are seen in states of acute psychotic turmoil. If the symptoms in C occur only during periods of alcohol or drug use or withdrawal from them, the diagnosis should be unspecified functional psychosis.

B. At least five of the following symptoms are required for definitive and four for probable:
   1. Poor appetite or weight loss or increased appetite or weight gain (change of 1 lb. per week over several weeks or 10 lb. per year when not dieting).
   2. Sleep difficulty or sleeping too much.
   3. Loss of energy, fatigability, or tiredness.
   4. Psychomotor retardation or agitation (but not mere subjective feeling of restlessness or being slowed down).
   5. Loss of interest or pleasure in unusual activities, including social contact or sex (do not include if limited to period when delusional or hallucinating). (The loss may or may not be pervasive).
   6. Feeling of self-reproach or excessive inappropriate guilt (either may be delusional).
   7. Complaints or evidence of diminished ability to think or concentrate, such as slowed thinking, or indecisiveness (do not include if associated with obvious formal thought disorder, or preoccupation with delusions or hallucinations).
   8. Recurrent thoughts of death or suicide, or any suicidal behaviour.

C. At least one of the following is present:
   1. Delusions of being controlled (or influenced) or of thought broadcasting, insertion or withdrawal.
   2. Nonaffective hallucinations of any type throughout the day for several days or intermittently throughout a 1 week period.
   3. Auditory hallucinations in which either a voice keeps up a running commentary on the subject's behaviours or thoughts as they occur or two or more voices converse with each other.
   4. At some time during the period of illness had more than 1 month when he exhibited no prominent depressive or manic symptoms but had delusions or hallucinations (although typical depressive delusions such as delusions of guilt, sin, poverty, nihilism, or self-deprecation, or hallucinations of similar content).
   5. Define instances of marked formal thought disorder accompanied by either blunted or inappropriate affect, delusions or hallucinations of any type, or grossly disorganised behaviour.

D. Signs of the illness have lasted at least one week from the onset of the noticeable change in the patient's usual condition (current signs of the illness may not now meet criteria A, B or C and may be residual affective or residual schizophrenic symptoms only, such as mood disturbance, blunted or inappropriate affect, extreme social withdrawal, mild formal thought disorder, or unusual thoughts or perceptual experiences).

E. Affective syndrome overlaps temporally to some degree with the active period of schizophrenic-like symptoms (delusions, hallucinations, marked formal thought disorder, bizarre behaviour, etc).

F. Signs of the illness have lasted at least one week from the onset of the noticeable change in the patient's usual condition (current signs of the illness may not now meet criteria A, B or C and may be residual affective or residual schizophrenic symptoms only, such as mood disturbance, blunted or inappropriate affect, extreme social withdrawal, mild formal thought disorder, or unusual thoughts or perceptual experiences).

G. Affective syndrome overlaps temporally to some degree with the active period of schizophrenic-like symptoms (delusions, hallucinations, marked formal thought disorder, bizarre behaviour, etc).

Table 2: DSM-IV-R diagnostic criteria for schizoaffective disorder (APA, 2000).

DSM-IV-TR criteria for schizoaffective disorder
A. An uninterrupted period of illness during which, at some time, there is either a major depressive episode, a manic episode, or a mixed episode concurrent with symptoms that meet Criterion A for schizophrenia.
Note: the major depressive episode must include depressed mood.
B. During the same period of illness, there have been delusions or hallucinations for at least 2 weeks in the absence of prominent mood symptoms.
C. Symptoms that meet criteria for a mood episode are present for a substantial portion of the total duration of the active and residual period of the illness.
D. The disturbance is not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition.
Specify type:
Bipolar type (manic or mixed episode or either of these and a depressive episode)
Depressive type (major depressive episodes only)

For the new DSM-V (APA, 2013), removing schizoaffective disorder as a separate category was initially considered, with mood symptoms instead being added as a dimension to schizophrenia and schizophreniform disorder. However, the category was ultimately maintained, with a perceived lack of neurobiological validating data being cited as the reason (Allin *et al.*, 2010, Cosgrove and Suppes, 2013). In DSM-V the diagnosis of schizoaffective disorder can be only made if full mood disorder episodes have been present for the majority of the total active and residual course of illness, from the onset of the psychotic symptoms up until the time of current diagnosis. In a review of these latest criteria, it has been suggested that this change "should provide a clearer separation between schizophrenia with mood symptoms from schizoaffective disorder and should also likely reduce rates of diagnosis of schizoaffective disorder while increasing the stability of this diagnosis once made" (Malaspina *et al.*, 2013). A summary of DSM-V criteria is shown in Table 3.

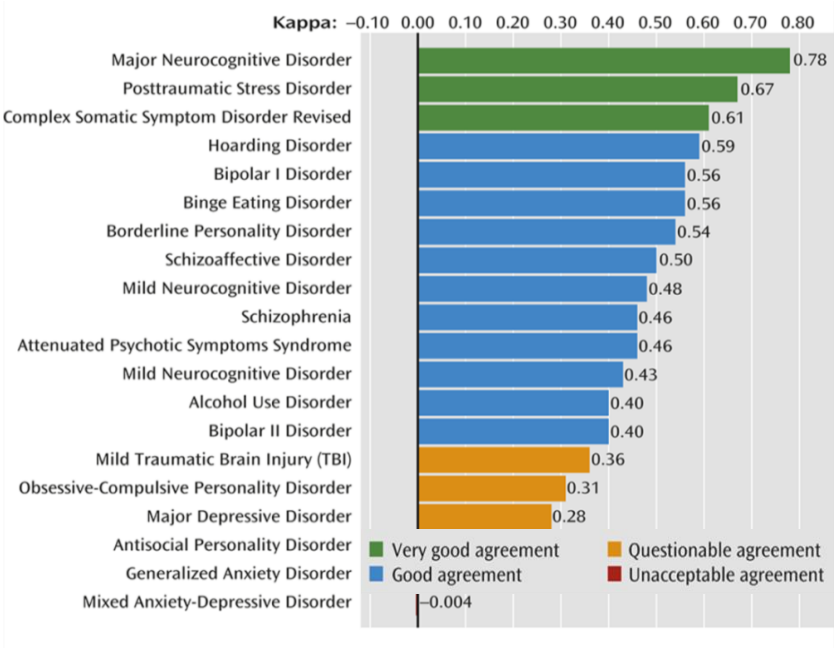
Table 3: DSM-V diagnostic criteria for schizoaffective disorder (APA, 2013).

DSM-5 diagnostic criteria for schizoaffective disorder
Main criteria A. An uninterrupted period of illness during which there is a major mood episode (major depressive or manic) *concurrent* with Criterion A of schizophrenia.[a] B. Delusions or hallucinations for 2 or more weeks in the *absence* of a major mood episode (depressive or manic) during the lifetime duration of the illness. C. Symptoms that meet criteria for a major mood episode are present for the *majority* of the total duration of the active and residual portions of the illness. D. The disturbance is not attributable to the effects of a substance (e.g. a drug of abuse, a medication) or another medical condition.
Specifiers 1. Specify whether: –*Bipolar type* (mania +/− depressive episodes) or –*Depressive type* (only has depressive episodes). 2. Specify if: With *catatonia* Current episode has three or more of the following: *agitation, catalepsy, echolalia, echopraxia, grimacing, mannerisms, mutism, negativism, posturing, stereotypes, stupor* and *waxy flexibility*. 3. Specify *course*: Only to be used after a 1-year duration of the disorder and if not in contradiction with the diagnostic criteria a. *First* episode, *multiple* episodes or *continuous* b. Current episode is *acute*, or in *partial remission*, or *full remission*. 4. Specify *current severity* (5-point scale) of primary symptoms of psychosis. (Not essential for diagnosis of schizoaffective disorder.)
[a]Schizophrenia Diagnostic Criterion A Two or more of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be (1), (2) or (3): 1. Delusions 2. Hallucinations 3. Disorganized speech (e.g. frequent derailment or incoherence) 4. Grossly disorganised or catatonic behaviour 5. Negative symptoms (i.e. diminished emotional expression or avolition)

A problem for schizoaffective disorder in the past has been its low diagnostic reliability. Maj *et al.* (2000) recruited 150 patients with a manic, major depressive or schizoaffective episode, and were independently interviewed by two psychiatrists. The inter-rater reliability of the DSM-IV criteria for schizoaffective disorder was not satisfactory (kappa=0.22). An ICD-10 study, however, evaluated the diagnostic stability of 500 first episode psychosis patients after two years and found a high level of diagnostic stability of schizoaffective disorder over this period (Salvatore, Baldessarini et al. 2011). Furthermore, Freedman *et al.* (2013), reporting on the initial reliability results from the

DSM-V field trials, found a kappa index of agreement for schizoaffective disorder of 0.50; this was in fact somewhat higher than for schizophrenia (kappa = 0.46) and bipolar disorder type II (kappa=0.40) and only slightly lower than for bipolar I disorder (kappa=0.56) (see Figure 2).

Figure 2. Interrater Reliability of Diagnoses From the Initial DSM-V Field Trials (Freedman *et al.*, 2013).



Clinical studies of schizoaffective disorder

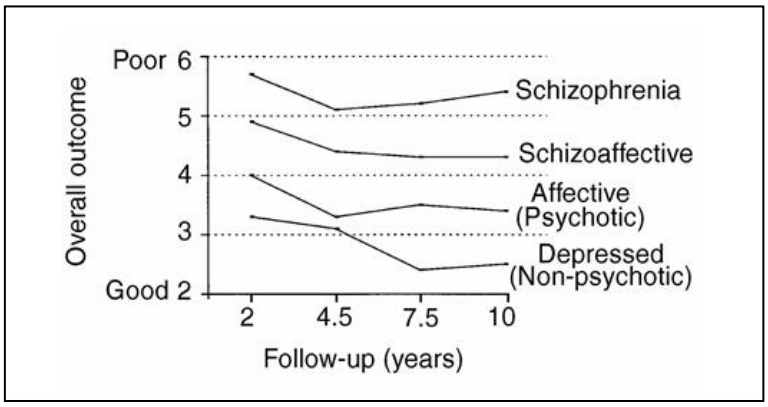
A number of studies have examined the clinical features of schizoaffective disorder in relation to schizophrenia and bipolar disorder. These studies have been systematically reviewed by Cheniaux *et al.* (2008) and subjected to a meta-analysis by Pagel *et al.* (2013).

Cheniaux *et al.* (2008) reviewed clinical trials, that compared schizoaffective disorder with schizophrenia and mood disorder. Demographic characteristics, symptomatology, dexamethasone suppression test, neuroimaging, response to treatment, evolution and family morbidity were evaluated. Studies reviewed failed to indicate a clear cut distinction between schizoaffective disorder and the other disorders. They suggested that schizoaffective disorder might constitute a heterogeneous group composed by both schizophrenia and mood disorder patients or a middle point of a continuum between schizophrenia and mood disorder, but not an atypical form of schizophrenia or mood disorder nor an independent mental disorder.

Pagel *et al.* (2013) reviewed 50 studies that simultaneously compared schizophrenic, schizoaffective and bipolar patients. The findings indicate some, often minor, differences among the diagnostic groups in the numerical values of a large sampling of demographic, clinical, and psychometric measures. In most categories, pooled measures for schizoaffective disorder patients were intermediate between, or not significantly different from, measures in comparison with subjects diagnosed with schizophrenia or bipolar disorder. The authors supported the view that schizoaffective disorder, as currently defined, lies between, or shares features of both, schizophrenia and bipolar disorder. Notably, statistically significant exceptions were that schizoaffective disorder patients had the highest proportion of women and the youngest reported onset age of all three disorders. However, schizoaffective disorder resembled schizophrenia and not bipolar disorder in seven out of nine demographic and clinical categories as well as in five out of eight psychometric measures. The findings for schizoaffective disorder patients tended to be somewhat closer to those for patients with schizophrenia than to those for patients with bipolar disorder, supporting the hypothesis that schizoaffective disorder is not primarily an affective disorder; the authors stated that it remains unclear, however, whether the findings reflect the nature of the disorder or whether they are simply an artifact of current diagnostic criteria.

There have been numerous studies of outcome in schizoaffective disorder. In a review of these, Mckenna (2007) noted that the outcome has been found to be intermediate between schizophrenia and manic-depressive psychosis (Jager *et al.*, 2004, Tsuang and Dempsey, 1979) similar to schizophrenia (Himmelhoch *et al.*, 1981, Tsuang and Coryell, 1993, Welner *et al.*, 1977), similar to manic-depressive psychosis (Marneros *et al.*, 1990, Pope *et al.*, 1980), or heterogeneous (Berg *et al.*, 1983, Brockington *et al.*, 1980a, Brockington *et al.*, 1980b). One study stands out from the others because of its use of rigorous RDC for schizoaffective disorder and also because of the length and detailed nature of the follow-up. During 10 years, Harrow *et al.* (2000) followed 36 patients with schizoaffective disorder, 70 patients with schizophrenia, 44 patients with psychotic forms of affective disorder (26 with bipolar and 18 unipolar depressed), and 60 patients with unipolar, non-psychotic major depression. Across the whole follow-up period the schizoaffective patients were found to occupy an intermediate position between those with schizophrenia and those with psychotic forms of affective disorder. At some points (7.5 years and 10 years) their outcome was significantly better than patients with schizophrenia, whereas at other time points (2 years and 4.5 years) it was not. The schizoaffective patients showed a significantly poorer outcome than patients with unipolar major depression at all-time points, but their outcome was not significantly worse than the psychotic affective group outcome, except at 4.5 year follow-up. The results are shown in Figure 3.

Figure 3: Outcome for schizoaffective disorder, schizophrenia and affective disorder groups at four consecutive follow-ups (Harrow *et al.*, 2000).



A further recent study is also worthy of note. Kotov *et al.* (2013) employed a statistical technique, nonlinear modelling, to examine for presence of discontinuities in outcome among different forms of psychosis. They followed up 413 psychotic inpatients over ten years, rating presence of symptoms, numbers of affective and psychotic episodes, and also functioning using the Global Assessment of Functioning (GAF) scale. They found evidence for a discontinuity in outcome between cases in which psychotic symptoms were limited to mood episodes and cases in which at least some of the psychotic symptoms occurred outside affective episodes, supporting the Kraepelinian dichotomy between schizophrenia and major affective disorder. However, no discontinuities emerged within the category of nonaffective psychosis – in terms of long-term outcome schizoaffective disorder appeared to be continuous with (although somewhat better than) schizophrenia.

Treatment

Patients with schizoaffective disorder often receive complex medication regimes, as clinicians attempt to target both psychotic and affective symptoms (Cascade *et al.*, 2009). With respect to antipsychotic drugs, clinical trials are scarce, and have typically mixed schizoaffective patients with those with either schizophrenia or bipolar disorder. Clear evidence of efficacy and tolerability exists for just a few atypical antipsychotics, mainly paliperidone (Canuso *et al.*, 2010) and risperidone (Janicak *et al.*, 2001). Evidence from large schizophrenia trials that have included a subset of patients with schizoaffective disorder also supports the effectiveness of aripiprazole, olanzapine and ziprasidone (Murru *et al.*, 2011). Jager *et al.* (2010) reviewed 33 treatment trials for schizoaffective disorder. They argued that results from reviewed trials did not permit consistent recommendations as to whether schizoaffective disorder should be treated primarily with antipsychotics, mood stabilizers or combinations of these drugs during acute or maintenance treatment.

