The neural correlates of cognitive impairment in schizophrenia

Els correlats neurals del dèficit cognitiu en l'esquizofrènia

Jordi Ortiz Gil

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Tesi doctoral

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Programa de Doctorat "Medicina"
Línia de recerca: Neurociències clíniques i experimentals

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Somebody's reading your mind

Damned if you know how it is

They're digging through all of your files

Stealing back your best ideas

You cover your window with lead

Even keeping the pets outside

Then you hear a moment too late

this sound coming over the phone

'This is the spawning of the cage and aquarium…'

Cage & Aquarium *(They Might Be Giants, 1988)*

En ocasiones oigo ecos, ecos de voces eléctricas, ultrasónicas (…). Parecen reverberaciones sobrenaturales, pero son códigos cifrados, señales de otra dimensión.

Testimoni recollit per Ruiz Garzón (2005)

Dedicat a les persones a qui roben les millors idees de la seva ment, a les persones que senten ecos sobrenaturals xifrats... ; amb l'esperança que algun dia els podem permetre plenament el seu dret a la felicitat i l'autonomia.

En recuerdo de mi padre, que no pudo ver acabada esta tesis,
su última gran ilusión respecto a mí.

Agraïments personal(itzat)s

A Benito Menni CASM, la gent que hi treballa, les seves persones usuàries, perquè elles són la causa, el fi i els principals mitjans d'aquesta feina.

A Lucha, mi compañera de vida, por los ánimos que me has dado, por las comidas que me has preparado y por el mal genio que me has aguantado.

A mi padre y mi madre, porque el esfuerzo y el amor van de la mano. Porque soy como soy gracias a vosotros.

A Edith, per donar-m'hi l'oportunitat, per tot el coneixement i per totes les facilitats.

A Carme, per la supervisió precisa i sàvia i per tot el que has fet per la neuropsicologia.

To Peter, for your time, wisdom and dedication.

A Teresa, pel que m'has ensenyat i per la confiança que demostres en mi.

A Miguel y Helena, a Cristina y a Carlos, a la tía Aurelia, por la generosidad y por estar ahí, cada cual a su manera.

A Lucía, Pablo y Gloria, por la inmediatez que enseñáis.

A Marina, Luís Diego, Luzga, Ana, Pablo, Felipe y el resto de familia paisa, por incluirme como uno más.

A Erick, por tu disposición tan buena pa' lo que haga falta.

A Salva, pel teu ajut eficaç i pels ànims. Segur que aviat també ho aconsegueixes.

A Rai, per les anàlisis marxistes (des de les vessants de Karl i de Groucho) i pels múltiples ajuts tècnics. Som Energia!

A Marisa, Mónica, Jaime, Paco, Mª Àngels, Roser, Raül, Miguel, Pedro,… por haber despertado en mí la pasión por el cerebro.

A Ramón, Bàrbara y Bene, por las múltiples sesiones de tapaterapia de grupo...

A Antònia, Rocío, Natàlia, Montse, Bea, Chema i resta de gent de la Guttmann, pel que hi vaig poder aprendre i compartir.

A Bibiana, pel temps que vam ser companys de lluita.

A Bea, per la teva confiança i complicitat.

A Eulàlia, per les converses socials i artístiques i pels múltiples ajuts administratius.

A Jesús, por lo que me has enseñado y lo que me has compartido. ¡Mucha suerte en NY!

A Gemma, per tot el que dones amb un somriure.

A Silvia, a Pilar, a Èlia, a Teresa, a Maria, a Quim, a Laura, Amalia, Mercè, Laura, Paloma, Eva,... perquè, en la vostra companyia, la feina és més fàcil.

A Silvia, Naroa, Davinia, Joana i Guisi, pel vostre ajut i acollida en el temps amb vosaltres.

A Yolanda, Capri, Pablo, Bibiana, Roger, Laura, Sergi, Isa,... per humanitzar Barcelona i rodalies.

A Isaac, Montse, Pep, Mireia, Theo, Julie, Laia, Sergio, Sergi, Txell, Julie... per fer de Sants un barri de debò.

A Raquel, per fer més fàcil i humana la feina quotidiana.

A Lídia, per la confiança i facilitats donades.

A Òscar, Anuncia, Pilar, Lola, Carlos, Marta, Núria... i la resta de gent de Granollers, per la rebuda i per crear, tantes vegades, un bon ambient a la feina.

A Germán, por las alegrías y penas compartidas, incluido el doctorado.

A la Jose, por la complicidad.

A Marien, Paco, Malini, Empar, Sergi, Àngel, les Lauretes, Floreta i les vostres circumstàncies, que m'heu acompanyat des que començí amb la psicologia i abans. Per tot el que continuarem compartint!

Al tren, la meva musa en molts moments durant el darrer any.

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Abbreviations

ANOVA: Analysis of Variance

BA: Brodmann's area

BADS: Behavioural Assessment of the Dysexecutive Syndrome

BOLD: Blood-Oxygenation-Level-Dependent

C: Healthy Control Participants

CGI: Clinical Global Impression

CNVs: Copy number variants

CPZ: Chlorpromazine

CSF: Cerebrospinal Fluid

CT: Computed Tomography

DLPFC: Dorsolateral prefrontal cortex

DMN: Default Mode Network

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4^{th} Ed.

DTI: Diffusion tensor imaging

ES: Effect Size (using Cohen's *d*)

ESs: Effect Sizes (using Cohen's *d*)

F: Female

FA: Fractional Anisotropy

FE: First Psychotic Episode

FEAT: FMRI Expert Analysis Tool software

FIRST: FMRIB's Integrated Registration and Segmentation Tool software

fMRI: Functional Magnetic Resonance Imaging

FSL: FMRIB Software Library software

GE: General Electrics

GLM: General Linear Model

GM: Gray Matter

I: Cognitively Impaired Participants with Schizophrenia

IQ: Intelligence Quotient

K-W: Kruskal-Wallis (χ^2-test)

M: Male

MMSE: Mini-Mental State Examination

MNI: Montreal Neurological Institute

MRI: Magnetic Resonance Imaging

M-W: Mann-Whitney's (U-test)

NART: National Adult Reading Test

P: Cognitively Preserved Participants with Schizophrenia

PANSS: Positive and Negative Syndrome Scale

PET: Positron Emission Tomography

RBMT: Rivermead Behavioural Memory Test

ROI: Region of Interest

SD: Standard deviation

SIENAX: Structural Image Evaluation, using Normalisation, of Atrophy software

SPECT: Single Photon Emission Computed Tomography

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

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

WASI: Wechsler Abbreviated Scale of Intelligence

WCST: Wisconsin Card Sorting Test

WM: White Matter

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

1. Introduction

Schizophrenia is a severe and debilitating psychiatric disorder. It is considered to be one of the ten medical disorders that cause the most severe long-term disability (Mueser and McGurk, 2004). According to the World Health Organisation, it is also the third leading contributor to the global burden of mental, neurological and substance use disorders, and the fifth among high-income countries (Collins *et al.*, 2011). The economic burden of schizophrenia can be divided into direct costs and indirect costs. Direct costs refer to medical care, including pharmacological and non-pharmacological treatment and hospital admissions, and criminal justice costs. Indirect costs relate to the decrease in economic productivity of individuals with the disorder and the people taking care of them, mainly relatives (McEvoy, 2007), plus costs derived of increased comorbid health problems, such as obesity, cardiovascular disease, smoking, substance abuse and some types of infection such as HIV or hepatitis (Goff *et al.*, 2005; Tandon *et al.*, 2009; Jeste *et al.*, 2011). In Spain, the direct and indirect costs of schizophrenia have been estimated to be €1,970.6 million, including about 2.7% of public investment in health care (Oliva-Moreno *et al.*, 2006).

Schizophrenia has a prevalence of between 0.3 and 2%, with an average of 0.7-1% throughout the world (Jablensky, 2010). It has been estimated to affect about 24 million people worldwide (http://www.searo.who.int/en/Section1174/Section1199/Section1567_6744.htm) Prevalence seems higher in richer countries and among lower socio-economic classes. However, these differences in prevalence have been found to decrease when stricter diagnostic criteria are applied (Mueser and McGurk, 2004). Some authors consider that males have a slightly higher risk of

developing schizophrenia than females with a ratio of 1.3-1.4:1 (Aleman *et al*., 2003), whilst others do not find sex differences (Mueser and McGurk, 2004). However, it is well-established that males with schizophrenia have a worse outcome (Mueser and McGurk, 2004; Malla and Payne, 2005).

Schizophrenia usually develops between the ages of 15 and 45 years of age (Tandon *et al*., 2008), most commonly in late adolescence or early adulthood (DeLisi, 2008a). On average the onset is about five years earlier in males than females (Häfner *et al*., 1998b). Despite the peak in age onset occurring between 18 and 30 years in both sexes, females show a second peak later in life, after the menopause (Häfner *et al*., 1998a; Stilo and Murray, 2010).

1.1. The clinical features of schizophrenia

The clinical picture of schizophrenia is characterised by a remarkable diversity of symptoms. Acording to the reviews by Schultz and Andreasen (1999), McKenna (2007) and Tandon *et al*. (2009), these can be divided into the following main classes:

- *Positive or psychotic symptoms*: These include abnormal ideas, such as delusions, and abnormal perceptions, for instance auditory hallucinations. Some of the most common delusional themes in schizophrenia are persecutory (beliefs that there is a conspiracy to harm the patient), grandiose (beliefs that the person has special powers and abilities, is especially close to God, that he/she is famous or related to someone famous) and hypochondriacal (where the patient describes often bizarre changes in bodily function). Another class of delusion is referential delusions, where the patient believes neutral events have special significance for him/her. Hallucinations are defined as perceptions without

the existence of an object that causes them, that are accepted as real by the person experiencing them. The most common type in schizophrenia is auditory -hearing voices- and these can take many forms, such as 3rd person and commenting hallucinations (hearing other people commenting on him or her), imperative hallucinations (voices that order the person to carry out an action) or so-called extracampine hallucinations (the person hears something beyond the limits of normal perception, for instance happening thousands of kilometres away). Hallucinations can also be somatic (perceptions in the own body, often appearing together with related delusions), and less frequently visual, olfactory or gustatory.

- *Negative symptoms*: These are characterized by the loss or diminution of certain normal functions. These are usually considered to comprise three main classes of symptom, lack of volition (reduced motivation sometimes amounting to complete apathy), poverty of speech or alogia (marked aspontaneity of speech output), and affective flattening (reduced emotional responsiveness).
- *Formal thought disorder* (incoherent speech): This symptom affects the organization of thinking, speech and communication, so that it becomes difficult to follow. The patient's speech may appear to be wandering (derailment and loss of goal), without logic (illogicality), or include new, self-invented words (neologisms).
- *Catatonic symptoms*: These refer to changes in motor function, and more complex aspects of behaviour. Patients with catatonia show meaningless repetitions of actions, slowing and hesitancy of motor actions, or disorders of cooperation such as negativism or excessive compliance. These symptoms

frequently occur in the context of stupor (marked reduction in all motor activity) or excitement (high levels of disorganized and often destructive activity). Catatonia can also affect speech, producing symptoms such as aprosodia (marked lack of inflection), echolalia (repeating part or all everything that is said to the patient) or mutism (complete lack of speech).

- *Lack of insight*: Many patients with schizophrenia do not believe that they are ill, misattributing the symptoms to other causes or rejecting the need of treatment (Mintz *et al.*, 2003). Lack of insight often includes an inaccurate awareness of the own cognitive performance (Medalia and Lim, 2004; Medalia and Thysen, 2008; Donohoe *et al.*, 2009; González-Suárez *et al.*, 2011).

Positive symptoms and negative symptoms are common features of schizophrenia, although they are not always present at the same time (e.g. McKenna, 2007). In particular, positive symptoms are often intermittent, worsening with relapses of illness and improving or disappearing between episodes. In contrast, negative symptoms are not seen in all patients, but when they are present they are usually unchanging. Unlike positive and negative symptoms, for unknown reasons catatonia is nowadays rare.

Correlational studies have consistently found that positive and negative symptoms are unrelated to one another, suggesting that they have different underlying causes (Andreasen and Olsen, 1982; Lewine *et al.*, 1983; Rosen *et al.*, 1984; Kay *et al.*, 1986). A factor analytic study carried out by Liddle (1987b) suggested that there is a more complicated grouping of symptoms, into reality distortion (delusions and hallucinations), disorganization (formal thought disorder, plus inappropriate affect) and negative symptoms. Most subsequent

studies have supported this division (Thompson and Meltzer, 1993; Andreasen *et al.*, 1995).

A further important area of symptomatology in schizophrenia is impaired cognition. This forms the topic of this thesis and is discussed in detail later.

1.2. Course and outcome of schizophrenia

The course of schizophrenia is very variable. In general, it can be divided into the following sequential phases (Tandon *et al.*, 2009):

1. *Prodrome:* A period lasting weeks to months or occasionally years characterized by subthreshold positive and/or negative symptoms and other nonspecific changes. These include suspiciousness, strange ideas, sleep disturbance, anxiety, irritability, depressed mood, social isolation, decline in functioning, and lack of motivation (Malla and Payne, 2005).
2. *Onset of illness*: This represents the first time when the person presents overt psychotic symptoms. These almost always usually take the form of positive symptoms, but sometimes patients show a worsening evolution of negative symptoms like withdrawal and apathy, against which only minor delusions or hallucinations can be elicited. After the psychotic phase, there tend to remain depressive and negative symptoms.
3. *Chronicity*: During this phase the illness becomes established. This generally takes place over a period of two to five years. Positive symptoms tend to become less severe while negative symptoms tend to worsen. There may be exacerbations and remissions of active psychotic symptoms, sometimes, but not always, the overall degree of deterioration becomes worse with each episode.

The outcome of schizophrenia is also very variable, ranging from complete recovery to permanent severe disability requiring institutional care. McKenna (2007) has reviewed the literature in this area. The findings of the best designed studies are not fully consistent, but broadly suggest that around 20% of patients will show a full or nearly full recovery between episodes of acute illness. At the other end of the spectrum, between a third and a half of patients will ultimately have a poor outcome, showing moderate or severe ongoing positive symptoms accompanied by deterioration in social and occupational functioning to the extent that they are not able to live independently. Despite this, the most common outcome includes an attenuated presence of positive symptoms and more prominent negative symptoms and the need to a certain support and supervision to fulfil daily activities.

1.3. Treatment of schizophrenia

The most important treatment modality in schizophrenia is pharmacological, specifically the class of antipsychotic or neuroleptic drugs. The first drug of this type, chlorpromazine (CPZ), was introduced in the 1950s. Beginning with haloperidol, other antipsychotic drugs progressively appeared, but none were found to have superior effectiveness to CPZ (Davis, 1985). Their effectiveness of treatment was also found to be limited, with around 25% of patients showing little or no response (Goldberg *et al.*, 1965). Antipsychotic drugs were also found to produce significant side-effects, especially the so-called extrapyramidal side-effects, including parkinsonism and tardive dyskinesia, among others (Cunningham Owens, 1999). Tardive dyskinesia, in particular, is potentially serious, since although it only affects a minority of

patients it is usually irreversible. These drugs would be later be termed 'conventional' or 'first-generation' antipsychotic drugs.

In 1990, clozapine, a drug which had been in existence since 1967, but whose use was restricted because of an uncommon but potentially fatal effect on the blood, was re-introduced worldwide. This followed a trial by Kane *et al*. (1988) which demonstrated that it showed superior effectiveness to chlorpromazine in treatment resistant patients with schizophrenia. Unlike all other antipsychotic drugs, clozapine was also found to have only a minimal risk of producing extra-pyramidal side effects. Since then, a number of other 'atypical' or 'second-generation' antipsychotic drugs have been developed (Edlinger *et al.*, 2005).

All antipsychotic drugs are dopaminergic antagonists, acting postsynaptically to produce a blockade of D2 receptors (Coyle *et al.*, 2010). This finding was one of the factors that gave rise to the dopamine hypothesis of the disorder (discussed in section 14). Apart of the risk of extra-pyramidal side-effects, the most common side-effects of antipsychotic medication are weight gain, increase of the hormone prolactin, and QTc prolongation in the heart rate (Buchanan *et al.*, 2010). The risk and magnitude of the side-effects vary among the different drugs, although they tend to be more important in first-generation than in second-generation antipsychotic drugs (Buchanan *et al.*, 2010; Kane and Correll, 2010).

Antipsychotic drugs exert their principal effect on positive symptoms in acute phases (Edlinger *et al.*, 2005; Kane and Correll, 2010). In contrast, their effect on negative symptoms is less marked, or minimal according to some authors (Dixon *et al.*, 1995; Buchanan *et al.*, 2010; Kane and Correll, 2010).

However, clozapine and some other second-generation antipsychotic drugs may show a better effect in negative symptomatology than other antipsychotic drugs (Leucht *et al.*, 2009).

The fact that currently existing antipsychotic drugs just improve positive symptoms and have little effect in negative and cognitive symptoms is leading to searching for new drugs acting in serotoninergic, GABAergic and cholinergic systems. To date, no drugs of these types have shown clear evidence of effectiveness (Coyle *et al.*, 2010).

Non-pharmacological strategies have been considered to show effectiveness in schizophrenia, although they are only recommended as adjunctive to psychopharmacotherapy. These include assertive community treatment in order to reduce the probability of re-hospitalization or homelessness, supported employment, training in everyday skills, token economy interventions and others (Dixon *et al.*, 2010). The most important non-pharmacological treatment, however, is cognitive behavioural therapy (CBT) which has been argued to show effectiveness against both the positive and negative symptoms of schizophrenia and to be effective in preventing relapse (Tai and Turkington, 2009). The effectiveness of this treatment has been supported by meta-analysis (Zimmermann *et al.*, 2005; Wykes *et al.*, 2008). However, Lynch *et al.* (2010) have argued that the effect sizes (ESs) are smaller and mostly non-significant when only studies using blind evaluations and a control intervention are considered.

1.4. The aetiology of schizophrenia

Schizophrenia is a disorder whose cause or causes remain essentially unknown (Macher, 2010). Nevertheless, there is a consensus about the

importance of several different genetic, neurochemical and neurodevelopment factors.

Genetic predisposition is the most well-established risk factor for schizophrenia. Numerous twin and family studies have been carried out and reviewed (Gottesman, 1991; Cardno and Gottesman, 2000) and there is a consensus that having a monozygotic twin with schizophrenia confers a risk of about 50%. There is a similar level of risk when both parents have the illness. Beyond this, the probability of developing the illness decreases progressively when the closeness of the relative with schizophrenia decreases. For instance, siblings, children of one affected parent and dizygotic twins have around a 10% chance of becoming ill, and when first cousins or aunts/uncles have the illness, the probability is of about 2-3%.

Many susceptibility genes for schizophrenia have been proposed, but there is only strong evidence for three: DISC 1, neuregulin and dysbindin. All three genes are involved in potentially relevant neurochemical and brain developmental processes. However, according to current evidence the effect of each of these genes is at most small (Harrison and Weinberger, 2005; Tiwari *et al.*, 2010; Balu and Coyle, 2011; Johnstone *et al.*, 2011; Rico and Marín, 2011).

Some uncommon copy number variants (CNVs) have recently been implicated as strongly causative but individually uncommon causes of schizophrenia. CNVs are genomic variants of normality consisting of small additions, small deletions or changes in the position of the human DNA. Their presence does not determine the presence of the disorder, as in highly penetrant mutations in Mendelian, single-gene diseases, and increases significantly more the probability of having the disorder, unlikely to genetic

variants associated with complex genetic diseases. Some rare and large CNVs have been related to schizophrenia and other psychiatric disorders with high odds ratios, although they only account for a very small proportion of cases (Tiwari *et al.*, 2010; Gershon *et al.*, 2011). The CNVs implicated in schizophrenia also increase susceptibility to a range of developmental disorders, including autism, mental retardation, attention deficit-hyperactivity disorder and epilepsy (Williams *et al.*, 2009).

As regards neurochemical factors, the dominant theory of schizophrenia over many years has been that of a functional dopamine excess. As reviewed by Howes and Kapur (2009), this is based on indirect evidence a) that neuroleptic drugs exert their therapeutic effect via blockade of dopamine D2 receptors, and correspondingly b) that drugs with dopamine agonist actions, including amphetamine, cocaine and also L-dopa, can induce a state indistinguishable from schizophrenia. Until recently, direct evidence for the dopamine hypothesis has been lacking. In particular, studies examining for evidence for increased dopamine D2 receptors in the striatum in schizophrenia in never-treated patients had mostly negative findings (Laruelle, 1998; McKenna, 2007). However, three other studies (Laruelle *et al.*, 1996; Breier *et al.*, 1997; Laruelle *et al.*, 1999) have found evidence for increased dopamine release from synaptic vesicles under the influence of amphetamine. Most recently, Howes *et al.* (2009) found an increased dopaminergic striatal activity in people with prodromal psychotic symptoms. In contrast, Shotbolt *et al.* (2011) found a normal striatal dopamine synthesis capacity in schizophrenia patients with no marked symptomatology at the moment as well as in their illness-free monozygotic twins.

The major alternative neurochemical theory of schizophrenia is the glutamate hypothesis, which postulates that glutamate transmission is decreased in schizophrenia. It was developed following the recognition that an anaesthetic and drug of abuse, phenycyclidine, often provoked symptoms similar to schizophrenia (Javitt and Zukin, 1991). These studies have been extended with demonstrations that a related drug, ketamine, can induce symptoms showing a degree of resemblance to schizophrenia in healthy volunteers. However, the similarity of this state to schizophrenia has been questioned (Pomarol-Clotet *et al.*, 2006).