Neurobiological findings

The aetiology of major mental disorders like schizophrenia and bipolar disorder is currently considered to be multifactorial involving genetic, neurobiological and also environmental factors (Craddock *et al.*, 2009). Publications concerning neurobiological findings in schizoaffective disorder have increased in the last years, but the findings have to be considered as being still preliminary (Murru *et al.*, 2012).

Genetics

Coryell and Zimmerman (1988) reviewed 14 family history studies of schizoaffective disorder carried out between 1973 and 1983. The rates of schizophrenia among first-degree relatives varied considerably in these studies, from zero to nearly 11%. The rates of bipolar disorder were similar to those seen in the relatives of affective patients, and in some cases slightly higher. Five studies assessed for presence of schizoaffective disorder in relatives of patients with the same disorder: they found rates of 1.0%, 2.2%, 2.5%, 3.8% and 6.1%. Further studies have continued to find evidence of familial overlap between schizoaffective disorder and both schizophrenia and bipolar disorder (Coryell and Zimmerman, 1988, Laursen *et al.*, 2005, Maier *et al.*, 1993). Additionally, a large, epidemiologically-based study, the Roscommon Family Study (Kendler *et al.*, 1995), which interviewed 1753 relatives of probands with diagnoses of schizophrenia or affective illness, found that relatives of schizoaffective patients had significantly higher rates of affective illness than relatives of schizophrenic patients, and also significantly higher rates of schizophrenia than relatives of patients with affective illness, suggesting increased liability to both disorders.

To date, only one twin study has been carried out. Cardno *et al.* (2012) examined manic and depressive subtypes of schizoaffective disorder in twins affected with all psychotic disorders (the Maudsley twin series). They found a marked degree of familial overlap in monozygotic twin pairs for schizomania, schizodepression, schizophrenia and manic bipolar disorder, with the highest degree of overlap between schizomania and manic bipolar disorder. Results of the above family history studies are to some extent in line with molecular genetic studies of major psychiatric disorders. These have been interpreted to suggest a common vulnerability that increases the risk for schizophrenia and affective disorder (Craddock *et al.*, 2009). Nevertheless, it has still been suggested that some susceptibility pathways may be specific for schizophrenia, others for bipolar

disorder, or for mixed schizophrenic and affective psychoses (Malaspina, Owen et al. 2013).

Neurocognition

A review carried out as part of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative in the USA concluded that schizophrenia and schizoaffective disorder share a similar pattern of cognitive deficits which is distinct from that seen in major depression and bipolar disorder (Buchanan *et al.*, 2005). However, this conclusion was based on only two studies, one comparing schizoaffective and schizophrenic patients (Miller *et al.*, 1996), and the other comparing schizoaffective patients with schizophrenia and non-psychotic mood disorder groups (Evans *et al.*, 1999). Since then more studies have been carried out, most of which compared schizoaffective patients with those with bipolar disorder. Torrent *et al.* (2007) found that schizoaffective patients showed significantly more impairment than bipolar patients on tests of short- and long-term verbal memory, and on two out of four executive measures. In contrast, Studentkowski *et al.* (2010) reported more mixed findings: schizoaffective patients showed more impairment than bipolar patients on tests of attention, psychomotor speed and memory, but there were no significant differences on measures of cognitive flexibility and emotional memory. Another study found no significant differences on executive tests in schizoaffective patients compared to patients with psychotic and non-psychotic forms of bipolar disorder (Szoke *et al.*, 2008). Similarly, Amann *et al.* (2012) showed that schizophrenic, schizomanic and both psychotic and not psychotic bipolar manic patients show a broadly similar degree of executive and memory deficits in the acute phase of illness. Two further studies have raised the possibility that the conflicting findings might be related to the presence or absence of psychotic symptoms in the bipolar comparison group. For example, Simonsen *et al.* (2011) found no differences between schizoaffective and bipolar patients with a history of psychotic

symptoms on a battery of seven tests covering memory, processing speed and executive function, but the schizoaffective patients showed significantly worse performance compared to patients with non-psychotic forms of bipolar disorder on four of these tests. Glahn *et al.* (2006) found no differences between schizoaffective and psychotic bipolar patients on three tests of short-term and working memory. Greater differences from non-psychotic bipolar patients were evident on all the tests, but the authors did not state whether these reached significance. So far, it is still not certain how cognitive functioning changes over time. A recent longitudinal study in schizophrenia showed an absence of decline for most measures (except of visuospatial and constructional performance) and modest gains in immediate memory and attention measures (Dickerson *et al.*, 2014).

A meta-analysis of 31 studies compared the cognitive performance of patients with schizophrenia with that of patients with affective psychosis or schizoaffective disorder (Bora *et al.*, 2009). The patients with schizophrenia were found to perform significantly worse than those with schizoaffective disorder or affective psychosis in 6 of 12 cognitive domains. However, the between-group differences were small and the distribution of effect sizes showed substantial heterogeneity. When schizophrenia was compared separately with schizoaffective disorder and affective psychosis, the magnitude of the differences between schizophrenia and affective psychosis were similar or larger than differences between schizophrenia and schizoaffective disorder in some domains of cognitive function, but in others schizoaffective disorder showed non-significantly smaller effect sizes than those for affective psychosis.

Neuroimaging

Structural imaging studies in schizoaffective disorder

On the basis of many studies, the existence of brain structural changes is well established in schizophrenia. Computed tomography (CT) scan studies originally

established the presence of lateral ventricular enlargement in the disorder (for a review see Andreasen *et al.*, 1990). Magnetic resonance imaging (MRI) studies confirmed this, and demonstrated a small degree of brain volume reduction, of the order of 2-3% (Wright *et al.*, 2000). Regional volume reductions range from 2% in the temporal lobes, to 5% in the frontal lobes and 7% in the hippocampus (Haijma *et al.*, 2013, Wright *et al.*, 2000). An increasing number of studies in schizophrenia are using voxel-based techniques such as voxel-based morphometry (VBM). They have found a pattern of cortical grey matter reductions, that are widespread but not generalized and affect particularly the frontal lobe and cingulate cortex, the insula, the thalamus, the post-central gyrus, and medial temporal regions (Shepherd *et al.*, 2012).

Lateral ventricular enlargement has been a regular finding in studies of bipolar disorder and is supported by meta-analyses (Arnone *et al.*, 2009, Kempton *et al.*, 2008). However, these meta-analyses found only small effect sizes for whole brain volume reduction, which were significant in one (Arnone *et al.*, 2009) but not in the other (Kempton *et al.*, 2008). In contrast, studies using VBM have found more consistent evidence of abnormality, which affect principally the anterior cingulate cortex, insula and inferior frontal cortex (Bora *et al.*, 2010, Selvaraj *et al.*, 2012).

So far, few studies have examined brain structural changes in schizoaffective disorder. An early CT study by Rieder *et al.* (1983) found no differences in lateral ventricular volume and an index of cortical atrophy in 28 schizophrenic patients and 15 schizoaffective patients; this study also failed to find differences from 19 bipolar patients. Similarly, a more recent study using MRI found that 12 schizoaffective and 12 bipolar patients showed a similar decreased whole-brain volume compared to 12 healthy controls (Getz *et al.*, 2002). Other neuroimaging studies in schizoaffective disorder have focused on specific brain structures. Smith *et al.* (2011) used CT to examine thalamic morphology in schizophrenic and schizoaffective patients. They found that both groups showed similar volume reductions compared to controls, and also similar shape

deformations in the medio-dorsal and ventro-lateral thalamic regions. However, distinct deformations in medial and lateral thalamic regions were only found in schizoaffective patients. Two MRI studies focused on hippocampal volume found that this was significantly reduced in both schizophrenic and schizoaffective patients compared to both bipolar patients and healthy subjects (Arnold *et al.*, 2015, Radonic *et al.*, 2011). By contrast, a recent study by Mathew *et al.* (2014) compared hippocampal volume in 219 schizophrenic, 142 schizoaffective and 188 psychotic bipolar patients versus 337 healthy controls. Hippocampal volumes reductions were comparable within all the disorders and positively correlated with psychosis severity and cognitive impairment.

To date, only two studies have applied whole brain voxel-based techniques to schizoaffective disorder. Ivleva *et al.* (2013) compared groups of 146 schizophrenic patients, 90 schizoaffective patients (both unipolar and bipolar type) and 115 psychotic bipolar patients with 200 healthy controls, recruited from four different sites. They found that both the schizophrenic and schizoaffective patients showed grey matter volume reductions compared to the healthy controls in numerous and overlapping areas. In contrast, compared to the healthy controls, the psychotic bipolar patients showed volume reductions that were limited to the fronto-temporal cortex. A study by our group found similar results, as both 45 patients with schizophrenia and 45 patients with schizoaffective disorder showed areas of volume reduction in widespread and broadly similar cortical locations, whereas 45 bipolar patients showed no areas of volume reduction (Amann *et al.*, 2015, under review). When all patient groups combined was compared with the healthy controls, no significant differences in volume between schizoaffective and schizophrenic patients were found. Taken together, these findings replicate and extend those of Ivleva *et al.* (2013), and provide evidence that, at the level of gray matter brain structure, schizoaffective disorder resembles schizophrenia more than it does bipolar disorder.

Recently, our group has performed a multimodal structural study, investigating group differences in cortical volume and its constituent parts, cortical thickness and surface area, as well as in fractional anisotropy (FA) and mean diffusivity (MD) in 45 schizoaffective patients versus 45 matched healthy controls (Landin-Romero *et al.*, 2015, under review). Resulting abnormalities were widespread and pointed to reduced gray and white matter tissue in the patient group and surface-based morphometry indicated that gray matter abnormality is mainly driven by cortical thinning. The multimodal abnormalities were mainly detected in areas that have been consistently reported to be altered in schizophrenia, and to some extent in bipolar disorder, which may explain part of the common symptomatology related to these disorders.

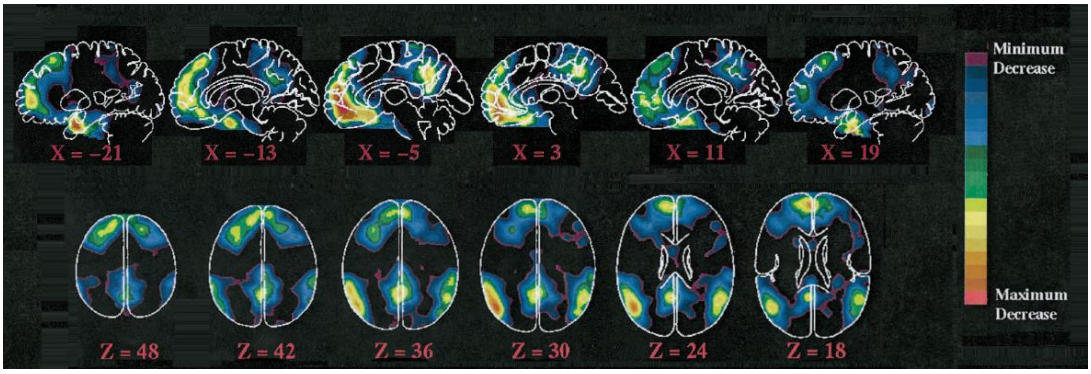
Functional imaging studies in schizoaffective disorder

Functional imaging studies of schizophrenia have consistently implicated the prefrontal cortex, but the nature of the dysfunction in this brain region is increasingly recognized as being complex. The original finding was hypofrontality, i.e. reduced activity particularly in the DLPFC, first documented at rest (Ingvar and Franzen, 1974) and later during performance of the Wisconsin Card Sorting Task (Weinberger *et al.*, 1986). Although not consistently replicated in early studies, both resting and task-related hypofrontality have been supported by meta-analysis (Hill *et al.*, 2004). Subsequent studies have documented a second form of frontal dysfunction, hyperfrontality, that is increased activation during performance of working memory and other frontal-activating tasks (Tan *et al.*, 2006). It has been proposed that hyperfrontality is present simultaneously with hypofrontality, with the two having different prefrontal locations, something that has been supported by two meta-analyses, one of studies carried out during performance of a working memory task, the n-back task (Glahn *et al.*, 2005), and the other during a range of cognitive tasks (Minzenberg *et al.*, 2009). Alternatively, it has been suggested that which of the two abnormalities is seen depends on the demands of

the task: hyperfrontality appears when the task is easy and schizophrenic patients 'work harder to keep up'. At higher levels of task difficulty, schizophrenic patients reach their limit of performance earlier than controls and thereafter fail to activate their prefrontal cortex, resulting in hypofrontality (Johnson *et al.*, 2006, Weinberger *et al.*, 2001).

Recently, a third form of frontal dysfunction has been found: failure of de-activation in the MPFC. Beginning in 2008, several studies have reported failure of de-activation in the MPFC, using a variety of different tasks (Milanovic *et al.*, 2011, Pomarol-Clotet *et al.*, 2008, Whitfield-Gabrieli *et al.*, 2009). Some studies have additionally found failure to de-activate in the posterior cingulate cortex (Salgado-Pineda *et al.*, 2011, Schneider *et al.*, 2011). The MPFC and the posterior cingulate cortex form the two midline nodes of the so-called DMN. The DMN is a series of interconnected brain regions which are active at rest but which reduce in activity during performance of a wide range of cognitive tasks (Gusnard and Raichle, 2001, Raichle *et al.*, 2001). The parietal cortex, lateral temporal cortex and hippocampus also form part of the network (Buckner *et al.*, 2008) (see Figure 4). Clues to the function of the DMN come from a small number of studies using tasks which, rather than producing de-activation, increase activity in parts of it. Such tasks often share a component of introspective or self-related thought: recall of personal experiences, making social and emotional judgements, envisioning the future and performing theory of mind tasks (Gusnard, 2005).

Figure 4: Default mode network in normal subjects (Raichle *et al.*, 2001). The figure depicts the regions of the brain regularly observed to decrease their activity during attention demanding cognitive tasks shown in sagital projection (upper) and transverse projection (down) in healthy participants. These data represent a meta-analysis of nine functional brain imaging studies performed with PET. In each of the studies included, the subjects processed a particular visual image in the task state and viewed it passively in the control state. One hundred thirty-two individuals contributed to the data in these images. These decreases appear to be largely task independent. The images are oriented with the anterior at the top and the left side to the reader's left. The numbers beneath each image represent the millimetres above or below a transverse plane running through the anterior and posterior commissures.