Although early studies claimed therapeutic effects of glutamate agonist drugs on negative, but not positive, symptoms in schizophrenia (Tuominen *et al.*, 2005), more recent studies have failed to confirm this (Buchanan *et al.*, 2007). As yet, McKenna (2007), after reviewing the evidence, concluded that direct evidence of changes in indices of glutamatergic function in the brains of schizophrenic patients is conflicting. It is noteworthy that glutamate also interacts with dopamine (Harrison and Weinberger, 2005; Stephan *et al.*, 2006).

According to the neurodevelopmental hypothesis of schizophrenia, brain damage or injury sustained early in life is initially dormant but produces symptoms when it interacts with normal brain maturational processes occurring later, i.e. in adolescence. Key proposals of this theory are a) that individuals who subsequently go on to develop schizophrenia show an excess of adverse events during pregnancy, birth or early life, and b) that the brain injury is not entirely silent during early life, but shows itself as minor developmental delays, behavioural changes, etc.

An important line of evidence in favour of the neurodevelopmental hypothesis is the finding of a higher rate of obstetric complications in babies who later develop schizophrenia (Jones *et al.*, 1998; Cannon *et al.*, 2000). However, not all studies have found evidence of this (Done *et al.*, 1991; Buka *et al.*, 1993). Nevertheless, a meta-analysis by Cannon *et al.* (2002) found overall evidence in support of a higher rate of birth complications.

The neurodevelopmental hypothesis has received more consistent support from longitudinal studies of child development. As Mckenna (2007) reviewed, a series of so-called birth cohort studies -which have followed children from birth to early adult life or later- have all found that children who will later develop schizophrenia have a lower IQ. They also show more anxiety and behavioural disorders in childhood (Done *et al.*, 1994; Jones *et al.*, 1994), and have a higher frequency of speech delay and other speech problems (Jones *et al.*, 1994). Some of these studies have also found that children who later develop the disorder show a higher frequency of tics and other minor motor disorders (Rosso *et al.*, 2000) and report having experienced minor psychotic symptoms at the age of 11 (Poulton *et al.*, 2000).

Based on the above evidence, schizophrenia is widely considered to have a multifactorial aetiology (Andreasen, 1999). The presence of a set of susceptibility genes, together with environmental factors such as pre- and perinatal adverse events, produce subtle neurodevelopmental changes. These, possibly in conjunction with altered cerebral maturation and abnormalities in dopaminergic pathways, then lead to the development of illness.

1.5. Neural bases of schizophrenia

There is a large body of evidence examining brain structure and function in schizophrenia. At the macroscopic level, it has been accepted for a long time that the brain shows no obvious changes post-mortem on visual examination (David, 1957). However, a meta-analysis of studies of post-mortem brain weight found a 2% reduction (Harrison *et al.*, 2003). Whether there are microscopic changes is controversial. There were many early claims for histological abnormality in schizophrenic post-mortem brain such as cell loss, cell shrinkage and ballooning, dwarf cells, metachromatic bodies, cellular inclusions, demyelination and gliosis. Subsequently, David (1957) concluded in a review that there were grounds for doubting all these findings. A more recent review by Harrison (1999) concluded that only three microscopic findings were well supported: absence of gliosis; decreased neuronal size in the hippocampus and reduced numbers of neurons in the dorsal thalamus. This last finding could be considered doubtful as it was based on only two studies.

Much of our current knowledge on the neuroanatomical basis of schizophrenia derives from structural and functional imaging studies. Structural imaging studies began to be carried out shortly after computerized tomography (CT) was introduced in the 1970s. There are now many studies using the more sophisticated technique of magnetic resonance imaging (MRI). Another important source of research knowledge is functional neuroimaing, including the techniques of Positron Emission Tomography (PET), Single Photon Emission Computed Tomography (SPECT) and functional magnetic resonance imaging (fMRI).

1.5.1. Brain structure

The first structural imaging study in schizophrenia was carried out in 1976. Using CT, Johnstone *et al*. (1976) originally reported that a sample of 13 chronically hospitalized schizophrenic patients had significantly larger lateral ventricles than a control group of eight normal controls. This finding has later on been replicated in most of around 50 further studies (Andreasen *et al*., 1990).

1.5.1.1. Gray matter

MRI gives a much better resolution than CT and permits the differentiation of gray matter (GM) and white matter (WM). A meta-analysis of 58 structural MRI studies including 1588 participants (Wright *et al*., 2000) found support for the following structural changes in schizophrenia: lateral ventricular enlargement of around 25% and a 2% reduction in whole brain volume. Volume reductions were somewhat more marked in the frontal lobe (5%), hippocampus (6%) and thalamus (4%) and amygdala (7%). Volume reductions in the temporal lobe (2-3%) were no more marked than in the brain as a whole. A summary of the results of this meta-analysis is shown in Table 1.

Steen *et al*. (2006) had similar findings in a meta-analysis of 52 studies of first-episode (FE) schizophrenia patients including 1424 patients and 1315 healthy controls. There was a reduction of whole brain volume (2.7%) and hippocampal volume (9.3%) plus ventricular enlargement (33.7% for the right ventricle; 24.7% for the left ventricle and 25.3% for the third ventricle). Steen *et al*. (2006) also found support for reduced volume in Heschl's gyrus, part of the superior temporal lobe cortex, and other parts of the temporal lobe GM.

Table 1. Comparison of regional brain volume of participants with schizophrenia and healthy controls in 58 studies, as adapted from Wright *et al*. (2000).

Brain structure	Number of studies	Number of subjects		Comparative volume in schizophrenia compared to control in %
		Schizophrenia	controls	
Ventricles				
Left lateral ventricle	18	557	496	130
Right lateral ventricle	18	557	496	120
Third ventricle	22	595	548	126
Fpurth ventricle	5	119	134	107
Total ventricles	30	984	912	126
Cortical and limbic structures				
Left frontal volume	13	395	367	95
Right frontal volume	13	395	367	95
Left temporal lobe	25	693	669	98
Right temporal lobe	25	693	669	97
Left superior temporal gyrus	10	314	271	97
Right superior temporal gyrus	10	314	271	97
Left anterior superior temporal gyrus	8	194	183	93
Right anterior superior temporal gyrus	7	179	168	95
Left posterior superior temporal gyrus	5	94	128	93
Right posterior superior temporal gyrus	4	79	113	103
Left parahippocampus	8	185	168	89
Right parahippocampus	8	185	168	92
Left hippocampus	24	677	621	93
Right hippocampus	24	677	621	94
Left amygadala	7	146	137	91
Right amygdala	7	146	137	91
Subcortical structures				
Left caudate	10	308	257	101
Right caudate	10	308	257	99
Left putamen	7	169	151	104
Right putamen	7	169	151	104
Left globus pallidus	2	36	48	118
Right globus pallidus	2	36	48	121
Left thalamus	3	111	99	96
Right thalamus	3	111	99	96
Whole brain measures				
Whole brain	31	946	921	98
Left hemisphere	15	463	434	97
Right hemisphere	15	463	434	97
Gray matter	6	155	194	96
White matter	5	126	155	98

The above structural studies were based on region-of-interest (ROI) analysis. That is, brain regions of interest were selected a priori and segmented manually or automatically in the images. More recently, whole brain, voxel-based techniques, such as voxel-based morphometry (VBM), have been

developed: these map clusters of significant difference between groups of subjects throughout the brain without the necessity of preselecting ROIs (Ashburner and Friston, 2000; Davatzikos, 2004). These techniques potentially have more power to detect small and/or localised volume differences in schizophrenia. Originally, these techniques provided a measure of GM and WM density or concentration. However, by means of a technique known as modulation or optimization, it is possible to generate a measure of volume (Mechelli *et al.*, 2005).

A meta-analysis on 31 VBM studies found GM density reductions in sites in frontal, temporal, insular and thalamic regions in 1195 participants with schizophrenia in comparison to 1262 controls (Glahn *et al.*, 2008). A more recent meta-analysis by Fornito *et al.* (2009) supported some but not all of these findings. Altogether, 37 VBM studies of schizophrenia were included, with data from 1646 participants with the disorder and 1690 controls. When data were combined from studies using non-modulated VBM, alteration in the medial and lateral prefrontal cortex, temporal cortex and insula bilaterally was found: However, the studies using modulated/optimized VBM yielded more restrictive results: clusters of significant volumetric differences were seen only in the left medial superior frontal gyrus, the left orbitofrontal region and fusiform gyrus.

The largest and most recent meta-analysis of this type has been carried out by Bora *et al.* (2011b) on 52 studies including 2090 participants with schizophrenia and 2284 healthy controls. They found GM volume reductions in bilateral inferior, medial frontal, and insular regions, as well as the thalamus and the left superior temporal gyrus (see Figure 1 in

http://journals.cambridge.org/action/displayAbstract?fromPage=online&aid=8468483).

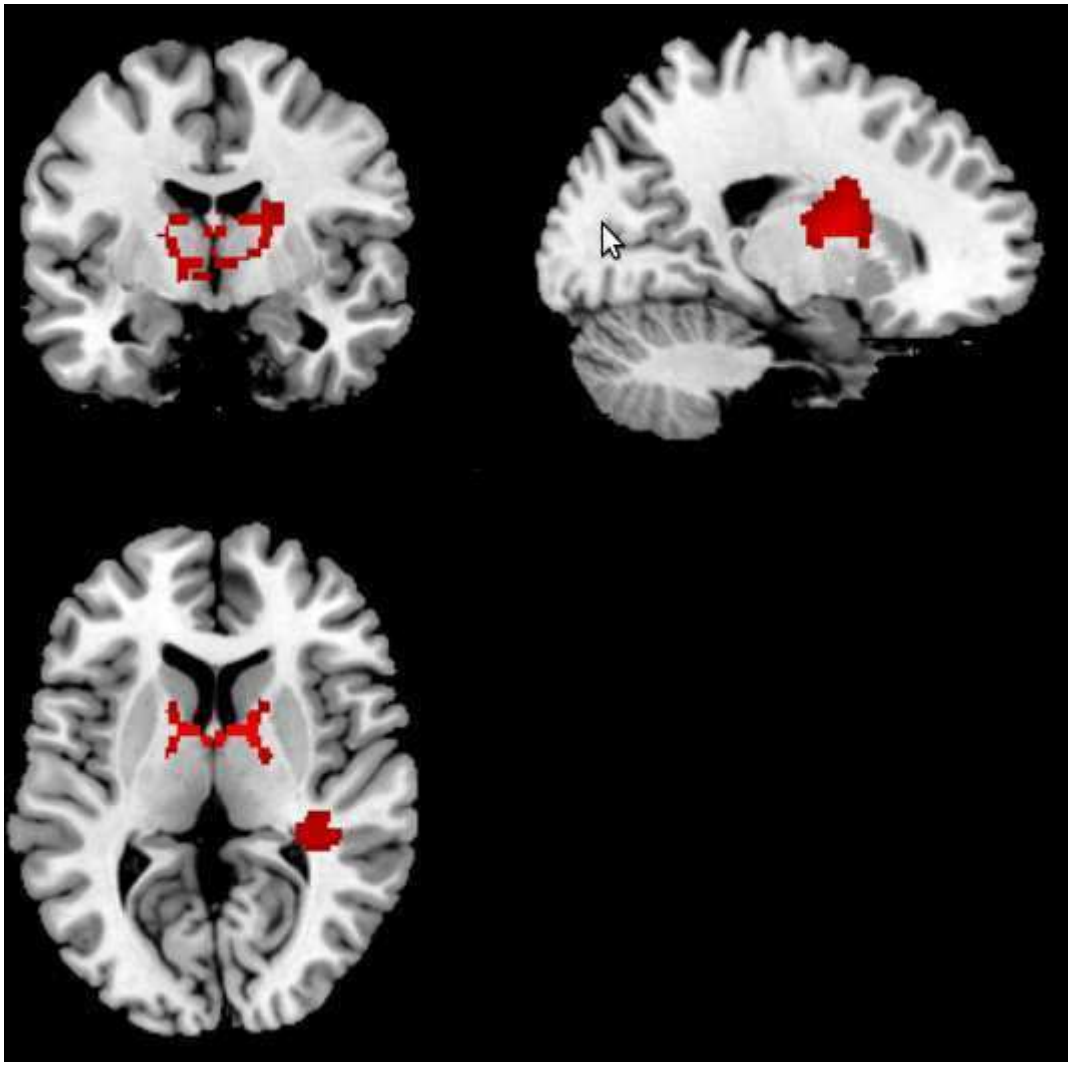
A further meta-analysis by the same group (Bora *et al.*, 2011a), carried out on 18 studies of FE patients comprising 578 participants with psychosis and 636 healthy controls, revealed GM volume reductions in the right posterior insula and superior temporal gyrus and in the anterior cingulate. The pattern of changes was more restricted than in patients with chronic schizophrenia.

1.5.1.2. White matter

Brain structural changes in schizophrenia involve not just GM but also WM. For example, Wright *et al*. (2000), in the meta-analysis cited above, found evidence for a 4% reduction in GM volume and a 2% reduction in WM volume across the whole brain. Bora *et al*. (2011a) meta-analyzed 24 VBM studies (*n*=885 of the patient sample) examining WM volume in schizophrenia. They found reductions in the anterior limb of the internal capsule bilaterally and in the right temporal lobe when compared with 883 healthy controls. The findings are shown in Figure 1.

Another technique for examining WM pathology is diffusion tensor imaging (DTI). This quantifies the extent to which water can diffuse in different directions, giving a measure referred to as fractional anisotropy (FA). Normally the direction of diffusion is highly constrained in the direction of the axon because most of the water is inside axons surrounded by myelin. However, when myelin is absent or damaged or its thickness is decreased, water is more free to move in directions perpendicular to the axon and so the FA decreases.

Figure 1. Volumetric reductions in WM in schizophrenia according to a recent meta-analysis of 24 studies (adapted from Bora *et al.*, 2011a).



The left side in the image represents the left brain hemisphere.

Other properties of the WM fibre tracts, such as their density, their average diameter and the directionality (or coherence) of the fibres in each voxel, can also affect the diffusion of water molecules (Kanaan *et al.*, 2005; Kubicki *et al.*, 2007).

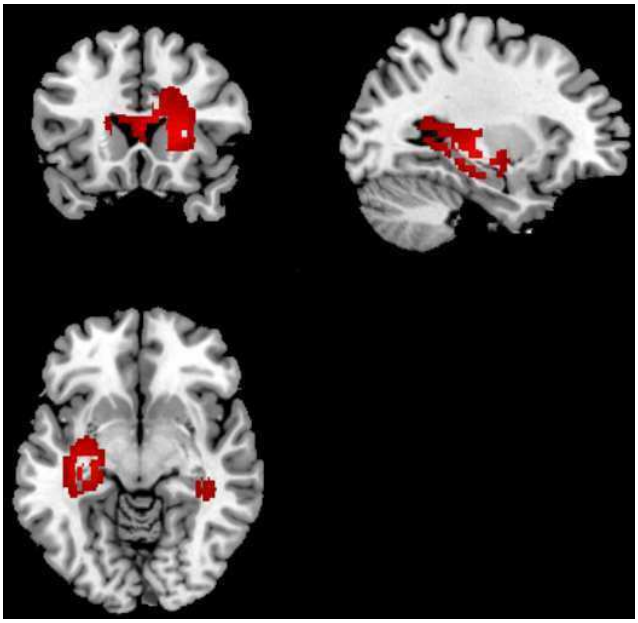
In an early review of DTI studies in schizophrenia, Kanaan *et al.* (2005) concluded that there was preliminary evidence for WM alterations in the corpus callosum and in the cingulum bundle. The cingulum bundle is a bundle of WM

running along the length of the cingulate gyrus which carries fibres interconnecting the temporal pole, the parietal lobe and the orbitofrontal cortex (Schmahmann and Pandya, 2006). Two more recent reviews have also found support for decreased FA in the corpus callosum, and also in cingulate and frontal WM in schizophrenia (Keshavan *et al.*, 2008; White *et al.*, 2008). Kubicki *et al*. (2007), on the other hand, found evidence for abnormalities in a wider range of WM tracts within prefrontal and temporal lobes, as well as abnormalities within the fibre bundles connecting these regions (including uncinate fasciculus, cingulum bundle and arcuate fasciculus). Kyriakopoulos *et al*. (2008), in a more recent review, found WM alterations in the corpus callosum, arcuate fasciculus, cingulum bundle and cerebellar peduncles, as well as trends into alterations in frontal and temporal WM tracts.

The authors of these reviews (Kanaan *et al*., 2005; Kubicki *et al.*, 2007; Kyriakopoulos *et al*., 2008) also recognized that the findings were inconsistent. Kanaan *et al*. (2005) and Kubicki *et al*. (2005) emphasised the need for use of more homogenous samples, whereas Kyriakopoulos *et al*. (2008) argued that the use of restricted ROI in many of the studies is another potential confounding factor. With respect to this last potential confounding factor, Bora *et al.* (2011a) meta-analyzed 23 studies using studies which used a whole brain approach (688 schizophrenia vs. 665 healthy participants). FA was reduced in three clusters in the patients: the largest cluster included the bilateral genu of the corpus callosum, the anterior cingulate cortical/medial frontal WM and the right anterior limb of the internal capsule and the right external capsule/corona radiata. A second cluster was in the left temporal WM and retrolenticular internal capsule, extending to the external capsule and the fornix/stria

terminalis. The third cluster included right temporal WM. The findings are shown in Figure 2.

Figure 2. FA reduction using DTI in schizophrenia according to a recent meta-analysis of 23 studies (adapted from Bora *et al.*, 2011a).



The left side in the image represents the left brain hemisphere.

1.5.2. Brain functioning

1.5.2.1. Early findings

Functional imaging studies of schizophrenia began in 1974 with a study by Ingvar and Franzén (1974). Using the technique of ^{133}Xenon inhalation, they examined brain activity at rest in 11 patients with dementia and two groups of chronic schizophrenic patients, one consisting of nine chronically hospitalised patients and the other of 11 younger patients. There were 15 normal controls. The demented patients showed significantly reduced cerebral blood flow in all cortical areas compared to the controls. In contrast, global blood flow was not significantly different from the controls in the schizophrenic patients, but there

was a changed regional pattern of flow in both groups of schizophrenic patients, with a reversal of the normal pattern of greater flow in anterior as compared to posterior regions. Ingvar and Franzén (1974) referred to this abnormality as hypofrontality.

Subsequent studies which examined resting brain activity had conflicting findings concerning hypofrontality; while some studies found support for hypofrontality (Ariel *et al.*, 1983; Buchsbaum *et al.*, 1984; DeLisi *et al.*, 1985), others did not (Mathew *et al.*, 1982; Gur *et al.*, 1983; Gur *et al.*, 1985). Chua and McKenna (1995) reviewed 27 studies carried out up to 1994 and found that only 10 of 27 studies found evidence for hypofrontality at rest.

Partly because of these inconsistencies, Weinberger *et al.* (1986) proposed that hypofrontality in schizophrenia might be easier to demonstrate when cognitive demands were made on the prefrontal cortex. They carried out functional imaging using the ^{133}Xenon technique, both at rest and during performance of an executive task, Wisconsin Card Sorting Test (WCST), in 20 chronic schizophrenic patients and 25 controls comparable in age and sex. The schizophrenic patients showed only a non-significant trend to hypofrontality at rest, but hypofrontality during WCST performance was significantly more evident. Once again, however, this finding was not consistently replicated: Chua and McKenna (1995) found that summarising seven studies examining task related activations in schizophrenia, just four presented positive and three presented negative findings.

A limited meta-analysis on 22 PET studies including 537 schizophrenia patients and 427 healthy controls found support for hypoactivation with a moderate effect size (ES) at rest (-0.64) and with a large effect when performing

an executive task (-1.13) (Zakzanis and Heinrichs, 1999). Hill *et al*. (2004) confirmed these findings in a meta-analysis of a larger set of studies. This found support for hypofrontality at rest (ES of –0.32 in 38 studies with a total sample of 1474 participants using absolute measures of blood flow/metabolism and ES -0.55 in 25 studies with 950 participants using a relative measure, i.e. dividing frontal blood flow/metabolism by global blood flow/metabolism). It also found support for hypofrontality during cognitive task performance (ES of –0.42 in 10 studies with a total sample of 347 participants using absolute measures and ES -0.37 in 17 studies with 685 participants using a relative measure). However, this meta-analysis did not confirm the proposed greater magnitude of task-related compared to resting hypofrontality -the ESs were similar in both.

1.5.2.2. Contemporary functional imaging studies

The above studies used the ROI approach, typically restricting the analysis to the prefrontal cortex or subregions of this, especially the dorsolateral prefrontal cortex (DLPFC). More recently, studies have begun to use voxel-based techniques, which do not preselect areas of interest. Whereas early studies used radioisotope-based techniques such as PET, SPECT and ^{133}Xenon inhalation, contemporary studies have increasingly employed fMRI, which does not depend on radiation-emitting isotopes, but is restricted by the fact that only activation related changes can be studied. An important finding from this new generation of studies was that schizophrenic patients showed evidence not just of hypofrontality, but also of 'hyperfrontality', i.e. increased prefrontal activation, sometimes in isolation and sometimes alongside areas of decreased activation, while they performed the n-back task (a standard working

memory task in imaging studies explained in section 3521) (Manoach *et al.*, 1999; Callicott *et al.*, 2000; Callicott *et al.*, 2003; Tan *et al.*, 2006).