Bipolar disorder has been associated with diverse functional imaging findings. Several studies have documented reduced prefrontal activation (Blumberg *et al.*, 2003, Mazzola-Pomietto *et al.*, 2009, Rubinsztein *et al.*, 2001), which has most often been found in the orbitofrontal cortex (Altshuler *et al.*, 2005, Blumberg *et al.*, 2003, Elliott *et al.*, 2004), the ventrolateral prefrontal cortex (Mazzola-Pomietto *et al.*, 2009) and the frontal pole (Blumberg *et al.*, 1999, Rubinsztein *et al.*, 2001). However, reduced DLPFC activation has been found in studies that have used the n-back working memory task. This has been documented during both manic (Pomarol-Clotet *et al.*, 2012) and depressive episodes (Fernandez-Corcuera *et al.*, 2012), and also in euthymic patients (Monks *et al.*, 2004). Recent evidence suggests also that bipolar disorder, like schizophrenia, is characterized by medial frontal failure of de-activation. This has been described both in mania (Pomarol-Clotet *et al.*, 2011) and in depression (Fernandez-Corcuera *et al.*, 2012), in

studies carried out during performance of a working memory task. Using a verbal fluency task, Allin *et al.* (2010) also found failure of de-activation in the posterior cingulate and retrosplenial cortex in euthymic patients, which is in the posterior midline node of the DMN, supporting the concept of a 'trait' DMN dysfunction. There is a consensus that bipolar disorder is associated with other functional imaging abnormalities which have been broadly characterized as overactivity in subcortical structures such as the amygdala, hippocampus and basal ganglia, coupled with reduced activity in prefrontal and some other cortical regions (Green *et al.*, 2007, Savitz and Drevets, 2009, Strakowski *et al.*, 2012, Strakowski *et al.*, 2005). Recent meta-analyses suggest that this pattern is seen both at rest and in studies using task activation (Kupferschmidt and Zakzanis, 2011), although the pattern differs to some extent depending on whether cognitive or emotional tasks (typically facial emotion processing) are used (Chen *et al.*, 2011).

So far, there are a small number of longitudinal functional neuroimaging studies in bipolar disorder, comparing the different mood states. Lim *et al.* (2013) reviewed these and concluded that there was some evidence for an improvement in activation patterns in the fronto-limbic circuitry from mania/depression to euthymia. However, a study that compared manic, depressive and euthymic patients using predetermined regions of interest (ROI) in the left and right DLPFC and the left and right posterior parietal cortex found reduced activation in both areas compared to healthy controls but with no significant variation across phase (Townsend *et al.*, 2010). Only one study has investigated whether DMN dysfunction is mood-state-related or persists into euthymia: Pomarol-Clotet *et al.* (2014) found that manic, depressed and euthymic patients were characterized by failure of de-activation in the medial frontal cortex, supporting the concept of 'trait' DMN dysfunction.

To date, few functional imaging studies have been carried out in schizoaffective patients. A first study has reported some preliminary evidence of DMN dysfunction in schizoaffective patients (Ongur *et al.*, 2010). In a sub-analysis, they found reduced resting

state connectivity in the medial frontal cortex in seven schizoaffective patients, which was similar in degree to that seen in 7 schizophrenic patients but greater than in 14 patients with bipolar disorder. Recently, Yuhui *et al.* (2014) used a proposed group information guided ICA method, which captures accurately individual functional networks and simultaneously preserves correspondence of networks across subjects. Resting-state fMRI data of 20 schizophrenic, 20 bipolar, 20 schizomanic and 13 schizodepressed subjects were compared with 20 healthy subjects. They found that subjects from the same group had in general similar network patterns; however, schizomanic and schizodepressed subjects were found to be the most similar groups to each other. Furthermore, bipolar subjects were more similar to healthy subjects, and schizodepressed and also schizomanic patients (even though less pronounced) shared high similarity with schizophrenic subjects. The authors suggested that schizoaffective disorder is an independent pathology in functional network pattern but with a high similarity to schizophrenia. So far, no longitudinal studies in schizoaffective disorder have evaluated whether possible neurofunctional changes persist into clinical remission or not.

HYPOTHESES AND OBJECTIVES

As noted, current evidence concerning neurobiological aspects of schizoaffective disorder is still preliminary. The overall aim of this thesis was to provide new neurobiological insights into schizoaffective disorder, in this case via neuropsychological and neuroimaging studies. Furthermore, we hope that our findings might contribute to enhance knowledge about its nosological position in relation to schizophrenia and bipolar disorder. More broadly, research in neuroimaging and neurocognition provides a powerful source for exploring the relationship between the different psychiatric phenotypes and could be used to improve conceptualization, classification, and diagnosis in psychiatry.

Objectives

The specific objectives of the two studies were as follows:

Study 1:

1. To examine activation and de-activations patterns in the acute phase of schizomanic and schizodepressive episodes.
2. To investigate differences in patterns of activation and de-activation between acute schizoaffective patients and healthy subjects.
3. To compare brain functioning differences between schizomanic and schizodepressive episodes.

Study 2:

1. To determine to what extent activation and de-activation patterns of acute schizoaffective patients persist in clinical remission.

2. To investigate differences in patterns of activation and de-activation between the schizoaffective patients in clinical remission and healthy subjects.
3. To examine whether cognitive dysfunctions in acute schizoaffective patients persist in clinical remission.
4. To compare cognitive performance between remitted schizoaffective patients and healthy subjects.

Hypotheses

Based on the above, four principal hypotheses were established:

1. Acutely ill schizoaffective patients will show different patterns of activation and de-activation during performance of a working memory task compared to healthy subjects.
2. Schizoaffective patients will show an improvement in task-related activations and de-activations dysfunctions, once in clinical remission.
3. Schizoaffective patients will show memory and executive dysfunction compared with healthy subjects.
4. Acutely ill schizoaffective patients will show an improvement in memory and executive performance when they are in clinical remission.

METHODS

Participants

The schizoaffective sample was recruited from three Spanish psychiatric hospitals: Hospital Benito Menni in Sant Boi de Llobregat, Hospital Clínic of Barcelona and General Hospital of Granollers. The patients were required to meet Research Diagnostic Criteria, RDC (Spitzer *et al.*, 1978), for schizoaffective disorder, bipolar type, based on psychiatrist interview and review of case-notes. RDC criteria were used as they are the most detailed of all available criteria for schizoaffective disorder and require not only that patients show schizophrenic symptoms but also that the affective symptoms meet requirements for a full affective syndrome similar to those demanded for depression and mania/hypomania in DSM-IV and ICD-10. They are also more explicit than DSM-IV and ICD-10 about the temporal overlap with schizophrenic symptoms (for details see also chapter: Diagnosis).

Inclusion criteria:

1. Age 18-65 years.
2. Meeting RDC criteria for schizoaffective disorder, bipolar type (Spitzer *et al.*, 1978)
3. Premorbid IQ in the normal range (i.e. ≥ 70), as estimated using the Word Accentuation Test (Test de Acentuación de Palabras, TAP) (Del Ser *et al.*, 1997) (for details see section: Cognitive assessment).
4. Right handedness to ensure homogeneity in the functional imaging part of the study.

Exclusion criteria:

1. History of brain trauma or neurological disease.
2. Alcohol/substance abuse within 12 months prior to participation.

The healthy control group consisted of right-handed individuals 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. They met the same exclusion criteria as the patients. They underwent a detailed diagnostic interview and were excluded if they reported a personal or first-degree relative with a history of mental illness and/or treatment with psychotropic medication.

The investigation was carried out in accordance with the latest version of the Declaration of Helsinki, the study design was reviewed by the ethical committee "Comité Ético de Investigación Clínica de las Hermanas Hospitalarias" (Barcelona, Spain). Written informed consent of the participants was obtained after the nature of the procedures had been fully explained.

Design of the study

The study design used a sample of schizoaffective patients who were mainly recruited and first assessed while in an acute schizomanic or schizodepressive episode. At this time they were administered a neuropsychological test battery and underwent a functional neuroimaging. The patients then received a bi-weekly follow-up to determine when they reached clinical remission. Once in clinical remission for at least two months, the patients underwent the second assessment of both, the neuropsychological test battery and functional neuroimaging. Healthy controls were also assessed.

The design of the study was as follows:

a) First assessment

Patients in a schizomanic episode were required to have a YMRS score >18 and a HAMD score <8. Conversely, patients in a schizodepressive episode were required to have a

HAMD score >18 and YMRS score <8. Psychotic symptoms were also required to be present in both acute phases, defined on the bases of the following PANSS items: P1 ≥4, or P3 ≥4, or P5 ≥5, or P6 ≥6 or PG9 ≥5. More details on these scales are given in chapter: Psychopathological assessment.

b) Follow-up

Patients were followed up and re-assessed bi-weekly, using the YMRS, HAMD and PANSS, until they had reached clinical remission.

c) Second assessment

Clinical remission was required for at least 2 months of 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.

d) Final assessment

After the second assessment patients received two further bi-weekly follow-ups to confirm maintained clinical remission.

Recruitment

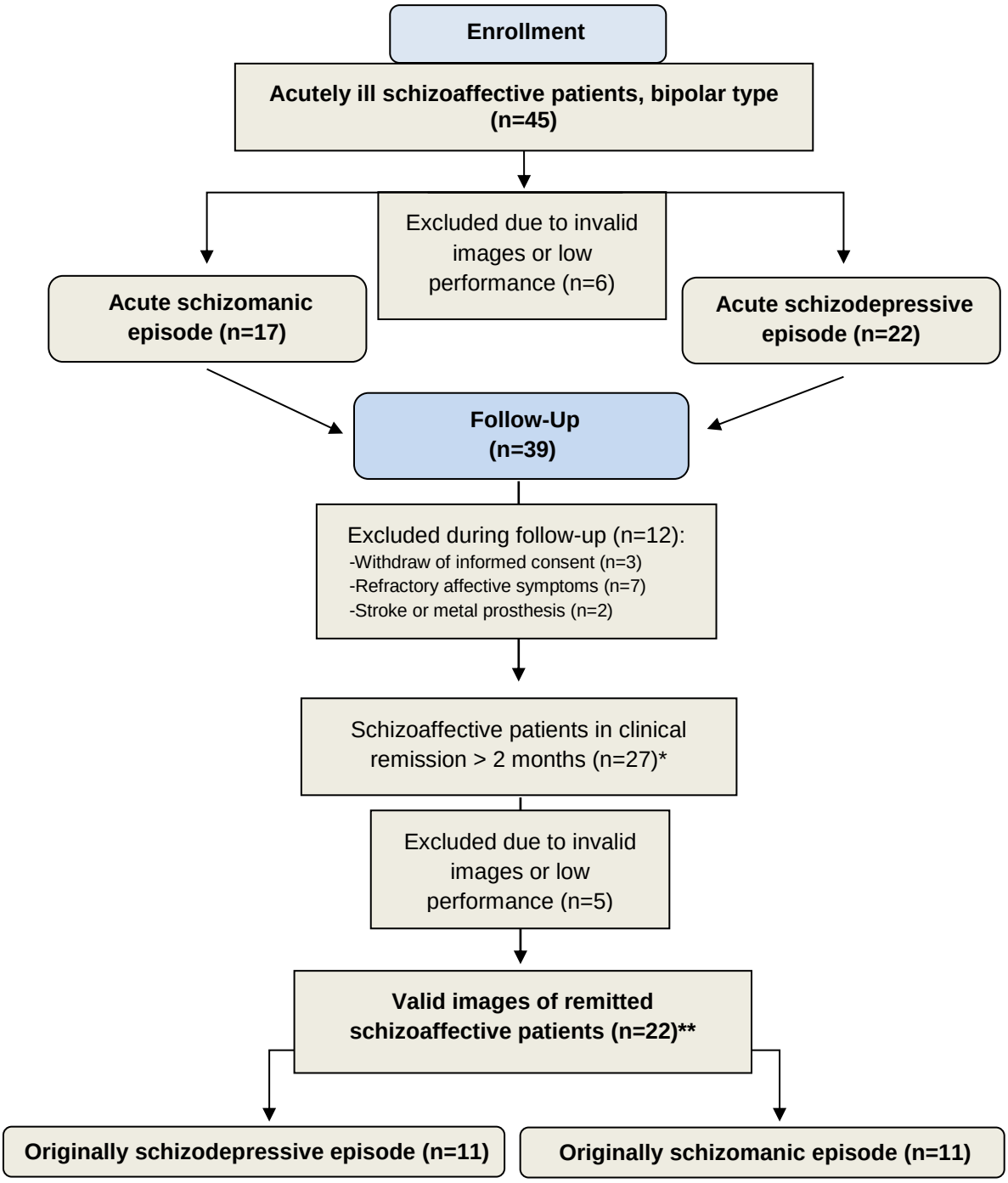
A total of 45 acute schizoaffective patients were enrolled and underwent the first assessment, 24 patients with a schizodepressive episode and 21 with a schizomanic episode. Six patients were excluded due to movement inside the MRI scanner or poor task performance. Thirty-nine patients, consisting of 17 patients who entered the study with a schizomanic episode and 22 with a schizodepressive episode, had a valid first-assessment and entered the follow-up. During the follow-up, 12 patients were excluded due to different reasons (for details see Figure 5), and 27 patients reached criteria for clinical remission and underwent the second assessment. Five more patients were excluded due to movement inside the second MRI scanner or poor task performance. Finally, 22 patients in clinical remission were valid deriving from 10 schizomanic, 10 schizodepressive and 2 patients who presented both schizodepressive and schizomanic

episodes and were re-assessed in both phases, as well as in clinical remission. It must be noted that in most cases the first assessment was while they were acutely ill and the second when they had recovered, but 2 schizomanic and 1 schizodepressive patients were first scanned in remission and later on in the acute phase of the disease. The patient flow is summarized in Figure 5.

All patients were taking psychiatric medication at the time of both assessments. Medication often changed slightly between the first and second evaluation. Treatment data for patients taking antipsychotics (measured in chlorpromazine equivalents), mood-stabilizers (valproate, lithium or combination) and antidepressants were collected.

Controls were also scanned twice, with a mean length of time from the first to second scan similar to the patient group. They underwent a single cognitive assessment.

Figure 5: Consort flowchart diagram of patient disposition during recruitment, first and second evaluation.



(*) In most cases the first scan was while they were acutely ill and the second when they had recovered, but 2 schizomanic patients and 1 schizodepressive patients were first scanned in remission. (**) Please note that two patients were scanned in both phases, the schizodepressive and schizomanic phases.

Psychopathological assessment

Manic symptoms assessment

Manic symptoms were assessed with the Young Mania Rating Scale (YMRS) (Young *et al.*, 1978), which has been adapted for use in Spanish populations (Colom *et al.*, 2002). The YMRS is an 11 items, semi-structured interview used to measure the severity of manic episodes in patients. Scores on individual items can be summed to provide an overall score. As stated above, acute schizomanic patients were required to have YMRS scores >18 and clinical remission was defined as YMRS scores <8.

Depressive symptoms assessment

Depressive symptoms were assessed with the spanish version of Hamilton Rating Scale for Depression (HAMD) (Ramos-Brieva and Cordero Villafafila, 1986), which was originally published by Hamilton (1960). The HAMD contains 17 items that can be summed to provide a measure of severity of depression. As stated before, acute schizodepressive patients were required to have HAMD scores >18 and in clinical remission the HAMD scores had to be <8.

Psychotic symptoms assessment

Psychotic symptoms were assessed with the spanish version of the Positive And Negative Syndrome Scale (PANSS) for schizophrenia (Kay SR, 1987, Peralta and Cuesta, 1994). The PANSS is a semi-structured interview that consists of 30 items evaluating a wide range of positive, negative and non-psychotic symptoms. As stated above, psychotic

symptoms were required to be also present in both acute phases (schizomanic and schizodepressive episodes), defined on the bases of the following PANSS items: P1 ≥4, or P3 ≥4, or P5 ≥5, or P6 ≥6 or PG9 ≥5. Remission of psychotic symptoms was defined as PANSS items P1, P3, P5, P6 and PG9 scores of ≤2.