The finding of hyperfrontality has subsequently been supported by two meta-analyses. Glahn *et al.* (2005) meta-analyzed 12 studies including 186 participants with schizophrenia and 172 healthy controls which used the n-back task. They found consistent evidence for decreased activation in the DLPFC bilaterally and in the right insular cortex as well as for increased activation in the anterior cingulate and left frontal pole regions in patients with schizophrenia compared to that in controls. The findings are shown in Figure 2 in http://onlinelibrary.wiley.com/doi/10.1002/hbm.20138/abstract;jsessionid=A60332B2A379F02D97EE9556BD26A710.d03t03.

Minzenberg *et al.* (2009) had similar findings in a larger meta-analysis of studies using a range of different executive tasks. They included 41 studies with a total sample of 584 participants with schizophrenia and 623 healthy participants. The schizophrenic sample were found to show significantly reduced activation in the bilateral DLPFC, the right medial frontal cortex, the left thalamus, the basal ganglia bilaterally and parts of the parietal and occipital cortex. They also showed significantly increased activation when compared to healthy controls: these included the dorsal anterior cingulate cortex and the frontal pole, areas similar to those found by Glahn *et al.* (2005), but also areas in the left dorsal and ventral premotor cortex, the ventrolateral prefrontal cortex and parts of the temporal and parietal cortex.

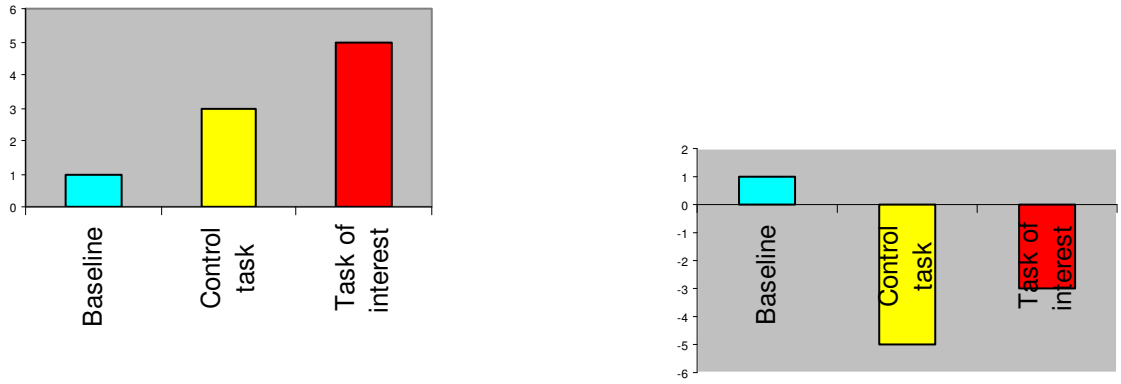
A further recent functional imaging finding in schizophrenia has been failure to de-activate in the medial prefrontal cortex. Examining 32 chronic schizophrenic patients and 32 controls during performance of the n-back task,

Pomarol-Clotet *et al*. (2008) found reduced activation in the right DLPFC and other frontal areas, and also failure of de-activation in a large area of the medial frontal cortex (see Figure 2 in http://journals.cambridge.org/action/displayAbstract?fromPage=online&aid=1927800). This finding has been replicated by a number of other authors, sometimes along with failure of de-activation in other regions including the posterior cingulate cortex (Whitfield-Gabrieli *et al*., 2009; John *et al*., 2011; Milanovic *et al*., 2011; Salgado-Pineda *et al*., 2011; Schneider *et al*., 2011).

Given that this area of failure of de-activation overlaps with some of the areas where hyperfrontality has been found in schizophrenia, Pomarol-Clotet *et al*. (2008; 2010) have proposed that the finding of hyperfrontality in schizophrenia could actually represent a failure to de-activate. This proposal is based on an argument by Gusnard and Raichle (2001) that the subtractive nature of functional imaging analysis can result in findings of apparent activation in healthy subjects during task performance when what is really taking place is reduction in activation from a high baseline. The argument was originally made in relation to control and target tasks in the same subjects, and is illustrated in Figure 3. In (a) the task of interest is associated with a greater increase above baseline than the control task; in (b) the task of interest is associated with less of a decrease from the baseline than the control task. However, in both cases, there is an increase in activity between the control task and the task of interest. Pomarol-Clotet *et al*. (2008) considered that this argument applies equally to differences between groups of subjects, in this case schizophrenic patients and controls.

Figure 3. Two different ways in which an apparent activation can be found in a task of interest, as described by Gusnard and Raichle (2001).

a) b)



In *a*, the task of interest is associated with a greater increase above baseline than the control task. In *b*, the task of interest is associated with less of a decrease from the baseline than the control task.

This latter finding is interesting because the medial frontal cortex forms one of the two midline nodes of the so-called default mode network (DMN), a series of interconnected brain regions which are active at rest but de-activate during performance of a wide range of cognitive tasks (Gusnard and Raichle, 2001; Buckner *et al.*, 2008). Other parts of the DMN include the posterior cingulate/retrosplenial cortex, the inferior parietal cortex, the hippocampus and parahippocampal cortex, and less reliably the lateral temporal cortex (Buckner *et al.*, 2008). Studies examining the DMN using independent component analysis or whole brain resting state connectivity have also found evidence of DMN dysfunction in schizophrenia (Broyd *et al.*, 2009). In several of these studies the anterior midline node in the medial frontal cortex seems particularly implicated (Whitfield-Gabrieli *et al.*, 2009; Salvador *et al.*, 2010; Camchong *et al.*, 2011). The DMN is additionally of interest in schizophrenia because its activity is inversely correlated with 'task positive' networks involved in task

performance (Buckner *et al*., 2008), one of which is an 'executive control' network involving the bilateral DLPFC and other frontal regions (Seeley *et al*., 2007).

1.6. Cognitive impairment in schizophrenia

Although it was not considered an important feature of schizophrenia by Kraepelin and particularly by Bleuler (Mckenna *et al*., 2002), cognitive impairment has since become accepted as an important feature of the disorder. Early studies reviewed by Chapman and Chapman (1973) established that patients with schizophrenia performed more poorly than normal individuals on virtually every cognitive task. Later, IQ testing revealed that schizophrenic patients had lower IQs than the rest of the population. Overall, the disadvantage was found to be minor, on average of the order of less than five IQ points, but groups of patients with severe and chronic forms of illness were found to have a mean IQ of just over 80 (Payne, 1973). Finally, three reviews of the performance of patients with schizophrenia on a wide range of neuropsychological tasks all found that groups of acute, mixed and chronically hospitalised schizophrenic patients were increasingly difficult to distinguish from the patients with various forms of brain damage (Goldstein, 1978; Heaton *et al*., 1978; Malec, 1978).

Heinrichs and Zakzanis (1998) meta-analyzed neuropsychological studies comparing schizophrenic patients and controls carried out between 1980 and 1997 and which covered areas of memory, motor skills, attention, intelligence, visual and visuospatial function, executive function, language and tactile perception. They included 204 studies with 7420 participants with schizophrenia and 5865 comparison subjects. The ESs for impairment were all

moderate or large, ranging from 0.46 (for WAIS-III Block Design) to 1.41 (for verbal memory). The degree of non-overlap between the schizophrenic and the normal controls varied from 30% to 70% on different tests. Heinrichs and Zakzanis (1998) concluded that schizophrenic cognitive impairment affected most areas of function and took the form of a continuum from a mild impairment overlapping with the levels of function seen in many healthy individuals, to the kind of severe dysfunction found in patients with central nervous system disease.

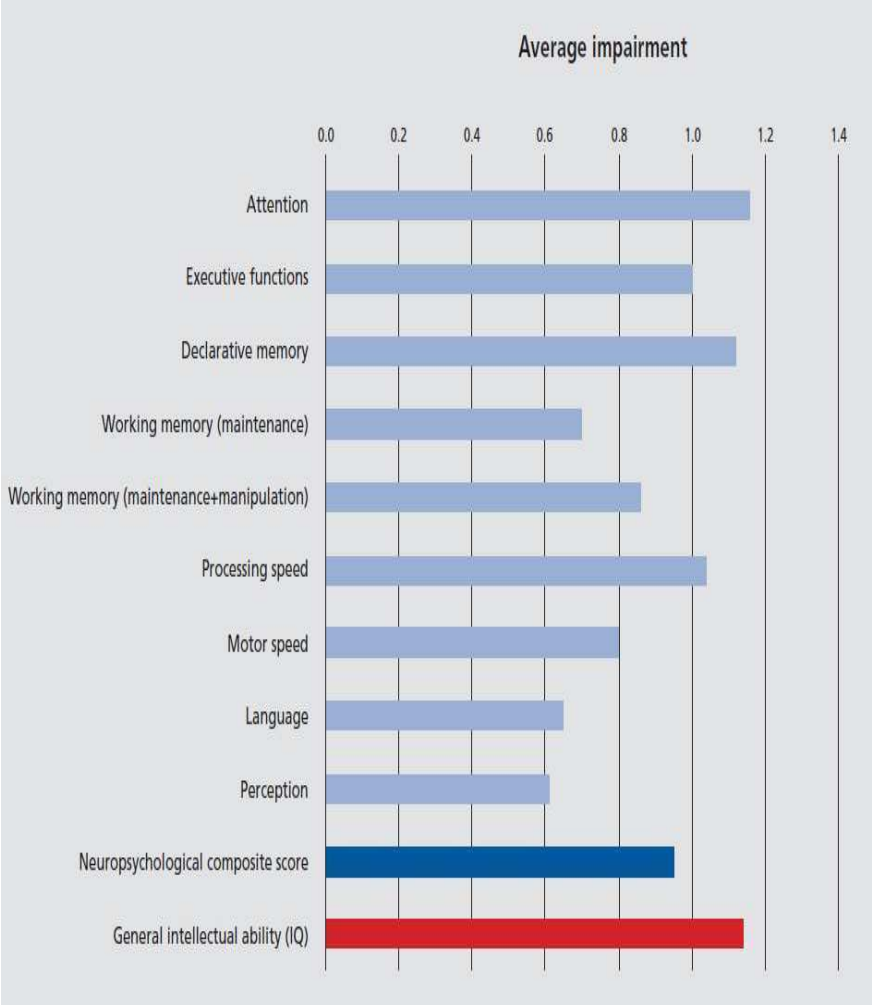
Fioravanti *et al*. (2005) confirmed these findings in a more recent meta-analysis of 113 studies including 4365 participants with schizophrenia and 3429 healthy controls. IQ impairment showed a severe impairment (ES=1.01). Language impairment was found to be the same as for IQ (ES=1.01). Memory impairment, however, was found to be larger than impairment in IQ (ES=1.18). The same happened for impairment in reaction time (ES=0.70 to 1.53).

Reichenberg (2010) has recently summarized the findings of these and other meta-analyses (see Figure 4). He noted that schizophrenia is characterised by a severe degree of general intellectual impairment, as indexed by studies measuring IQ in the disorder. Against this background, meta-analytic studies suggest moderate to marked impairment in attention, specifically the subdomain of sustained attention. He also found evidence for a severe deficit in executive function. With respect to declarative memory, he noted that deficits in declarative memory have been consistently reported, with meta-analyses finding severe impairments in immediate and delayed verbal and nonverbal long-term memory. Non-declarative memory has been considerably less studied in schizophrenia, and has not been the focus of meta-analytic investigations.

However, the available evidence suggested that this aspect of memory is relatively preserved in schizophrenia patients, and schizophrenia patients show near perfect performance or only mild impairment on tasks of procedural learning. As regards working memory functions, meta-anaytic results refer that tasks that just require active maintenance of information -most typically Digits Forward- are markedly less impaired than those that include both maintenance and manipulation of information -most typically Digits Backward-. Another domain that would show a severe substantial impairment in schizophrenia is processing speed. Perceptual tasks and simple motor tasks would also present moderate to severe impairment. On the contrary, a relatively preservation of linguistic skills, with just mild impairment, would be observed in the results of different meta-analyses.

There is wide agreement that schizophrenic cognitive impairment is not caused by neuroleptic drug treatment. King (1990) reviewed the evidence on the effects of administration of these drugs to normal subjects and found that they had only minor effects on cognitive function. King (1990) and also Mortimer (1997) reviewed studies comparing schizophrenic patients before and after they received neuroleptic treatment. These studies invariably found no deterioration with treatment and sometimes slight improvement in test performance. Finally, several studies (Saykin *et al.*, 1991; Blanchard and Neale, 1994; Saykin *et al.*, 1994) have examined drug-free or never-treated schizophrenic patients using wide-ranging batteries of neuropsychological tests and have found much the same pattern and degree of impairment as in treated patients.

Figure 4. Median effect size of cognitive impairment among cognitive domains, with data from several meta-analyses. Taken from Reichenberg (2010).



A small number of studies have aimed to determine the extent to which cognitive impairment in schizophrenia can be attributed to factors such as poor motivation and co-operation (Goldberg *et al.*, 1987; Kenny and Meltzer, 1991; Duffy and O'Carroll, 1994). These found little evidence that these factors play an important role. McKenna (2007) additionally argued that impairment cannot be attributed to these factors because a minority patients with schizophrenia show deficits which are so marked that they can be demonstrated on clinically-

oriented tests such as the Mini-Mental State Examination (MMSE) which are not demanding of attention and concentration.

All authors are in agreement that the degree of cognitive impairment in schizophrenia varies markedly from patient to patient. Additionally, several studies have documented that between 15% and 30% of patients show cognitive function that is within the normal range (Palmer *et al.*, 1997; Weickert *et al.*, 2000; Hill *et al.*, 2002; Allen *et al.*, 2003; Chan *et al.*, 2006; Holthausen *et al.*, 2007; Palmer *et al.*, 2009). Some authors have argued that there is subtle evidence of cognitive impairment even among this group of patients, since some cognitive functions, such as memory and processing speed, have been found to be mildly affected in some of the studies (Seaton *et al.*, 1999; Wilk *et al.*, 2005). However, others have disagreed, and this remains an ongoing debate (Palmer *et al.*, 1997; Kremen *et al.*, 2000; Weickert *et al.*, 2000; Keefe *et al.*, 2005).

1.6.1. Cognitive deficits in relation to the clinical features of schizophrenia

1.6.1.1. Relationship to symptoms

The relationship of cognitive impairment and different types of neuropsychological deficit to the symptoms of schizophrenia has been extensively investigated. In a seminal paper, Liddle (1987a) found that impairment on a range of neuropsychological tests was correlated with scores on negative symptoms and disorganization, but not with reality distortion (i.e. delusions and hallucinations), with suggestions of a differential pattern of association with the two syndromes. Disorganization was associated particularly

with poor performance on sustained attention, visual short-term memory, verbal learning and orientation, while the negative syndrome was associated with impairment on tests of naming and reasoning. This study did not include executive tests; however, Liddle and Morris (1991) carried out a further study that included a range of executive tasks. This also found significant inverse correlations between test scores and negative symptoms and disorganization, but not positive symptoms. It also found evidence for a relationship between negative symptoms and tests requiring generation of responses, such as verbal fluency, and between disorganization and tests requiring the inhibition of inappropriate responses, such as the Stroop Test.

Mckenna and Oh (2005) reviewed these and 25 further studies which examined the association between Liddle's three syndromes and performance on a wide range of cognitive tests. Their findings are summarized in Table 2.

There was a clear pattern of association of poor neuropsychological test performance with both negative symptoms and disorganization, but very few studies found an association with reality distortion. The pattern of association with negative symptoms and disorganization affected not just executive function, but also memory, attention and all other areas of cognitive function that were evaluated. However, no clear pattern of a relationship between specific cognitive functions and negative or disorganization syndromes was evident.

Table 2. Summary of the positive findings of a review of 27 studies relating cognition and psychopathology, adapted from Mckenna and Oh (2005).

	Positive	Disorganization	Negative
Executive function			
WCST		3, 5, 6, 9, 18, 19, 21, 22, 23, 24	4, 9, 12, 13, 17, 24
Verbal fluency[1]	9	2, 3, 9, 16	3, 4, 9, 12, 13, 16, 17, 19, 23
Stroop test	10	3, 10, 14, 22 ,26	3, 7
Trail Making Test-part B		3, 9, 18, 22, 23	4, 9, 13, 19, 23
Attentional Span			
Digits Forward		4, 18, 20, 22	8, 21
Corsi blocks		1	
Long-term memory			
General memory		15	13
Verbal memory	12	1, 8, 18, 25	12, 13, 17, 19
Visual memory		12, 13	8, 13, 17, 19
Other		2	1
Working memory		23, 24	23
General intellectual function			
Full scale IQ		13, 19	13
Verbal IQ		8	8
Performance IQ			17
Other IQ		2, 7, 8	1, 2, 7
Language		8	1
Visual/visuospatial function			11
Sustained attention		1, 2, 18, 21	2, 18, 19, 21

WCST: Wisconsin Card Sorting Test; Verbal fluency includes both semantic and/or phonetic cue.

1: Liddle (1987a)
2: Frith *et al*. (1991)
3: Liddle and Morris (1991)
4: Brown and White (1992)
5: Van der Does *et al*. (1993)
6: Bell *et al*. (1994b)
7: Brekke *et al*. (1995)
8: Cuesta and Peralta (1995)
9: Himelhoch *et al*. (1996)
10: Joyce *et al*. (1996)
11: Cadenhead *et al*. (1997)
12: Norman *et al*. (1997)
13: Basso *et al*. (1998)
14: Baxter and Liddle (1998)
15: Clark and O'carroll (1998)
16: Robert *et al*. (1998)
17: Mohamed *et al*. (1999)
18: Rowe and Shean (1997) / Eckman and Shean (2000)
19: O'Leary *et al*. (2000)
20: Tabarés *et al*. (2000)
21: Guillem *et al*. (2001)
22: Moritz *et al*. (2001)
23: Cameron *et al*. (2002)
24: Daban *et al*. (2002)
25: Roncone *et al*. (2002)
26: Woodward *et al*. (2003)

Dibben *et al.* (2009) examined these relationships more rigorously, using meta-analysis. They extracted data from 88 studies examining correlations between schizophrenic syndromes and performance on tests examining different aspects of executive function (the WCST and other set shifting tests, the Trail Making Test part B, verbal fluency, working memory and other tests such as dual task performance and multitasking). For all tests pooled, there

were significant correlations with negative symptoms (n=83, r=-0.21) and disorganization (n=40, r=-0.17), but not with reality distortion (n=34, r=0.01). This meta-analysis also provided support for there being partially different patterns of association with the different tests executive tests: negative symptoms were inversely correlated with verbal fluency at a significantly higher level than was disorganization (r=-0.27 v. -0.11, p<0.0001), whereas inhibition of automatic responses as measured with the Stroop Test showed the reverse pattern (r=-0.13 v. -0.29, p=0.0004).

1.6.1.2. Relationship to functional outcome

A separate body of literature has examined the relationship of cognitive impairment to functioning and functional outcome in schizophrenia. Green and co-workers, in different publications (Green, 1996; Green and Nuechterlein, 1999; Green *et al.*, 2000), have reviewed and meta-analyzed these studies. In a review of 37 studies, Green *et al*. (2000) concluded that there was evidence that verbal memory, vigilance and performance in the WCST appeared to be associated with functional outcome. Meta-analysis of selected studies in the same publication (188-1002 participants) supported the importance of the relationship between verbal memory and functional outcome. Furthermore, cognition was found to account for 20-60% of the variance in functional outcome in schizophrenia. A more recent meta-analysis on 48 studies comprising 2692 participants confirmed the association between several different areas of cognitive function and of functional outcome, with pooled correlations ranging from small (r=0.16 for attention/vigilance and community functioning) to medium ES (r=0.39 for attention/vigilance and social-skills) (Fett *et al.*, 2011).

Taking together the current scientific evidence, schizophrenic cognitive impairment -mainly memory and executive compromise- appears to be especially related to negative and disorganized symptoms but not to psychotic symptoms. At the same time cognitive deficits seem the most powerful clinical features that explain functional outcome in schizophrenia.

1.7. The neural basis of cognitive impairment in schizophrenia

Cognitive impairment in neurological disorders typically results from, and is related to the severity of, changes in brain structure and function. For example, the degree of cortical and hippocampal atrophy in Alzheimer's disease shows a clear relationship to the degree of cognitive impairment the patients show (Whitwell, 2010). Similarly, the extent and place of brain damage in patients with head injury determines the nature and extent of cognitive deficits the trauma causes (McDonald *et al.*, 2002). Functional brain changes without structural abnormality can also cause cognitive impairment, the obvious example being delirium (MacLullich *et al.*, 2009). In some circumstances, such as the cognitive impairment and dementia associated with Parkinson's disease, both structural and functional (neurochemical) factors may be important (Seppi and Schocke, 2005; Bohnen and Albin, 2011).

Schizophrenia is a disorder associated with both structural and functional brain changes. Here, however, the relationship of these changes to the cognitive impairment that also characterizes the disorder is unclear, and studies have had complex and contradictory findings.

1.7.1. Cerebral structure

Lewis (1990) reviewed studies which examined the association between the CT finding of lateral ventricular enlargement in schizophrenia, with cognitive impairment. He concluded that, although some studies reported an association, others did not, and overall there was no convincing evidence for a relationship.