Illness severity and functioning

Overall severity of illness was assessed using the spanish version of the Clinical Global Impression (CGI) scale (Garcia-Portilla *et al.*, 2011, NIMH, 1976). The CGI grades severity according to seven levels: from 1 (normal) to 7 (very severe illness). Psychosocial functioning was rated with the General Assessment of Functioning (GAF) scale (Wechsler, 1997), which considers psychological, social, and occupational functioning on a hypothetical continuum of mental health-illness.

Cognitive assessment

General cognitive assessment

Premorbid IQ was estimated using the spanish version of the Word Accentuation Test, 'Test de Acentuación de Palabras' (TAP) (Del Ser *et al.*, 1997), which requires pronunciation of spanish words whose accents have been removed. This is conceptually similar to the National Adult Reading Test (NART) used in the United Kingdom (Nelson and Willis, 1991) and the Wide Range of Achievement Test (WART) used in the USA (Jastak and Wilkinson, 1984). These tests measure the subject's ability to pronounce words which do not follow the rules of pronunciation: ability to pronounce a word indicates that the person knows the meaning of the word, and it is known that pronunciation tends to be preserved even when knowledge of the word has been lost due

to disease. Since pronunciation of all spanish words can be derived from their spelling, the TAP instead utilizes low-frequency spanish words whose accents have been removed. A recent study has shown that the TAP gives a reliable estimate of IQ in normal subjects, and is sensitive to estimated premorbid-current IQ difference in schizophrenic patients (Gomar *et al.*, 2011).

Current IQ was assessed using four subtests of the Wechsler Adult Intelligence Scale III (WAIS-III) (Wechsler, 2001): two verbal tests, Vocabulary and Similarities, and two performance tests, Block design and Matrix reasoning. These are the same subtests used at the WAS-I scale (Wechsler, 1999), which is an abbreviated version of the WAIS-III validated for the English-speaking population.

Neuropsychological assessment

This consisted of two batteries of memory and executive function respectively, the Spanish version of the 3rd edition of the Wechsler Memory Scale (WMS-III) (Pereña *et al.*, 2004, Wechsler, 1997) and the Behavioural Assessment of the Dysexecutive Syndrome (BADS) (Wilson, 1996), which has been adapted for use in Spanish populations (Vargas *et al.*, 2009).

Memory was assessed using four subtests of the WMS-III: 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 were summed to provide a composite score.

The BADS consists of six tests examining different aspects of executive function. Performance on the individual tests can be combined to give an overall 'profile' score that can also be adjusted for age (the standardized score).

- ✓ The Rule Shift Cards: this examines set shifting ability.

- ✓ The Action Programme Test: this requires the subject to devise a strategy to remove a cork from a container, using simple tools such as a stick and water.
- ✓ The Key Search Test: the subject has to devise an efficient plan to search a field for a lost object.
- ✓ The Temporal Judgement Test: the subject has to respond to questions they are unlikely to know the exact answer to, such as, for example, how long it takes to clean a window, or how long a dog lives.
- ✓ The Zoo Map Test: this requires strategic planning of a route in a diagram of a zoo, while following certain rules.
- ✓ The Modified Six Elements Test: this is a task requiring multi-tasking in which the subject has to carry out various elements of six different activities according to a set of rules.

Neuroimaging procedure

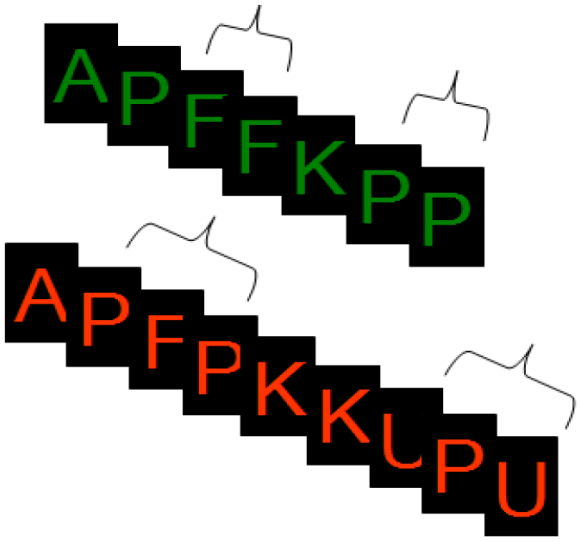
All subjects underwent functional MRI scanning twice, using a 1.5 Tesla GE Signa scanner (GE Medical Systems, Milwaukee, Wis) located at the Sant Joan de Déu Hospital in Barcelona, Spain.

N-back task

The paradigm used was a sequential-letter version of the n-back task (Gevins and Cutillo, 1993). This paradigm assesses the ability to maintain previous items in memory while attending to the current item and so is a working memory task. The working memory load can be varied by varying the number of items that have to be kept in mind. For this study, two levels of memory load (1-back and 2-back) were presented in a blocked design manner; in the 1-back task, participants had to detect when one letter

was repeated twice consecutively, with no other letter in-between, whereas in the 2-back task there was one letter between the model and the goal letter. Each block consisted of 24 letters that were shown every 2 seconds (1 s: on, 1 s: off) and all blocks contained five repetitions (1-back and 2-back depending on the block) located randomly within the blocks. Individuals had to indicate repetitions by pressing a button. Four 1-back and four 2-back blocks were presented in an interleaved way, and between them a baseline stimulus (an asterisk flashing with the same frequency as the letters) was presented for 16 s. To identify which task had to be performed, characters were shown in green in 1-back blocks and in red in the 2-back blocks (see Figure 6). All participants first went through a training session outside the scanner.

Figure 6: Example of 1-back -green letters- and 2-back -red letters sequences.



Behavioral data analysis

N-back performance was measured using the signal detection theory index of sensitivity (d') which measures ability to discriminate between targets and non-targets (Swets *et al.*, 1978). Higher values of d' indicate better ability to discriminate between targets and non-targets. Negative d' values indicate that the participant is not performing the task. Participants with negative d' values either in the 1-back or in the 2-back versions of the task were excluded from the study.

FMRI data acquisition

In each individual scanning session 266 volumes were acquired from a 1.5-T GE Signa scanner. A gradient echo echo-planar imaging (EPI) sequence depicting the blood oxygenation level dependent (BOLD) contrast was used. Each scanning volume contained 16 axial planes acquired with the following parameters: TR= 2000 ms, TE= 40 ms, flip angle= 70º, section thickness= 7 mm, section skip= 0.7 mm, in-plane resolution= 3x3 mm. The first 10 volumes were discarded to avoid T1 saturation effects.

Analysis of fMRI activations and de-activations

FMRI image analyses were performed with the fMRI Expert Analysis Tool (FEAT) module included in FMRIB Software Library (FSL) (Smith *et al.*, 2004). The following standard pre-statistics processing was applied: motion correction, non-brain removal, 5mm Gaussian smoothing, grand-mean intensity normalization, and highpass temporal filtering. To minimize unwanted movement-related effects, participants whose scans had an estimated maximum absolute movement >3.0mm or an average absolute movement >0.3mm were also excluded from the study.

Statistical analyses

Clinical data

Baseline demographic, psychopathological and cognitive data were compared using appropriate tests (t-tests for continuous variables and χ^2-tests for categoric variables) with SPSS statistical software for Windows.

Regarding neuropsychological test performance, changes between schizomania and clinical remission or schizodepression and clinical remission were assessed with paired t-tests, and differences between schizoaffective patients in remission and controls were assessed using independent sample t-test. In both cases significance levels were Bonferroni-corrected for multiple comparisons (two neuropsychological tests).

Neuroimaging data

During the imaging analyses, general linear models (GLMs) were separately fitted for each individual and run to generate individual activation maps for the contrasts: baseline versus 1-back and baseline versus 2-back. Additionally, in study 1, the effect of increasing working memory load on the differences between patients and controls, was also examined by estimating the regression slope of a model that assumes a linear relationship through the baseline, 1-back and 2-back levels of the task. The resulting individual statistical images were then registered to a common stereotactic space (the Montreal Neurological Institute, MNI). Changes between the acute phase and clinical remission were assessed by fitting paired mixed effects GLM models, and group comparisons between patients and controls were performed by fitting mixed-effects GLM models (Beckmann *et al.*, 2006).

Statistical significance was assessed at the cluster level with a corrected p-value of 0.05, using Gaussian random field methods. We used FSL default threshold settings (z=2.3 to define the initial set of clusters), but in study 2 results were extensive with this threshold and thus we increased the minimum z to 2.7 obtaining identical but more delimited results. Finally, due to task performance differing between patients and controls, group comparisons were conducted twice, i.e. once without including any covariate and once including the performance index as a covariate.

RESULTS

Study 1

Brain functional abnormality in schizo-affective disorder: a fMRI study

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ORIGINAL ARTICLE

Brain functional abnormality in schizo-affective disorder: an fMRI study

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Background. Schizo-affective disorder has not been studied to any significant extent using functional imaging. The aim of this study was to examine patterns of brain activation and deactivation in patients meeting strict diagnostic criteria for the disorder.

Method. Thirty-two patients meeting Research Diagnostic Criteria (RDC) for schizo-affective disorder (16 schizomanic and 16 schizodepressive) and 32 matched healthy controls underwent functional magnetic resonance imaging (fMRI) during performance of the n-back task. Linear models were used to obtain maps of activations and deactivations in the groups.

Results. Controls showed activation in a network of frontal and other areas and also deactivation in the medial frontal cortex, the precuneus and the parietal cortex. Schizo-affective patients activated significantly less in prefrontal, parietal and temporal regions than the controls, and also showed failure of deactivation in the medial frontal cortex. When task performance was controlled for, the reduced activation in the dorsolateral prefrontal cortex (DLPFC) and the failure of deactivation of the medial frontal cortex remained significant.

Conclusions. Schizo-affective disorder shows a similar pattern of reduced frontal activation to schizophrenia. The disorder is also characterized by failure of deactivation suggestive of default mode network dysfunction.

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Key words: Default mode network, DLPFC, fMRI, n-back task, schizoaffective disorder.

Introduction

Schizo-affective disorder, as the name suggests, refers to a psychotic disorder that is characterized by both schizophrenic symptoms and those of mania and/or major depression. The two classes of symptom may occur simultaneously or at different times, although current diagnostic criteria require some temporal overlap, and affected patients tend to have an outcome intermediate between schizophrenia and bipolar disorder (for a review see McKenna, 2007). The nosological status of schizo-affective disorder remains a matter of controversy, with arguments that it represents a third independent form of psychosis (Procci, 1976), a form of bipolar disorder (Pope *et al*. 1980), a midpoint on a psychotic continuum (Crow, 1986), or the expression of genetic risk factors for both disorders (Bertelsen & Gottesman, 1995). One traditional method for resolving such uncertainties, family history studies, has not provided decisive support for any of these positions: first-degree relatives of schizo-affective patients have variously been found to show elevated rates of schizophrenia, affective disorder or both illnesses (Coryell & Zimmerman, 1988; Maier *et al*. 1993; Kendler *et al*. 1995; Laursen *et al*. 2005). Similarly, examples of all forms of psychotic disorder are seen among the monozygotic co-twins of patients with schizo-affective disorder (Cardno *et al*. 2012).

Another source of evidence potentially relevant to this question is brain imaging, but here the examination has been severely limited. Only two structural imaging studies of schizo-affective disorder have been carried out: an early computed tomography (CT) study found no differences in lateral ventricular

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volume among schizophrenic, schizo-affective and bipolar patients (Rieder *et al*. 1983), whereas a more recent magnetic resonance imaging (MRI) study found that both schizo-affective and bipolar patients had a decreased whole-brain volume compared to healthy controls (Getz *et al*. 2002). Functional imaging studies of schizophrenia have sometimes included some patients meeting diagnostic criteria for schizo-affective disorder; typically, however, the two groups are not separated in the analysis. It is unknown, therefore, whether patients with schizo-affective disorder show the hypofrontality that characterizes schizophrenia at rest and during task activation (Hill *et al*. 2004; Minzenberg *et al*. 2009), but which has been found less consistently in bipolar disorder, at least in the dorsolateral prefrontal cortex (DLPFC; Haldane & Frangou, 2004; Chen *et al*. 2011). Nor is it known whether schizo-affective patients show the prefrontal hyperactivation that has been documented in schizophrenia during performance of working memory (Glahn *et al*. 2005) and other cognitive tasks (Minzenberg *et al*. 2009).

A further functional imaging finding in schizophrenia is failure of deactivation. This has been found in the medial frontal cortex (Pomarol-Clotet *et al*. 2008; Whitfield-Gabrieli *et al*. 2009; Milanovic *et al*. 2011), sometimes along with failure of deactivation in the posterior cingulate cortex (Salgado-Pineda *et al*. 2011; Schneider *et al*. 2011). Because these regions form two main nodes of the default mode network, which is a series of interconnected brain regions that are metabolically active at rest but whose activity reduces during performance of a wide range of cognitive tasks (Gusnard & Raichle, 2001; Raichle *et al*. 2001), this finding has been interpreted as indicating default mode network dysfunction in schizophrenia. According to a currently limited amount of evidence, default mode network dysfunction also characterizes bipolar disorder, in terms of both failure of deactivation and abnormal resting state connectivity (Calhoun *et al*. 2008; Ongur *et al*. 2010; Pomarol-Clotet *et al*. 2011). Only one study has examined default mode network function in schizo-affective disorder (Ongur *et al*. 2010); this found reduced resting state connectivity in the medial frontal cortex in seven schizo-affective patients, which was similar in degree to that seen in seven schizophrenic patients but greater than in 17 patients with bipolar disorder.

The aim of the current study was to remedy the lack of functional imaging data in schizo-affective disorder. We examined activation patterns during performance of one of the most widely used tasks in functional imaging studies of schizophrenia, the n-back working memory task. We also examined task-related deactivations, which have been reliably demonstrated using the n-back task. Finally, we compared schizo-affective patients in manic and depressive phases of the disorder.

Method

Subjects

The patient sample consisted of 32 patients recruited from three Spanish psychiatric hospitals: Hospital Benito Menni in Sant Boi de Llobregat, Hospital Clínic of Barcelona and General Hospital of Granollers. Patients were required to meet Research Diagnostic Criteria (RDC; Spitzer *et al*. 1978) for schizo-affective disorder based on psychiatrist interview and review of case-notes. We used these criteria because they are the most detailed of all available criteria for schizo-affective disorder and require not only that patients show schizophrenic symptoms but also that the affective symptoms meet requirements for a full affective syndrome similar to those demanded for depression and mania/hypomania in DSM-IV and ICD-10.

Exclusion criteria included age <18 or >65 years, history of neurological disease or brain trauma, and alcohol/substance abuse within 12 months prior to participation. All of the schizomanic patients were taking antipsychotic medication (mean daily dose of chlorpromazine equivalents $=801\pm399$ mg) and 12 patients were taking mood stabilizers (valproate, $n=9$; lithium, $n=1$; combination, $n=2$). One patient was on antidepressant treatment. In the schizodepressive group 12 patients were taking antipsychotic medication (mean daily dose of chlorpromazine equivalents $=475\pm483$ mg), eight were on mood stabilizers (valproate, $n=2$; lithium, $n=3$; combination, $n=3$) and eight were taking antidepressants.

The patients were scanned while in an acute schizomanic or schizodepressive episode. Schizomanic patients were required to have a Young Mania Rating Scale (YMRS) score >18 and a Hamilton Rating Scale for Depression (HAMD) score <8. Similarly, schizodepressive patients were required to have a HAMD score >18 and a YMRS score <8.

Pre-morbid IQ was estimated using the Word Accentuation Test (Test de Acentuación de Palabras, TAP; Del Ser *et al*. 1997), a word reading test that requires pronunciation of Spanish words whose accents have been removed. Current IQ was measured using four subtests of the Wechsler Adult Intelligence Scale III (WAIS-III): vocabulary, similarities, block design, and matrix reasoning. In the patients, clinical ratings included the Positive and Negative Syndrome Scale (PANSS), the Global Assessment of Functioning (GAF) and the Clinical Global Impression (CGI).

The control sample consisted of 32 healthy individuals recruited from non-medical members of hospital staff, their acquaintances and independent sources in the community. They met the same exclusion criteria as the patients and were also excluded if they reported a history of mental illness and/or treatment with psychotropic medication.

All subjects were right-handed. The study was approved by the local ethical committee and all participants gave written informed consent.

Procedure

The participants were scanned while they performed a sequential-letter version of the n-back task (Gevins & Cutillo, 1993). Two levels of memory load (1-back and 2-back) were presented in a blocked design manner. Each block consisted of 24 letters that were shown every 2 s (1 s on, 1 s off) and all blocks contained five repetitions (1-back and 2-back depending on the block) located randomly within the blocks. Individuals had to indicate repetitions by pressing a button. Four 1-back and four 2-back blocks were presented in an interleaved way, and between them a baseline stimulus (an asterisk flashing with the same frequency as the letters) was presented for 16 s to identify which task had to be performed; characters were shown in green in 1-back blocks and in red in the 2-back blocks. All participants first went through a training session outside the scanner.

Behavioural data analysis

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

Functional MRI (fMRI) data acquisition

In each individual scanning session 266 volumes were acquired from the same 1.5-T GE Signa scanner (General Electric Medical Systems, USA). A gradient echo-planar imaging (EPI) sequence depicting the blood oxygenation level-dependent (BOLD) contrast was used. Each volume contained 16 axial planes acquired with the following parameters: repetition time (TR) = 2000 ms, echo time (TE) = 40 ms, flip angle = 70°, section thickness = 7 mm, section skip = 0.7 mm, in-plane resolution = 3 × 3 mm. The first 10 volumes were discarded to avoid T1 saturation effects.

fMRI data analysis

fMRI image analyses were performed with the FEAT module, included in FSL software (Smith *et al*. 2004). The following pre-statistics processing was applied: motion correction, non-brain removal, 5-mm Gaussian smoothing, grand-mean intensity normalization, and high-pass temporal filtering. To minimize unwanted movement-related effects, scans with an estimated maximum absolute movement >3.0 mm or an average absolute movement >0.3 mm were excluded from the study.

General linear models (GLMs) were fitted to generate individual activation maps for the contrasts: baseline *versus* 1-back and baseline *versus* 2-back. After registration to a common stereotaxic space [Montreal Neurological Institute (MNI) template], group comparisons between patients and controls were performed by mixed-effects GLM models (Beckmann *et al*. 2006).

We additionally examined the effect of increasing working memory load on the differences between patients and controls. To do this we fitted models that assume a linear relationship through the baseline, 1-back and 2-back levels of the task, reporting significant differences on regression slopes between the two groups.

Statistical tests were performed at the cluster level with a corrected p value of 0.05, using Gaussian random field methods. The default threshold of $z = 2.3$ was used to define the initial set of clusters.

Results

Demographic data

Demographic, psychopathological and neuropsychological data for the schizo-affective patients and controls are shown in Table 1.

Task performance

The patients performed more poorly than the controls on both the 1-back ($d' = 3.4 \pm 1.2$ *v.* $d' = 4.4 \pm 0.7$, $t = 3.89$, $p < 0.001$) and the 2-back ($d' = 2.1 \pm 1.03$ *v.* $d' = 3.2 \pm 0.9$, $t = 4.33$, $p < 0.001$) versions of the n-back task.

fMRI findings

Findings were generally more marked on the 2-back *versus* baseline contrast than the 1-back *versus* baseline contrast. However, plots of key regions were analyzed in their levels of activation/deactivation across baseline, 1-back and 2-back. Effects at the 1-back level are

Table 1. *Demographic characteristics of patients* ($n=32$) *and controls* ($n=32$)

	Controls ($n=32$)	Schizo-affective patients ($n=32$)	Schizomanic patients ($n=16$)	Schizodepressed patients ($n=16$)
Age (years)	44±10	44±7	41±8	46±6
Sex (male/female)	20/12	20/12	12/4	8/8
TAP (pre-morbid IQ)	22.5±4.8	22±5.2	23.5±5.2	20.3±5.2[a]
Current IQ (WAIS-III)	105.47±11.18[b]	95±13.8	100.73 ±16.49[a]	90.56±7.4
YMRS total score	–	13±10	22±3	3±3[a]
HAMD total score	–	16±12	4±4	27±5
PANSS total score	–	70±16	62±13	78±16
No. of affective episodes	–	17±20	14±12[a]	21±27[a]
Illness duration (years)	–	20±9.27	17 ±10[b]	22±8
GAF score	–	47±10	52±9	41.8±10.14
CGI score	–	5±0.93	5±1	5±0.99

TAP, Word Accentuation Test (Test de Accentuación de Palabras); WAIS-III, Wechsler Adult Intelligence Scale; YMRS, Young Mania Rating Scale; HAMD, Hamilton Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; GAF, Global Assessment of Functioning; CGI, Clinical Global Impression.

[a] Missing data for one patient.

[b] Missing data for two patients.

Values are given as mean ± standard deviation (range).

also taken into account in the analysis of working memory load (see below).

Average within-group task-related activations and deactivations

The healthy subjects showed significant activation compared to baseline in a wide network of areas. This included the insula bilaterally, the frontal operculum, middle frontal cortex and precentral gyrus extending to the bilateral DLPFC and the supplementary motor area. Also activated were the temporal, occipital and parietal cortices bilaterally, the bilateral basal ganglia and the thalamus.

The controls also showed regions of significant deactivation in the medial frontal cortex that were seen medially in the gyrus rectus and the anterior cingulate cortex anteriorly, and the precuneus posteriorly. Additionally, deactivation was observed to a lesser degree in bilateral clusters in the temporal poles extending to the hippocampus and the parahippocampus. The middle and superior temporal cortex, the posterior insula bilaterally and the left angular gyrus were also affected (Fig. 1*a*).

The schizo-affective patients showed activation in similar regions to the healthy subjects but this was generally less marked. They also showed deactivation in the anterior medial frontal cortex and the posterior cingulate cortex/precuneus, with the former cluster being markedly smaller than in the controls. Deactivation was also seen in the left angular gyrus. No deactivation was seen in the middle and superior temporal cortex, insula, hippocampus or parahippocampus (Fig. 1*b*).

Differences between schizo-affective patients and controls

The schizo-affective patients showed three clusters of significantly reduced activation compared to the controls. The largest cluster was located bilaterally (L > R) in the parietal cortex and precuneus [2620 voxels, peak activation in Brodmann area (BA) 7, MNI (24, −68, 52), z score = 4.18, $p = 1.41 \times 10^{-5}$]. A second cluster was in the left middle frontal cortex, extending to the left precentral gyrus and reaching the left DLPFC and the left supplementary motor area [2357 voxels, peak activation in BA 44/6, MNI (32, 4, 54), z score = 4.56, $p = 3.86 \times 10^{-5}$]. The third cluster was in the left middle and inferior temporal cortex [924 voxels, peak activation in BA 22, MNI (−58, −48, 14), z score = 3.71, $p = 0.02$]. These findings are shown in Fig. 2.

The schizo-affective patients also showed significant failure of deactivation compared to the controls. This was in a cluster that included the gyrus rectus and the anterior cingulate cortex extending to the medial and superior medial frontal cortex [6619 voxels, peak activation in BA 11, MNI (−2, 40, −6), z score = 5.01, $p = 4.77 \times 10^{-11}$]. This is also shown in Fig. 2.

Figure 3 demonstrates the plots of key regions showing levels of activation/deactivation across baseline, 1-back and 2-back. As mentioned earlier, findings were generally more marked on the 2-back

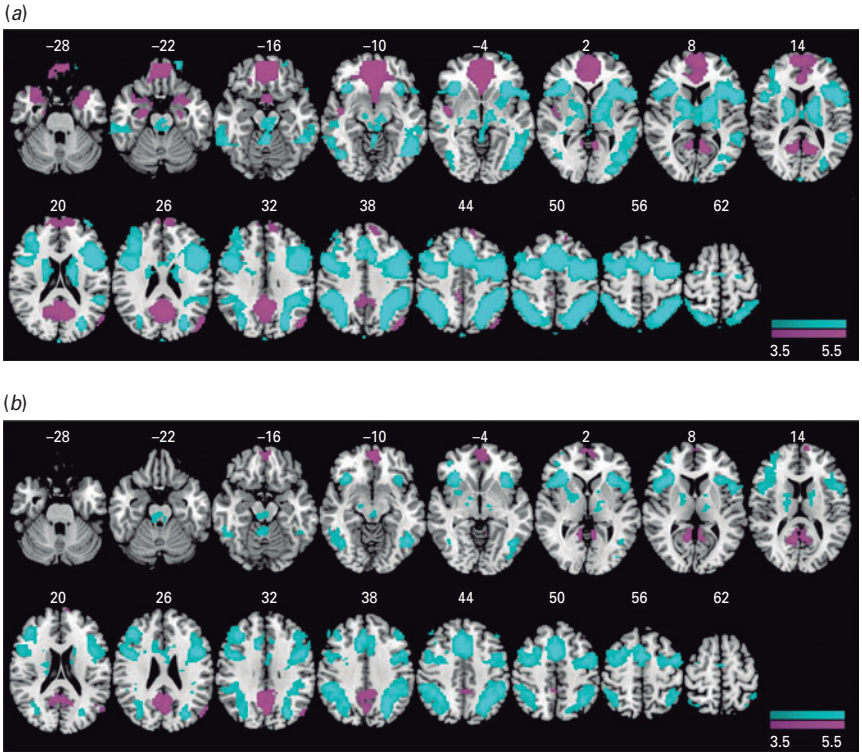

Fig. 1. Brain regions showing a significant effect in the 2-back *versus* baseline contrast in (*a*) 32 controls and (*b*) 32 schizo-affective patients. Blue indicates a positive association (activation) with the task. Pink indicates areas where the task led to a decrease in the blood oxygenation level-dependent (BOLD) response (i.e. deactivation). Numbers refer to Montreal Neurological Institute (MNI) *z* coordinates of the slice shown. The right side of each image represents the left side of the brain. Colour bars indicate *z* scores from the group-level analysis.

versus baseline contrast than in 1-back *versus* baseline contrast. There were no statistical differences between the three groups on the 1-back contrast but, as shown in Figs 2 and 3, there were statistical differences on all 2-back contrasts, including a significant difference in the failure to deactivate in the anterior cingulate cortex between the two patient groups.

Comparison of patients and controls by working memory load

This analysis had broadly similar findings to the 2-back *versus* baseline comparison. The schizo-affective patients showed clusters of significantly reduced activation compared to the controls in three clusters. The largest cluster was in the left middle frontal cortex, extending to the left precentral gyrus, and reaching the left DLPFC and the left supplementary motor area. This cluster also extended to the left insula, the left putamen and pallidum and the thalamus bilaterally [3845 voxels, peak activation in BA 44/6, MNI (−32, −4, 54), *z* score = 4.78, $p = 4.17 \times 10^{-7}$]. A second cluster was located bilaterally (L > R) in the parietal cortex and precuneus [3196 voxels, peak activation in BA 7, MNI (−34, −60, 50), *z* score = 4.3, $p = 3.5 \times 10^{-6}$]. The third cluster was located in the left middle and inferior temporal cortex [917 voxels, peak activation in BA 22, MNI (−56, −48, 16), *z* score = 3.8, $p = 0.03$].

In this analysis the patients again showed significant failure of deactivation in a cluster in the medial frontal cortex that included the gyrus rectus and the anterior cingulate cortex and extended to the medial and superior medial frontal cortex [6296 voxels, peak activation in BA 11, MNI (–2, 40, −6), *z* score = 5.01, $p = 3.6 \times 10^{-10}$].

Functional imaging findings in relation to task performance

To examine the extent to which the pattern of functional imaging differences between the patients and the controls was influenced by the difference they showed in task performance, we entered each subject's *d′* score as a covariate in the 2-back *versus* baseline contrast. Specifically, we mean-centred the behavioural covariate (*d′*) and entered it into the linear model. After doing this, the differences in activation between the schizo-affective patients and controls persisted but became smaller in the left frontal cluster

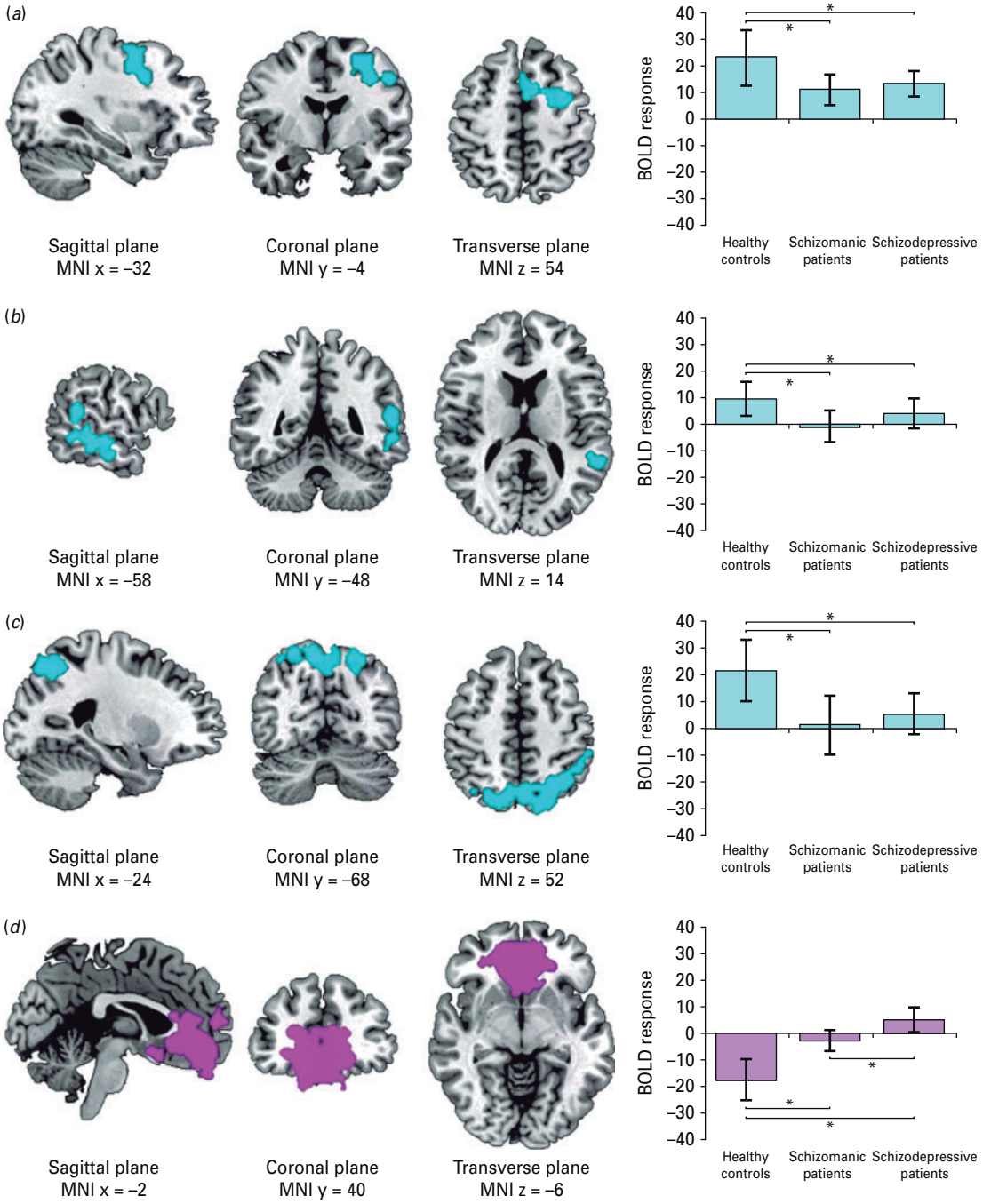

Fig. 2. Location of the (*left*) clusters and (*right*) blood oxygenation level-dependent (BOLD) response in healthy subjects ($n = 32$), schizomanic patients ($n = 16$) and schizodepressive patients ($n = 16$) of: (*a*) the left precentral activation, (*b*) the left middle temporal activation, (*c*) the bilateral parietal activation and (*d*) the anterior cingulate deactivation. The right side of the maps represents the left side of the brain.