Antonova *et al*. (2004) reviewed 34 papers and concluded that there was some evidence that whole brain volume, lateral ventricular volume, and frontal and temporal lobe volume reductions were associated with general intellectual impairment and/or specific neuropsychological deficits. However, they noted that there were conflicting findings in each case. Also, the numbers of studies were generally small, varying between eight for whole brain volume, seven for frontal lobe volume to 13 for temporal lobe volume. The findings were further complicated by sex differences in the associations found, and also by the existence of correlations between some volume measures and IQ in the controls but not in the participants with schizophrenia.

A more recent review on studies analyzing the relationship between ROI analysis and cognition in schizophrenia (Crespo-Facorro *et al*., 2007) reached similar conclusions. They included at least 36 studies, examining relationships between different measures of cognitive performance and several measures of brain volume -whole brain volume, different frontal regions, different temporo-hippocampal regions- parietal and occipital lobes, cerebellum, caudate nucleus, thalamus, and lateral ventricles- . The authors noted that “there are several and important methodological shortcomings in the revised literature”. For instance, “most of the studies published have posited to characterize the contributions of single brain regions to specific cognitive processes”. However, we know “that a

single cognitive deficit may result from alterations in different brain regions constituting the neural network associated to this specific cognitive process". They concluded that "...there is still a great need for more methodologically stringent investigations that would help in the advance of our understanding of the cognition/brain structure relationships in schizophrenia".

Some more recent studies have examined associations between brain structure and cognitive impairment using more recent voxel-based techniques. For example, Minatogawa-Chang *et al*. (2009) applied VBM to a large sample of patients with FE (*n*=88). They found that GM volume in the left anterior DLPFC, right inferior DLPFC, in the lateral parietal cortex bilaterally and in the left superior temporal cortex correlated with a composite score based on several attentional and executive tests. A similar pattern of correlations was found in the subgroup of 48 patients with a diagnosis of schizophrenia. Other studies examining correlations between cognitive function and brain structure as measured using VBM, however, have had negative findings (Bonilha *et al*., 2008; Wolf *et al*., 2008).

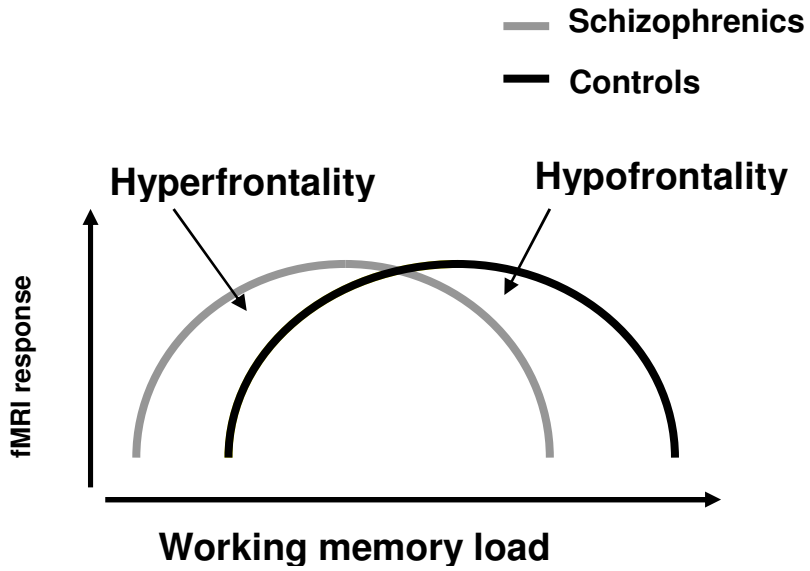
1.7.2. Cerebral functioning

In the first study to carry out functional imaging during performance of an executive task in schizophrenia, Weinberger *et al*. (1986) found that failure to activate in the DLPFC correlated with the degree of impairment the participants showed on the WCST. However, such an association was not found in two later studies which used executive (Frith *et al*., 1995) and memory (Fletcher *et al*., 1998) tasks. The relationship between frontal cortex activation and cognitive performance was subsequently investigated in two meta-analyses. Hill *et al*. (2004) examined the extent to which impairment on executive, memory or

vigilance tasks moderated the ES for hypofrontality during task performance in 14 studies (number of patients not stated). They found a trend level association (z=1.86, *p*=0.06) for poorer performance to be associated with greater hypofrontality. Van Snellenberg *et al*. (2006) meta-analyzed 30 fMRI studies which included 407 patients with schizophrenia and 393 controls. They found some evidence that DLPFC activation was lower in studies where schizophrenic patients showed impaired test performance. However, like in Hill *et al*.'s meta-analysis (2004), the correlation was only at trend level (*p*=0.09).

The 'hyperfrontality' recently documented in schizophrenia during performance of working memory and other executive tasks (see section 1522 above) has also been linked to cognitive impairment. Weinberger and co-workers (Weinberger *et al*., 2001; Tan *et al*., 2007) have argued that individuals with schizophrenia suffer from 'cortical inefficiency' and so have to 'work harder to keep up' with task demands. This leads to a compensatory functional response characterized by greater and/or wider activation of relevant cortical regions than in healthy subjects. Callicott *et al*. (2003) have elaborated this idea further, proposing that there is an inverted U-shaped function between working memory capacity and prefrontal cortex activation. In healthy subjects, increasing task demands are first associated with increasing activation, but this then falls off after the subject's working memory capacity is exceeded (see Figure 5). If, as a result of decreased cortical efficiency, this U-shaped curve were shifted to the left in schizophrenia, it would cause patients to show more activation than controls when tasks demands were low, but they would reach their point of maximum activation earlier, and thereafter would show less activation.

Figure 5. Model proposed by the group of Weinberger.



To date, only three studies have examined the relationship of increased prefrontal activation to cognitive impairment empirically, and these have not had clear findings. In a study comparing brain activations of 14 subjects with schizophrenia with 14 healthy comparison subjects during the performance of an n-back task, Callicott *et al*. (2003) found that seven schizophrenic patients who were low performers showed only hypofrontality when compared to the controls. In contrast, seven higher performing patients showed both hypo- and hyperfontality when compared to eight healthy controls who also showed good performance.

A later study from the same research group, which also used the n-back paradigm, had partially similar findings (Tan *et al*., 2006). They found that eight high performing participants with schizophrenia on the task showed hyperfrontality in the left ventral DLPFC cortex compared to 14 controls, whereas seven low performing patients showed both hyperfrontality in the left

ventral DLPFC and hypofrontality in the right DLPFC in comparison to 12 controls.

More recently, Karlsgodt *et al*. (2009) have found evidence of a more complicated pattern of brain activations related to task activation. They used a different paradigm, the Sternberg task, in which participants need to keep in mind a variable number of consonants presented at the same time and, seconds later, have to recognize whether further items were or not included among the former group. In the left DLPFC, both the patients and controls showed a pattern of increasing activation with increasing working memory load, which then decreased slightly at the highest levels. However, there was no clear evidence that the curve was shifted to the left in the patients, as the model of Weinberger's group suggested. Results were similar when the patient group was split into high- and low-performing groups, although the high-performing patients tended to show significantly higher activation than the control and the low performing patients at all levels of task difficulty in the left, but not in the right DLPFC.

1.7.3. Brain structural and functional change in studies examining groups of schizophrenic patients predefined for showing cognitive impairment

All the structural studies cited in the previous section used analysis of correlations to examine the question of the relationship between measures of global or regional brain volume and cognitive impairment in schizophrenia. This may not be the most appropriate strategy for determining whether or not there is an association, because brain volume is affected by a wide range of factors which are difficult to control for. In healthy subjects such factors include age,

sex and IQ. In schizophrenia, it is widely believed that illness factors other than cognitive impairment contribute to the degree whole brain or regional structural change. For example, at least some of the decrease in GM volume is considered to be 'neurodevelopmental' in origin, i.e. present before illness onset and not progressing (Pantelis *et al.*, 2003). Studies investigating the relationship between cognitive impairment and brain functional abnormality in schizophrenia have also relied heavily on correlational analyses; a few studies (Callicott *et al.*, 2003; Tan *et al.*, 2006; Karlsgodt *et al.*, 2009) have separated patient groups into low and high performers on the fMRI task used, but they have not examined cognitive impairment more generally.

An alternative strategy is to compare preselected groups of patients with and without cognitive impairment. This has the advantage of being able to eliminate other sources of variation in brain structure and/or function, such as age and estimated premorbid IQ. An additional advantage is that changes in structure and function which are due to schizophrenia and changes due to cognitive impairment complicating schizophrenia can be separated. Thus, brain changes attributable to schizophrenia without the complicating factor of cognitive impairment can be examined by contrasting a group of patients without moderate/marked cognitive impairment to healthy controls. In the same way, contrasting cognitively preserved and cognitively impaired groups of patients permits an assessment of changes due to cognitive impairment without the complicating factor of changes due to schizophrenia.

To date, only five studies have investigated the brain correlates of schizophrenic cognitive impairment using (or in one case approximating to)

such an approach. Four of these examined brain structural differences in cognitively impaired patients, and one examined brain functional differences.

de Vries *et al*. (2001) studied eight non-elderly patients with chronic schizophrenia who also met criteria for dementia in the absence of any neurological cause for this. They did not include a group of schizophrenic patients without cognitive impairment, but structural scans (CT and/or MRI) were compared to a database of 251 unselected patients with schizophrenia. All of the patients were found to be in the range of ventricular enlargement or sulcal widening found in schizophrenia in general.

Rüsch *et al*. (2007) used VBM to compare 21 participants with schizophrenia who showed impaired performance in the WCST with 30 who had preserved performance. The two patient groups were comparable in age, gender and handedness, but had a different educational status. Both groups also differed in the MMSE and in the Digits Backward test, but not in Digits Forward nor in Spatial Span Forward or Backward. Using a mask covering all subregions of the frontal lobes, they found that the schizophrenia group with a low performance on the WCST showed a lower volume in the DLPFC and the anterior cingulate cortex bilaterally.

Wexler *et al*. (2009) divided a sample of participants with schizophrenia into 'cognitively nearly normal' and 'cognitively impaired' subgroups depending on their performance on a set of four attention and working memory tests. Thirty healthy controls were also examined. The cognitively preserved participants (n=21) performed less than 0.5SD below the healthy controls. The mean score of the impaired group (n=54) was 1SD below that of the healthy controls. All three groups were comparable for age but differed partially in gender, years of

education and ethnicity. Structural MRI was carried out examining lateral ventricular volume and GM and WM volumes in the right and left frontal, temporal, parietal and occipital regions. The cognitively impaired participants showed similar degrees of lateral ventricular enlargement and GM volume reduction to the cognitively near-normal cases. However, the impaired patients showed significantly smaller WM volumes than the cognitively near-normal patients in two (sensorimotor and parieto-occipital) out of the eight cerebral regions examined), with a trend towards significant reduction in a third (inferior occipital). There were no differences between the near-normal and impaired patients in hippocampal, thalamic and cerebellar volume.