(1529 voxels *versus* 2357 voxels). The clusters of reduced activation in the bilateral parietal and temporal cortex disappeared. The medial frontal cluster, where there was failure of deactivation, remained evident after covarying for task performance, although it became smaller (4290 voxels *versus* 6619 voxels).

Relationship to clinical symptoms

For this, we correlated the mean BOLD response from each of the above clusters of significant differences and the following clinical variables: duration of illness, number of affective episodes, PANSS score and the

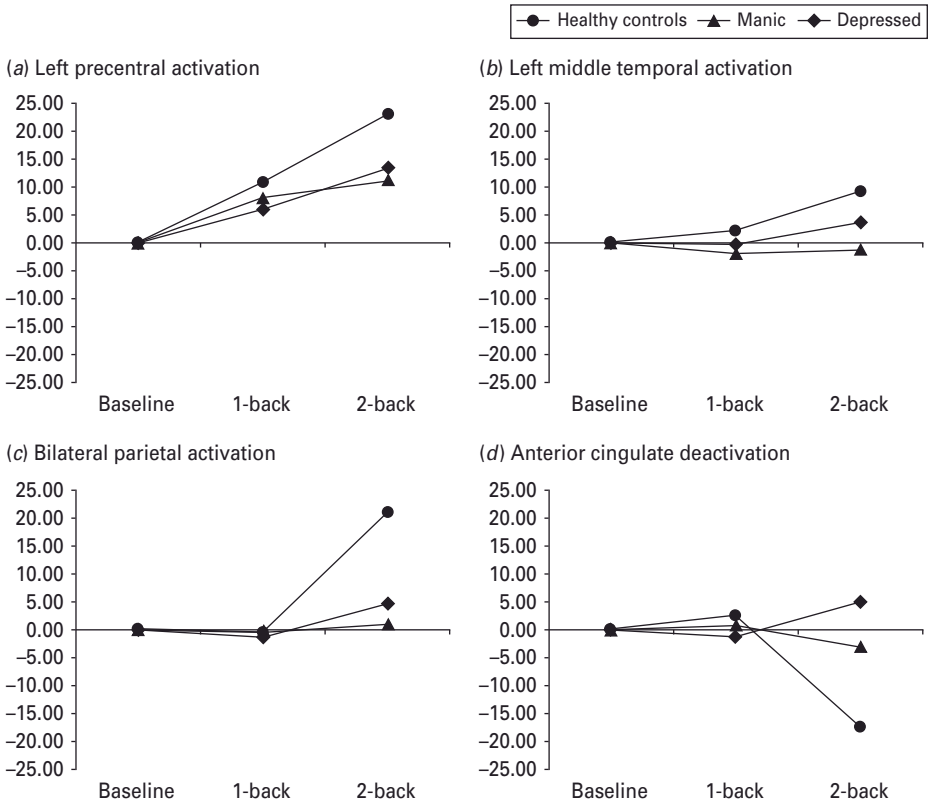

Fig. 3. Plots of (*a*) left precentral, (*b*) left middle temporal and (*c*) bilateral parietal levels of activation and (*d*) anterior cingulate deactivation across baseline, 1-back and 2-back of 16 schizomanic and 16 schizodepressive patients compared to 32 healthy controls. No differences were found in the three groups on the 1-back contrast; on all 2-back contrasts differences were statistically significant, including one between patient groups in region *d*.

two measures of overall severity of illness, GAF score and CGI score. No significant correlations were found between the left precentral, left middle temporal and bilateral parietal cortex and any clinical variable. There was a significant positive correlation between CGI score and the anterior cingulate cortex (Spearman's $p=0.45$, corrected $p=0.04$). However, the correlation with the other measure of severity of illness used, the GAF, was not significant.

fMRI differences between schizomanic patients, schizodepressive patients and controls

To examine these differences, the 16 schizomanic and 16 schizodepressed patients were compared in a similar whole-brain analysis to that used to compare the patients and controls (i.e. cluster threshold $z=2.3$, cluster corrected at $p=0.05$). However, because of differences in sex, the variable sex was entered as covariates in the analysis.

There were no differences between the schizomanic and schizodepressive patients in the 1-back *versus* baseline contrast. In the 2-back *versus* baseline contrast, the schizomanic patients showed two clusters of significantly reduced activation compared to the schizodepressive. As shown in Fig. 4, one of these was a large cluster that included the anterior cingulate gyrus, the bilateral caudate and the left putamen and pallidum, the left amygdala, the left hippocampus and the left posterior part of the insula extending to the superior temporal cortex [1233 voxels, peak activation in MNI (-52, 0, -4), z score $=3.77$, $p=0.004$]. The second cluster was located in the left postcentral, precentral and supramarginal cortex and the left rolandic operculum extending to the anterior part of the insula [771 voxels, peak activation in MNI (-58, -12, 18), z score $=3.6$, $p=0.05$].

Discussion

This is, to our knowledge, the first study to examine brain activations and deactivations in schizo-affective disorder. We examined patients who were diagnosed according to RDC, which are broadly similar to DSM-IV criteria but are more detailed in their requirements, in that the affective symptoms constitute a full affective syndrome and they exclude depression secondary to delusions and hallucinations. They are also more

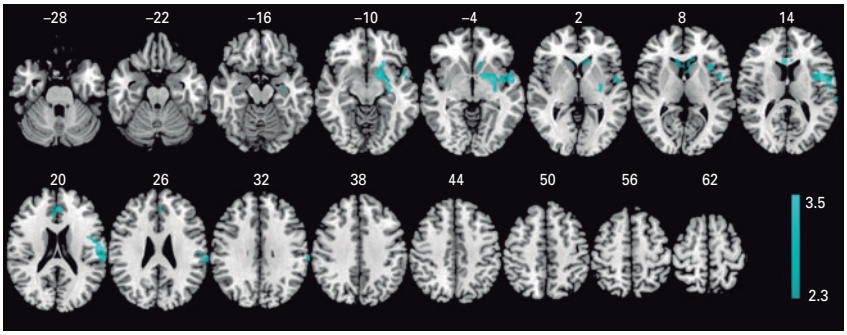

Fig. 4. In the 2-back *versus* baseline contrast 16 schizomanic patients showed two clusters of significantly reduced activation compared to 16 schizodepressive patients. Numbers refer to Montreal Neurological Institute (MNI) z coordinates of the slice shown. The right side of each image represents the left side of the brain. Colour bars indicate *z* scores from the group-level analysis.

explicit about the temporal overlap with schizophrenic symptoms. We found that the patients showed reduced activation during performance of a working memory task, which affected the left DLPFC among other regions. They also showed failure of deactivation in a large area centred on the medial frontal cortex.

During the n-back performance, the healthy controls in this study showed activation in the frontal, parietal and temporal cortex, areas that show a substantial overlap with the 'working memory network' identified in a meta-analysis of fMRI studies in normal subjects (Owen *et al*. 2005). Activation was found to be significantly lower in the schizo-affective patients in two parts of this network, the left middle frontal cortex including the DLPFC and the parietal cortex, and also in one area outside it, the left middle and inferior temporal cortex. The finding of reduced prefrontal activation aligns schizo-affective disorder with schizophrenia, where reduced DLPFC activation is supported by meta-analyses of studies using the n-back task (Glahn *et al*. 2005) and a wider range of executive tasks (Minzenberg *et al*. 2009). At first sight, our finding of reduced parietal activation does not support a proposal made by Gruber *et al*. (2006), who found that schizo-affective, but not schizophrenic, patients showed normal behavioural performance on tasks involving the articulatory loop component of working memory, and argued that activation in the premotor–parietal regions in the left hemisphere should therefore be preserved in patients with the former disorder. However, it should be noted that the parietal and temporal differences we found between the patients and controls disappeared when task performance was entered as a covariate in the analysis whereas those in the DLPFC remained, suggesting that dysfunction in this part of the working memory network may still distinguish schizophrenia and schizo-affective disorder. Further studies directly comparing schizophrenic and schizo-affective patients are necessary to confirm this.

Hypofrontality has been a more contentious finding in bipolar disorder. Early studies using the region-of-interest (ROI) approach (reviewed by Haldane & Frangou, 2004) had findings of reduced, normal and increased prefrontal activation during cognitive task performance; when changes were found, they were seen in different subregions of the prefrontal cortex and showed no obvious pattern in relation to phase of illness. More recently, Chen *et al*. (2011) meta-analysed 50 whole-brain, voxel-based studies that examined bipolar patients using both cognitive and emotional tasks. They found consistent evidence for reduced prefrontal activation only in the inferior frontal gyrus, which was present irrespective of mood state. However, it is important to note that only one of the studies included used a working memory task. Our group has recently examined 29 bipolar manic patients using the n-back task (Pomarol-Clotet *et al*. 2011). Similar to the schizo-affective patients in the present study, they showed reduced activation in the DLPFC bilaterally compared to controls that extended to the precentral and supplementary motor areas; reduced activation was also seen in the right parietal cortex, including the precuneus. Bipolar depressed patients have also been found to show reduced DLPFC activation in studies using the n-back task (Townsend *et al*. 2010; Fernández-Corcuera *et al*. 2012).

In addition to reduced activation, the schizo-affective patients in our study showed failure of deactivation in an area located principally in the medial frontal cortex. Like the reduced activation in the DLPFC, this also survived controlling for performance differences between the patients and controls. Failure of deactivation, affecting a similar region and sometimes more posterior areas of the cingulate cortex, is now a replicated finding 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). By contrast, studies reporting deactivations in bipolar disorder are few: our group has found failure of deactivation during n-back performance in a medial frontal/anterior temporal area very similar to that seen in the present study, which was present in both mania (Pomarol-Clotet *et al*. 2011) and bipolar depression (Fernández-Corcuera *et al*. 2012). Rubinsztein *et al*. (2001) also had findings consistent with failure of deactivation in the medial frontal cortex, along with the superior and middle temporal gyrus, in a study that compared manic patients and controls during performance of a gambling task.

Such findings suggest that the medial frontal cortex may be a locus of shared abnormality across major psychotic disorders. This region is of considerable topical interest because, along with the posterior cingulate cortex/precuneus, it forms one of the two important 'nodes' or 'hubs' of the default mode network. Activity in the default mode network is thought to underlie introspective or self-related thought, such as recall of personal experiences, making social and emotional judgements, envisioning the future and performing theory of mind tasks (Buckner *et al*. 2008). Current evidence suggests that default mode network dysfunction is a feature of a range of psychiatric and neuropsychiatric disorders including not only schizophrenia and bipolar disorder but also major depression, autism, attention deficit disorder and mild cognitive impairment (for a review see Broyd *et al*. 2009).

Comparing manic and depressed schizo-affective patients, both at the whole-brain level and using ROIs derived from the difference between the whole group of patients and controls, revealed differences in the medial frontal cortex. This finding should be interpreted with caution because, in the whole-brain analysis, medial frontal cortex differences were seen as part of a cluster that also included the insula and superior temporal cortex along with the basal ganglia, amygdala and hippocampus. However, it could suggest that the default mode dysfunction varies according to mood state in schizo-affective disorder. The meaning of this finding is uncertain but, given the role of the default mode network in introspection, it is tempting to speculate that it might be related to greater ruminative mental activity provoked by depressive and perhaps psychotic symptoms.

In conclusion, this study suggests that schizo-affective disorder is similar to schizophrenia in terms of being associated with hypofrontality during cognitive task performance but that it may differ from bipolar disorder in this respect (the evidence for hypofrontality not being decisive in this disorder). However, further studies directly comparing schizo-affective patients with those with schizophrenia and bipolar disorder are necessary before firm conclusions can be drawn on this point. The study also adds to evidence that the medial frontal cortex, and by extension default mode network dysfunction, plays a pivotal, albeit non-specific, role in several forms of major mental disorder. To gain more direct insight into this issue, studies directly comparing schizo-affective and schizophrenia and/or bipolar patients are urgently needed. In common with most functional imaging studies of psychosis, the patients in this study were medicated, which could have affected activation/deactivation patterns, and this limits the conclusions that can be drawn.

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Declaration of Interest

None

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RESULTS

Study 2

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

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

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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 ≥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.

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

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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 ± 583 days in patients vs 515 ± 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-tem 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-

planar imaging (EPI) sequence depicting the blood oxygenation level-dependent (BOLD) contrast. Each scanning volume contained 16 axial planes acquired with the following parameters: TR = 2000 ms, TE = 40 ms, flip angle = 70°, section thickness = 7 mm, section skip = 0.7 mm, in-plane resolution = 3 x 3 mm. The first 10 volumes were discarded to avoid T1 saturation effects.

fMRI data were analyzed with the FEAT module of FSL software (Smith et al., 2004). The following standard pre-statistics processing was applied: motion correction, non-brain removal, 5 mm Gaussian smoothing, grand-mean intensity normalization, and highpass temporal filtering. To minimize unwanted movement-related effects, participants whose scans had an estimated maximum absolute movement >3.0 mm or an average absolute movement >0.3 mm were also excluded from the study.

2.4. Statistical analyses

Changes in the neuropsychological test performance between schizomania and clinical remission or schizodepression and clinical remission were assessed with paired *t*-tests. Differences in the neuropsychological test performance between schizoaffective patients in remission and controls were assessed using independent sample *t*-test. In both cases significance levels were Bonferroni-corrected for multiple comparisons (two neuropsychological tests).

For the imaging analysis, general linear models (GLMs) were fitted to generate individual activation maps for the 2-back vs. baseline contrast, and resulting images were then registered to the MNI stereotactic space. Changes between session A and session B in both groups and between schizoaffective patients in remission and controls were assessed by fitting paired mixed-effects GLM models (Beckmann et al., 2006). We had initially used FSL default threshold settings (cluster level statistics based on Gaussian random field theory, $z = 2.3$ to define the initial set of clusters, corrected cluster p value = 0.05) to retrieve regions with statistically significant differences between groups. However, results were extensive with this threshold, and thus we increased the minimum z to 2.7 obtaining identical but more delimited results.

3. Results

3.1. Demographic and clinical data

Demographic and clinical data for the schizoaffective patients and controls are shown in Table 1.

3.2. Memory and executive test performance

When compared to clinical remission, the schizomanic group showed a significant improvement in memory (WMS: 29 ± 5 vs. 36 ± 9, $p = 0.036$) but not in executive function (BADS: 76 ± 21 vs. 80 ± 20, $p = 0.67$). In contrast, there were no changes on either measure in the schizodepressive patients in comparison to clinical remission (WMS: 30 ± 6 vs. 31 ± 9, $p = 1$; BADS: 67 ± 27 vs. 78 ± 28, $p = 0.55$). The whole group of schizoaffective patients in remission showed a significant impairment of WMS composite and BADS profile scores compared to the controls (WMS: 33 ± 9 vs. 42 ± 9, $p = 0.003$; BADS: 76 ± 24 vs. 98 ± 16, $p = 0.003$) (Table 2).

3.3. Neuroimaging findings

3.3.1. Task performance

Patients' performance did not significantly change from schizomanic episode to remission ($d' = 2.2 \pm 1.0$ vs. 2.7 ± 0.7, $p = 0.619$), or schizodepressive episode to remission ($d' = 2.2 \pm 1.0$ vs. 2.0 ± 0.9, $p = 0.070$). The whole group of patients in clinical remission performed more poorly than the healthy controls on the 2-back task ($d' = 2.3 \pm 0.8$ vs. $d' = 3.4 \pm 0.7$, $p < 0.001$).

Table 1
Demographic and clinical characteristics of the patient group ($n = 22$) and healthy controls ($n = 22$) during the acute episode (Session A) and in clinical remission (Session B).

		Patients with schizoaffective disorder			Healthy controls ($n = 22$)	P[a]
		Mania ($n = 12$)	Depression ($n = 12$)	All ($n = 22$)[c]		
Sex distribution (% females)		17%	67%	41%	41%	n.s.
Estimated premorbid IQ ± SD[b]		102 ± 11	96 ± 10	100 ± 11	104 ± 9	n.s.
Session A (episode)	Age ± SD (years)	41 ± 9	48 ± 8	45 ± 9	44 ± 11	n.s.
	Young score	23 ± 3	2 ± 3	13 ± 11	–	
	HDRS score	4 ± 4	27 ± 5	16 ± 12	–	
	PANSS score	64 ± 14	72 ± 15	68 ± 15	–	
	PANSS-P score	22 ± 4	15 ± 3	18 ± 5	–	
	PANSS-N score	13 ± 6	19 ± 6	16 ± 7	–	
	PANSS-GP score	29 ± 8	38 ± 8	34 ± 9	–	
	Antipsychotic dose (chlorpromazine equivalents)	851 ± 263	757 ± 579			
	Antipsychotics	12	10			
	Mood-stabilizers	7	7			
	Antidepressants	0	7			
	Benzodiazepines	6	9			
Session B (clinical remission)	Young score	3 ± 3	1 ± 2	2 ± 2	–	
	HDRS score	3 ± 3	3 ± 3	3 ± 3	–	
	PANSS score	49 ± 11	44 ± 10	46 ± 11	–	
	PANSS-P score	11 ± 3	10 ± 2	10 ± 3		
	PANSS-N score	13 ± 5	12 ± 4	12 ± 4		
	PANSS-GP score	25 ± 5	22 ± 6	24 ± 6		
	Antipsychotic dose (chlorpromazine equivalents)	527 ± 455	644 ± 603			
	Antipsychotics	9	9			
	Mood-stabilizers	7	8			
	Antidepressants	1	9			
	Benzodiazepines	7	6			

[a] Presence of significant differences (as derived from two-sample *t*-tests or Fisher tests) between patients with a manic episode and patients with a depressive episode, and between patients with schizoaffective disorder and healthy controls. Please note that statistical significance in variables involved in the recruitment may be useful for informative but not inferential purposes.

[b] Pre-morbid IQ was estimated using the Word Accentuation Test (Del Ser et al., 1997), a word reading test which requires pronunciation of Spanish words whose accents have been removed.

[c] Please note that the total number of recruited is 22 as two patients were scanned in both phases, the depressive and manic phases.

Table 2
Neuropsychological changes observed during schizomanic and schizodepressive episodes and during clinical remission in patients with schizoaffective disorder ($n = 22$).

	Scores	*t*-value	*p*-value[a]
SM episode vs. clinical remission (paired t-test)			
Memory (WMS)	29 ± 5 vs. 36 ± 9	2.89	0.036
Executive functions (BADS)	76 ± 21 vs. 80 ± 20	1.02	0.67
SD episode vs. clinical remission (paired t-test)			
Memory (WMS)	30 ± 6 vs. 31 ± 9	0.64	1
Executive functions (BADS)	67 ± 27 vs. 78 ± 28	1.16	0.55
Patients in clinical remission vs. healthy controls			
Memory (WMS)	33 ± 9 vs. 42 ± 9	3.35	0.003
Executive functions (BADS)	76 ± 24 vs. 98 ± 16	3.50	0.003

BADS: Behavioural Assessment of Dysexecutive Syndrome test; WMS: Wechsler Memory Scale; SM: schizomanic episode; SD: schizodepressive episode.
[a] Bonferroni-corrected for multiple comparisons (two neuropsychological tests).

3.3.2. Differences between schizomanic patients and clinical remission

During a schizomanic episode, patients hypoactivated the left frontal operculum (327 voxels, corrected cluster $p = 0.010$; peak at −56, 18, 10, $Z = 3.7$) (Fig. 1). In clinical remission, this normalized and even converted to relative overactivation. Schizomanic patients also had less activity in a set of regions that would activate during clinical remission. These mainly comprised the precuneus (1173 voxels, corrected cluster $p < 0.001$; peak at 0, −54, 20, $Z = 3.9$) and the lingual gyrus (494 voxels, corrected cluster $p = 0.001$; peak at −2, −90, 4, $Z = 3.7$).

To exclude the effects of potentially confounding factors, we extracted the mean of each of the three clusters and re-analyzed our results adding the factors age, PANSS scores and different medications as covariates. Medications tested were chlorpromazine equivalents, mood stabilizer, antidepressants and clonazepam equivalents. In each of the clusters, the manic hypoactivations remained significant independently of the inclusion of any of these covariates (Table 3).

3.3.3. Differences between schizodepressive patients and clinical remission

Patients included in the schizodepressed sample did not show episode-related significant differences in the brain response to the task.

3.3.4. Differences between all schizoaffective patients in clinical remission and healthy controls

The whole group of patients with schizoaffective disorder in clinical remission showed a failure of de-activation in the ventral medial frontal gyrus (MFG) as compared to session B in the healthy controls (1136 voxels, corrected cluster $p < 0.001$; peak at 10, 50, −24, $Z = 4.0$) (Fig. 2). Due to task performance differences this was included as a covariate (2441 voxels, corrected cluster $p < 0.001$; peak at 4, 24, −12, $Z = 4.2$).

Table 3
Statistical significance of the manic hypoactivations after controlling for several potentially confounding factors.

Covariate	Effect of mania		Effect of covariate	
	F-value	*p*-value	*F*-value	*p*-value
Left frontal operculum cluster				
(None)	29.9	<0.001		
Age	25.1	<0.001	4.0	0.074
PANSS	16.9	0.002	0.1	0.807
Chlorpromazine equivalents	17.6	0.003	0.2	0.651
Clonazepam equivalents	33.0	<0.001	0.3	0.571
Mood stabilizer	30.4	<0.001	0.2	0.661
Antidepressants	35.8	<0.001	6.2	0.042
Precuneus superior cluster				
(None)	36.5	<0.001		
Age	28.1	<0.001	1.4	0.266
PANSS	18.4	0.002	0.0	0.927
Chlorpromazine equivalents	26.5	<0.001	1.2	0.297
Clonazepam equivalents	30.2	<0.001	0.2	0.669
Mood stabilizer	28.7	<0.001	0.1	0.101
Antidepressants	22.8	0.002	0.1	0.758
Precuneus inferior cluster				
(None)	65.2	<0.001		
Age	50.1	<0.001	0.3	0.625
PANSS	35.5	<0.001	0.0	0.844
Chlorpromazine equivalents	33.8	<0.001	0.1	0.774
Clonazepam equivalents	64.7	<0.001	0.3	0.573
Mood stabilizer	66.4	<0.001	1.4	0.261
Antidepressants	45.6	<0.001	0.0	0.986
Calcarine cluster				
(None)	32.2	<0.001		
Age	24.3	<0.001	1.1	0.315
PANSS	15.6	0.003	0.0	0.833
Chlorpromazine equivalents	14.6	0.005	0.1	0.796
Clonazepam equivalents	29.4	<0.001	21.7	0.759
Mood stabilizer	29.0	<0.001	0.7	0.432
Antidepressants	16.6	0.005	0.0	0.888

4. Discussion

To the best of our knowledge, this study is the first to examine changes in neuropsychological performance and brain activation patterns in schizoaffective disorder longitudinally, comparing illness and remission. We found some evidence of improvement in memory in the schizomanic sample once in clinical remission but no changes in executive function in this group and no changes in either cognitive domain in the schizodepressive group. Furthermore, changes in brain activation were observed, although again only in schizomanic and not in schizodepressive patients. Failure of de-activation, a functional brain abnormality documented in both schizophrenia and bipolar disorder, emerged as a trait-like feature also in schizoaffective disorder; a result of the comparison of schizoaffective patients in clinical remission versus healthy controls.

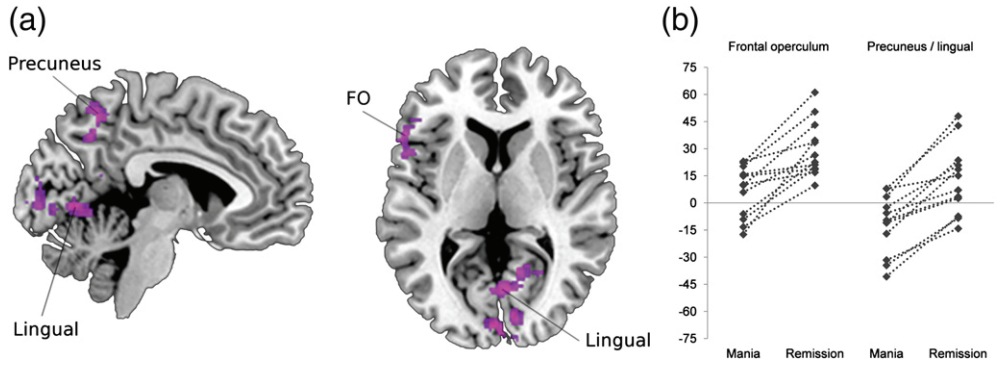

Fig. 1. (a) Hypo-activations observed during the schizomanic episode as compared with clinical remission (whole-brain paired *t*-test). (b) Mean blood oxygenation level-dependent (BOLD) response in the ROIs during the acute phase and clinical remission in schizomanic patients ($n = 12$).

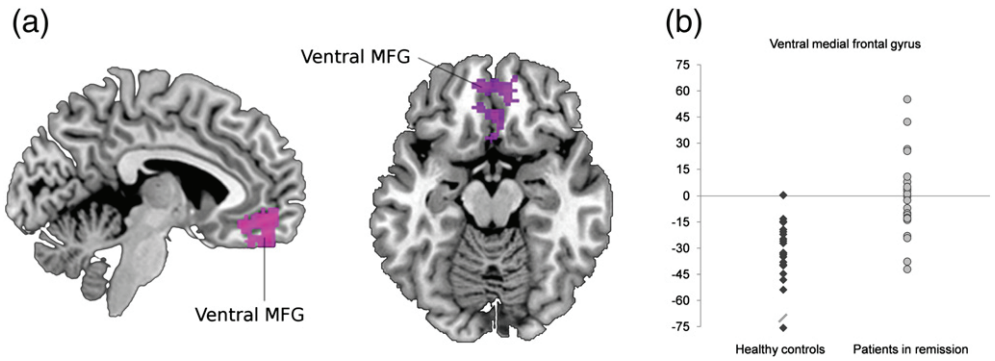

Fig. 2. (a) Failure of deactivation observed in patients with schizoaffective disorder during clinical remission as compared to matched healthy controls during session B. (b) Mean blood oxygenation level-dependent (BOLD) response in the ROIs during clinical remission in patients ($n = 22$) and in healthy controls ($n = 22$).

Cognitive impairment 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). It remains an open question whether this represents a stable, trait-like feature of the disorder, as in schizophrenia (e.g. Palmer et al., 2009), or whether it worsens with acute episodes and improves in remission, as is typically considered to be the case in bipolar disorder (e.g. Murray et al., 2004). This study found some evidence of improvement in memory but not in executive function between relapse and remission, suggesting that executive functioning in schizoaffective disorder is more a trait than a state feature of the disease. When comparing this finding with bipolar disorder, it needs to be borne in mind that the evidence base for changes in cognitive function in bipolar disorder between relapse and remission is currently very small. Thus, Martinez-Aran et al. (2004) examined groups of depressed, manic and euthymic bipolar patients on a battery of neuropsychological tests and found only few significant differences between the three groups, and there were no instances where the euthymic patients' performance clearly separated them from that of the manic or depressed patients. The only longitudinal study to date appears to be that of Xu et al. (2012): they found that groups of bipolar and unipolar depressed patients showed significant impairment compared to controls on 11/13 cognitive tests when ill, but only on 2/13 tests (bipolar patients) and 5/13 tests (unipolar patients) after 6 weeks of treatment.

Task-related hypofrontality is a well-established finding in schizophrenia (Hill et al., 2004; Glahn et al., 2005; Minzenberg et al., 2009). It has been also found in bipolar disorder, particularly in the DLPFC (e.g. Haldane and Frangou, 2004; Chen et al., 2010), both in manic episodes (Pomarol-Clotet et al., 2012), depressive episodes (Fernandez-Corcuera et al., 2013), but also in euthymia (Monks et al., 2004; Lagopoulos et al., 2007; Townsend et al., 2010). Interestingly, in the present study no differences were seen in frontal activations between schizoaffective patients in clinical remission and healthy subjects.

The schizomanic patients showed lower task-related activation in the left frontal operculum, the precuneus and the lingual gyrus when ill, but normalized and even converted to relative overactivation in remission. A finding, which did not change after adding age, PANSS scores and medications as covariates (see Table 3).

The schizodepressive sample did not show significant episode-related activation changes. The negative finding may be explained by a lack of power and, hence, a larger sample size possibly might have yielded comparable results to the schizomanic patients. Patients' number, however, were the same in both groups, the schizomanic and schizodepressive sample. At least with respect to schizomanic patients, our results suggest that activation patterns in the acute phase, in this case hypoactivations, reflect the clinical state.

As stated in the introduction, we used the same working memory task in a previous study and found that healthy controls showed activation in a network of frontal and other areas and also deactivation in the medial frontal cortex, the precuneus and the parietal cortex (Madre et al., 2013). Acutely ill schizoaffective patients activated significantly less in prefrontal, parietal and temporal regions than the controls, and also showed failure of deactivation in the medial frontal cortex. This last finding, the failure of deactivation in the medial frontal cortex, was maintained in clinical remission in the current analysis. We therefore suggest that failure of de-activation – and hence default mode network dysfunction – is a trait rather than a state phenomenon in schizoaffective disorder. Failure of de-activation, affecting particularly the medial frontal cortex, has been found repeatedly in schizophrenia (Pomarol-Clotet et al., 2008; Whitfield-Gabrieli et al., 2009; Mannell et al., 2010; Salgado-Pineda et al., 2011; Schneider et al., 2011; Dreher et al., 2012); however, as yet no studies have suggested that it is sensitive to clinical changes. In bipolar disorder, failure of deactivation has mostly been documented in manic (Pomarol-Clotet et al., 2012), depressed (Fernandez-Corcuera et al., 2013) or unselected patients (Calhoun et al., 2008). However, a recent study by our group (Pomarol-Clotet et al., 2014) also found that it was present in euthymic patients. Allin et al. (2010) also found failure of de-activation in euthymic patients in another area of the default mode network, the posterior cingulate region. Taken together, these results suggest that schizoaffective disorder, schizophrenia and bipolar disorder share failure of de-activation in the medial frontal cortex suggesting that this could be a trait-like abnormality.

Our study has several limitations. Firstly, small effects may have been missed because of the small cohort size. A larger cohort may have revealed more pronounced differences. Secondly, our patients were receiving pharmacological treatment which possibly influenced results; however, co-varying for medication did not change the results. Thirdly, all patients improved in their mental state for the second evaluation (as measured by the PANSS) but continued with some minor symptoms; it cannot be excluded that this influenced our results. Finally, another limitation was that the interval between the two evaluations was long in some participants. However, as the intervals between the two sessions were similar in patients and controls we think there was no potential effect of time on our results.

In conclusion, our study finds evidence that memory and activation patterns in schizomanic patients improve in clinical remission. In contrast, executive dysfunction in schizomanic, neurocognitive and functional deficits in schizodepressive patients and failure of de-activation in the medial frontal cortex appear to be independent of clinical status in schizoaffective disorder.

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Contributors

MM, EPC, and BLA designed the study and wrote the protocol. MM and BLA managed the literature searches. BLA, FP and MM recruited patients and followed them up. JR, MM,

SA and RL undertook the statistical and neuroimaging analysis. MM and BLA wrote the first draft of the manuscript which was revised by EPC. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors exclude any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three (3) years of beginning the work submitted that could have inappropriately influenced, or be perceived to influence, their work.

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GENERAL DISCUSSION AND CONCLUSIONS

The studies reported in this thesis aimed to add knowledge on the neurobiological underpinnings of schizoaffective disorder. Two studies, using functional neuroimaging and neuropsychological testing, were carried out on a sample of schizoaffective patients, and they examined both cross-sectional and longitudinal changes.

Summary of findings

The main aim of Study 1 was to examine the brain functioning during the acute phase of the illness. Activation and de-activation patterns during performance of a working memory task, the n-back task, were compared between 32 schizoaffective patients (16 in a schizomanic episode and 16 in a schizodepressive episode) and 32 healthy subjects. Results showed that healthy subjects activated a network of frontal and other areas. They also deactivated the medial frontal cortex, the precuneus and the parietal cortex, all parts of the DMN. The schizoaffective patients activated prefrontal, parietal and temporal regions significantly less than the healthy subjects, and also showed failure of de-activation in the medial frontal cortex. When differences in task performance were controlled for, the reduced activation in the DLPFC and the failure of de-activation of the medial frontal cortex seen in the schizoaffective patients remained significant, suggesting that these clusters were where the findings were most robust. There was no clear or convincing evidence for an association between the reduced activation/de-activation in these areas and a range of clinical variables. The schizomanic and schizodepressive patients were also examined separately to investigate for possible differences between them. Here, the main finding was of a significant greater failure of

de-activation in the medial frontal cortex in the schizodepressive patients than in the schizomanic patients.

One aim of Study 2 was to examine whether brain activation patterns in schizoaffective disorder change from acute illness to clinical remission. The whole group of schizoaffective patients in clinical remission showed a failure of de-activation in the medial frontal cortex, suggesting that DMN dysfunction is a state-independent feature of the illness. Additionally, acute schizomanic patients were found to show less activity in a set of regions – the left frontal operculum, the precuneus and the lingual gyrus – which normalized and even converted to relative overactivation in clinical remission. These changes in activation patterns did not change, after potential confounding factors such as age, PANSS score and antipsychotic dosage were controlled for. In contrast, activation patterns in ill and remitted schizodepressive patients were similar across relapse and remission.

A further aim of Study 2 was to examine neuropsychological performance during the acute phase and clinical remission. The main finding here was that the schizomanic patients showed an improvement of memory but not of executive function, while the schizodepressive patients showed no significant change in either domain. All schizoaffective patients in clinical remission continued to show memory and executive impairment compared to the healthy subjects.

Schizoaffective disorder: Neuroimaging findings in relation to schizophrenia

Task-related hypofrontality, affecting particularly the DLPFC, is one of the leading functional imaging findings in schizophrenia (e.g. Glahn *et al.*, 2005, Hill *et al.*, 2004, Minzenberg *et al.*, 2009), and is supported by meta-analyses of studies using both the n-back task (Glahn, Ragland et al. 2005) and a wider range of executive tasks (Minzenberg,

Laird et al. 2009). According to the studies reported in this thesis, schizoaffective disorder shows a similar pattern of reduced prefrontal activation, at least during the acute phase. This finding therefore aligns schizoaffective disorder with schizophrenia. It is interesting to note that reduced prefrontal activation was not evident in the schizoaffective patients in clinical remission, suggesting that task-related hypofrontality is a state rather than a trait abnormality. Surprisingly, it remains uncertain whether this is also the case in schizophrenia – there have been very few test-retest functional imaging studies in this disorder, suggesting that prefrontal cortex function may fluctuates over time (Cropley and Pantelis, 2014, Spence *et al.*, 1998).

Failure of de-activation in the medial frontal cortex is now a well-replicated finding in schizophrenia (eg Dreher *et al.*, 2012, Mannell *et al.*, 2010, Pomarol-Clotet *et al.*, 2008, Salgado-Pineda *et al.*, 2011, Schneider *et al.*, 2011, Whitfield-Gabrieli *et al.*, 2009). Study 1 makes it clear that this abnormality also characterises schizoaffective disorder. Study 2 suggests that failure of de-activation in schizoaffective disorder has enduring, trait-like characteristics.

Schizoaffective disorder: Neuroimaging findings in relation to bipolar disorder

Over the years bipolar disorder has been associated with diverse functional imaging findings. However, there is now a consensus that the disorder is broadly characterized by reduced activity in prefrontal and other cortical regions coupled with increased activity in limbic regions (Strakowski *et al.*, 2012). This view is supported by the findings of two meta-analyses (Chen *et al.*, 2011, Kupferschmidt and Zakzanis, 2011). However, these meta-analyses have not provided clear answers to the questions about, a) possible differences between the pattern of changes seen at rest vs. during activation; b) within activation studies, to what extent the pattern is different when cognitive vs.

emotional test paradigms are used; and c) whether the pattern differs between mania and depression, and between episodes of illness and euthymia.

The acutely ill schizoaffective patients in the studies reported in this thesis showed reduced activation in the DLPFC, as well as in a network of other cortical regions. Reduced DLPFC activation is a reported finding in bipolar disorder during both mania (Pomarol-Clotet *et al.*, 2011), and depression (Fernandez-Corcuera *et al.*, 2012, Townsend *et al.*, 2010), although appears to be seen only in studies using the n-back task. Other studies have found reduced activation in other areas of the prefrontal cortex such as the orbitofrontal cortex, the ventrolateral prefrontal cortex and the frontal pole (for review see Pomarol-Clotet *et al.*, 2014). Therefore, schizoaffective disorder likely resembles bipolar disorder in this respect.

Study 2 found that DLPFC hypo-activation was not present in remission, at least in the group as a whole. This finding appears to differentiate schizoaffective disorder from bipolar disorder, where a number of studies using the n-back task have found reduced DLPFC activation in euthymia (for a review see: Cremaschi *et al.*, 2013). However, it should be noted here that in the only study to date that has directly compared acutely ill and euthymic bipolar patients, Pomarol-Clotet *et al.* (2014) found evidence for partial improvement in DLPFC hypo-activation in euthymia.

With respect to failure of de-activation that was found in the schizoaffective patients, there is increasing evidence that this is a feature not only of schizophrenia but also of bipolar disorder. Thus, it has been documented in mania (Pomarol-Clotet *et al.*, 2011), depression (Fernandez-Corcuera, Salvador et al. 2012), and also in euthymia (Pomarol-Clotet *et al.*, 2014) with all three studies localizing the failure to the medial frontal cortex. Failure of de-activation in the posterior cingulate cortex/precuneus, i.e. the posterior midline node of the DMN, has also been reported in euthymia (Allin *et al.*, 2010). In this sense schizoaffective disorder again resembles bipolar disorder. The finding from Study 2 that failure of de-activation shows trait-like characteristics accords with the

study of Pomarol-Clotet *et al.* (2014) cited above, which found that failure of de-activation in the medial frontal cortex was present to a statistically indistinguishable degree in all three phases of bipolar disorder.

Schizoaffective disorder: Neuropsychological findings in relation to schizophrenia and bipolar disorder

Cognitive impairment is a well-established finding in both schizophrenia (eg Palmer *et al.*, 2009) and bipolar disorder (eg Mann-Wrobel *et al.*, 2011, Robinson *et al.*, 2006). The pattern of impairment appears to be broadly similar in both disorders: poor performance is seen in most or all domains of neuropsychological function, but deficits are disproportionately marked in executive function, long-term memory and sustained attention. Cognitive impairment is often considered to be quantitatively greater in schizophrenia than bipolar disorder, but a meta-analysis (Bora *et al.*, 2009) found only partial support for this view: the differences were generally small and not significant in around half the domains of function examined. In view of these findings, it would be surprising if evidence of memory and executive impairment were not found in schizoaffective disorder, and this is what was found in Study 2.

Study 2 also investigated the state vs. trait characteristics of cognitive impairment in schizoaffective disorder. The results were mixed: memory but not executive function improved significantly in clinical remission in schizomanic patients, but neither domain of function changed between relapse and clinical remission in schizodepressive patients. In schizophrenia, to what extent neuropsychological function changes between relapse and remission has been little examined (Palmer *et al.*, 2009, Rund, 1998), but is often assumed to be stable over time. The traditional view of cognitive impairment in bipolar disorder is that it is state-related and reverts to normal in remission (eg Murray *et al.*,

2004). However, the recognition of euthymic cognitive impairment over the last 15-20 years now makes this assumption questionable. Indeed, a large study by Martinez-Aran *et al.* (2004) found that significant differences among depressed, manic and euthymic bipolar patients were few and there were no instances where the euthymic patients' performance clearly separated from that of the manic or depressed patients. The neuropsychological findings in schizoaffective disorder are broadly consistent with the above pattern. There was some evidence of improvement over time, but this was partial and the patients still showed deficits in remission.

Schizoaffective disorder: Findings in relation to symptomatology

A relevant finding from the studies reported in this thesis is that schizodepressive patients showed a greater failure of de-activation than schizomanic patients. As noted in the introduction, activity in the DMN is believed to underlie introspective or self-related thought, such as recall of personal experiences, making social and emotional judgements, envisioning the future and performing theory of mind tasks (Buckner *et al.*, 2008, Gusnard, 2005). This could be relevant to this finding – for example, schizodepressive patients might be expected to be more prone ruminative (and hence self-directed) mental activity than schizomanic patients. On the other hand, there were no differences in failure of de-activation between acute (schizomanic and schizodepressive) episodes and clinical remission. While this argues against a role in symptoms, this finding might be related to cognitive impairment which, as Study 2 indicated, persists into remission. DMN function has been linked to general cognitive function – for example, in healthy subjects higher levels of activity are associated with memory lapses (Pereña *et al.*, 2004). It is also tempting to speculate that the worse executive performance found in schizodepressive

patients in Study 2 might be related with the more pronounced failure of de-activation they showed compared to the schizomanic patients.

Beyond this, no relationship was found between any neuroimaging findings in the studies reported in this thesis and a range of clinical variables. This suggests that neither DLPFC hypoactivation nor failure of de-activation/DMN dysfunction underlie the symptoms of the disorder, at least in any direct way.

Final conclusions

The present thesis finds that hypoactivation during fMRI cognitive task, seen in a range of regions including importantly the DLPFC, is a feature of schizoaffective disorder. It has been argued that this finding aligns the disorder with schizophrenia, where reduced DLPFC activity both at rest and during cognitive task activation has been a leading functional imaging abnormality over the years. It also aligns schizoaffective disorder with bipolar disorder, with the qualification that hypoactivations have been mainly found in prefrontal regions other than the DLPFC in this latter disorder - although this could reflect the different tasks used and reduced DLPFC has been found in studies using working memory tasks.

The other main finding of the thesis is that failure of de-activation in the medial frontal cortex characterizes schizoaffective disorder. The implication is that the DMN is dysfunctional, as increasing evidence suggests it is also the case in both schizophrenia and bipolar disorder, and probably certain cognitive and neuropsychiatric disorders as well. It is particularly interesting that failure of de-activation was seen in all phases of schizoaffective disorder, as this is similar to what has been found in bipolar disorder. The emerging conclusion seems to be that default mode dysfunction has 'trait' rather than

'state' characteristics in the disorders where it is found. This feature may also be relevant to its apparent non-specificity to diagnosis.

Cognitive impairment is a known feature of schizoaffective disorder, but a novel finding of the thesis is that this may show a capacity for improvement along with improvement in clinical symptoms. However, this improvement was only observed in schizomanic patients, and it was partial, i.e. the patients continued to show some deficits when they were in remission. The importance of this finding, if confirmed, lies in the fact that there is very little existing evidence that improvement in cognitive function can take place under any circumstances in schizophrenia. In bipolar disorder it is often assumed that cognitive impairment normalizes with clinical recovery, but the evidence base for this view is slender and may now even be under threat.

Limitations and future directions

The main limitation of the two studies reported in this thesis is their relatively small sample size, especially in study 2; larger group sizes might have revealed more pronounced significant differences. Furthermore, as in the majority of neuroimaging studies, patients were medicated and this might have influenced the results.

This thesis additionally highlights the relative lack of studies examining both neuropsychological and brain functioning in schizoaffective disorder. While there is a substantial body of literature on schizoaffective disorder, this has mainly concerned clinical and diagnostic issues, and the neurobiology of the disorder has been neglected. Longitudinal studies, especially, seem desirable, as these can confirm or refute the findings of change in functional imaging and neuropsychological parameters between relapse and remission. It also emerges that there is a surprising lack of longitudinal neuropsychological and functional imaging studies in schizophrenia and bipolar disorder.

Examining the longitudinal trajectories of neuropsychological/functional imaging changes in these two disorders may well add to our understanding of the similarities and differences between them at the brain level.

Family and genetic studies, evaluating the association of schizoaffective disorder with both schizophrenia and affective disorders, have begun to find evidence of common susceptibility genes for different forms of psychosis. In this respect, our neuropsychological and neuroimaging results appear to be consistent with such a view. However, larger family and genetic studies will be necessary to confirm these preliminary results.

Taken together, the results of these investigations should help to understand better schizoaffective disorder from a neurobiological point of view, and might even help resolve the nosology of this important form of psychotic disorder.

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