Cobia *et al*. (2011) carried out cortical thickness analysis in 45 cognitively nearly-normal schizophrenia participants, 34 cognitively impaired participants with the disorder and 65 healthy comparison subjects. All three groups were comparable in age and gender but differed in parental educational status and in ethnic origin. The two patient groups were separated based on a cluster analysis of their performance on a set of tests of reasoning, declarative and semantic memory, attention and executive function. No clusters of significant difference were found between the two patient groups, when a false discovery rate correction for multiple comparisons was employed. However, at an uncorrected level of significance, the impaired group showed more evidence of cortical thinning than the preserved group, which was most pronounced in lateral occipital and medial temporal cortices.

In the only study to examine groups of schizophrenic patients with and without cognitive impairment at the level of functional imaging, Fletcher *et al*. (1998) compared a group of six patients who showed performance in the

normal range on a memory battery (the Rivermead Behavioural Memory Test, RBMT), with six patients who all performed in the impaired or very impaired range on this test battery. Seven healthy controls were also examined. All three groups were comparable in terms of gender, age and estimated premorbid IQ. The three groups underwent functional imaging with PET while they remembered word lists of varying length, from one to 12 words. The controls showed a pattern of increasing activation in the left DLPFC as the task demand increased, but both groups with schizophrenia failed to do so, with no differences between them.

In summary, studies comparing predefined groups of schizophrenic patients with and without cognitive impairment appear to have scope for resolving the question of the relationship of cognitive impairment to structural and functional brain abnormality that also characterizes the disorder. However, to date, these studies have not resulted in a consensus. Several of the studies examining structural differences have failed to find evidence of marked differences, although more subtle differences have been found in some of them. The findings of functional studies are currently conflicting.

2. Hypothesis and objectives of the thesis

Hypothesis

According to the literature reviewed, our general hypothesis is that the cognitive deficits of schizophrenic patients are reflected in both structural and functional brain changes. Accordingly, we expect that patients with cognitive impairment will have more GM reductions and more dysfunctional patterns of brain activity than patents without such deficits.

Objectives

The objective of this study was to further investigate the brain correlates of schizophrenic cognitive impairment using a design of comparing groups of schizophrenic patients preselected for showing and not showing a marked cognitive impairment. Specifically, the aims were:

1. to investigate the relationship between brain structural changes and the cognitive impairment of schizophrenic patients.
2. to determine whether cognitive impairment of schizophrenic patients is specifically associated with brain functional changes.
3. to investigate the role of task-related de-activations in cognitive impairment.

Two principal predictions were established:

1. No significant structural differences will be found between patients with schizophrenia who show moderate/marked cognitive impairment compared to patients without moderate/marked cognitive impairment. This will apply to brain volumetric measures (i.e. whole brain volume, lateral ventricular volume, GM and WM volume) as well as to volumetric differences found using VBM.

2. Schizophrenic patients with moderate/marked cognitive impairment will not show significantly different patterns neither of activation in the DLPFC and other areas of the so-called working memory network nor in task-related de-activations compared to those patients without moderate/marked cognitive impairment during performance of the n-back working memory task.

3. Methods

3.1. Participants

The schizophrenia total sample consisted of two groups of adults with schizophrenia. One group (*n*=26) was selected for showing moderate/marked cognitive impairment and the other (*n*=23) was selected for not showing this, as defined below. The participants were recruited from long stay wards (*n*=15), and acute and subacute units (*n*=25), although a minority were out-patients/day hospital attenders (*n*=9).

Inclusion criteria were:

1. Age 18-65.
2. meeting DSM-IV (APA, 1994) criteria for schizophrenia.
3. Chronic illness, defined as duration >2 years from first overt psychotic symptoms.
4. Premorbid intellectual function in the normal range (see exclusion criteria 3 below).
5. Right handedness. This was to ensure homogeneity in the functional imaging part of the study.
6. Relatively stable clinical condition at the time of testing (i.e. outside a period of acute relapse or exacerbation of chronic symptoms).

Exclusion criteria were:

1. History of brain trauma or neurological disease.
2. Alcohol/substance abuse within 12 months prior to participation.
3. History of learning disability. This was determined based on attendance at a special school. Additionally, in cases where the estimated premorbid IQ measure was found to be low, relatives were interviewed.

All patients were interviewed and their casenotes were reviewed to establish the diagnosis. All were taking antipsychotic medication (atypical *n*=28, typical *n*=7, both kinds *n*=14).

The control group consisted of 39 healthy individuals. They were recruited from non-medical staff working in the hospital, their relatives and acquaintances, plus independent sources in the community. They were questioned and excluded if they reported a history of mental illness and/or treatment with psychotropic medication. The controls met the same exclusion criteria and were selected to be comparable to both groups with schizophrenia in terms of age, sex and premorbid IQ.

All participating subjects gave written informed consent. This research was designed and developed in accordance with the principles of the Declaration of Helsinki for ethical medical research involving human subjects (http://www.wma.net/en/30publications/10policies/b3/index.html). The Research committee of Benito Menni CASM Psychiatric Hospital (Sant Boi de Llobregat) approved the research protocol (see annex 3). Prior to taking part, subjects were informed of the aims of the study, and of their freedom to participate or not, and their right to leave the study at any time. They were informed that their decision would not influence the medical care they received.

3.1.1. Selection of patients according to presence and absence of moderate/marked cognitive impairment

Presence of cognitive impairment was defined on the basis of performance on two batteries of memory and executive function, the RBMT (Wilson *et al.*, 1985) and the Behavioural Assessment of the Dysexecutive Syndrome (BADS) (Wilson *et al.*, 1996). Both these tests have extensive

normative data for adults, and thresholds for levels of normal and impaired performance have been established.

The RBMT consists of 12 subtests examining different aspects of memory, including recall, recognition, orientation and prospective memory -the ability to remember to do things. Scores can be combined into an overall 'screening' score. The Spanish translation of the test (Mozaz, 1991), which has shown to discriminate among different populations of cognitively preserved and impaired participants as well as traditional memory tests do (Pérez and Godoy, 1998), was used. The subtests are summarised in Table 3.

The BADS is a wide-ranging battery of executive tests which has been standardized on groups of normal subjects and patients with head injury. Its reliability and validity has been shown in Spanish healthy subjects and patients with schizophrenia (Vargas *et al.*, 2009). Performance on the individual tests can be combined to give an overall 'profile' score which can also be adjusted for age (the standardized score). Table 4 presents a description of the subtests included in this battery.

Table 3. Subtests included in the RBMT and description, including the cognitive domains assessed by each test.

Name of the task	Description
Remembering a name	Verbal recall: The subject is told the name of a person shown in a picture and has to remember it approximately 20 minutes later.
Remembering a hidden belonging	Prospective memory: When the examiner says 'We have finished this test', the subject has to remember to ask for something they own which was previously hidden by the examiner.
Remembering an appointment	Prospective memory: The subject has to remember to ask when the next appointment is when a bell rings.
Remembering a newspaper article	Verbal recall: The subject is read a short news item and has to reproduce it immediately and after a delay.
Face recognition	Non-verbal recognition: The subject is shown five photos of faces and immediately afterwards has to recognize them from 10 consecutively presented photos.
Picture recognition	Non-verbal recognition: The subject is shown 10 drawings of animals and objects and immediately afterwards has to identify them from 20 consecutively presented pictures.
Remembering a route	Non-verbal recall: The subject watches the examiner follow a route and has to reproduce it, immediately and after a delay.
Delivering a message	Prospective memory: During the route task, the subject has to remember to pick up and leave an envelope.
Orientation	Orientation for time, place and current events.
Date	Orientation for time.

Table 4. Subtests included in the BADS and description, including the cognitive domains assessed by each test.

Name of the task	Description
Rule Shift Cards	Test using playing cards which examines flexibility and ability to shift cognitive set.
Action Program Test	Requires devising a strategy to remove a cork from a container, using simple tools such as iron stick and water.
Key Search Test	Requires devising an efficient plan to search a field for a lost object.
Temporal Judgment Test[1]	Estimation of the time taken to perform certain activities which the subject is unlikely to know the exact answer to, such as how long it takes to boil an egg.
Zoo Map Test	Requires strategic planning of a route in around a diagram of a zoo, while abiding by certain rules.
Modified Six Elements Test	Multitasking ability: The subject has to carry out parts, but not all, of six different activities according to a set of rules and with time constraints..

[1] Variant of the Cognitive Estimation Test (Shallice and Evans, 1978).

To determine whether this method of dividing patients into cognitively preserved and cognitively impaired categories also separated then on wider aspects of cognitive function, a separate study was carried out on 22 healthy subjects, 25 cognitively preserved patients with schizophrenia and 29 cognitively impaired patients with schizophrenia, defined according to the same criteria. The findings of this study are reported in detail in Annex 2. Briefly, however, it was found that the cognitively preserved patients had numerically lower, but mostly not significantly lower test scores on a battery of tests of executive function, memory, language and visual/visuospatial function than the healthy controls (significant differences just on 1 out of 16 tests). In contrast, the cognitively impaired patients scored significantly lower than the cognitively preserved patients on almost all tests (14 out of 16 tests).

3.2. Psychopathological assessment

Psychopathology was assessed with the Spanish version of the Positive and Negative Syndrome Scale -PANSS- (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. Scores for positive, negative and disorganization symptoms were calculated based on factor analytic studies of the PANSS (Bell *et al.*, 1994a; Lindenmayer *et al.*, 1995; Lee *et al.*, 2003).

Overall severity of illness was assessed using the Clinical Global Impression -CGI- (NIMH, 1976). The CGI scores severity according to seven levels, from one (normal) to seven (very severe illness).

3.3. Cognitive assessment

Premorbid IQ was estimated using the Word Accentuation Test (TAP) (Del Ser *et al.*, 1997). 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 used in the USA (Jastak and Wilkinson, 1984). These latter two 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 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 WASI scale (Wechsler, 1999), which is an abbreviated version of the WAIS-III validated for the English-speaking population.

3.4. Statistical analysis of the demographic, psychopathological and the cognitive data

Statistical analyses on demographic, psychopathological and cognitive data were carried out using the SPSS statistical software for Windows (version 15). Demographic data were compared using appropriate tests (χ^2, Mann-Whitney's U-tests, t-tests and ANOVA). In some cases, however, variables were transformed (e.g. through a log transformation) if data were heterogeneous, in order to stabilize variances or improve shape of the distribution (Howell, 1997).

All the analyses on demographic, psychopathological and the cognitive data were done for all subsamples used for the different neuroimaging subsets of the study.

3.5. Neuroimaging procedure

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

3.5.1. Structural neuroimaging

3.5.1.1. Image acquisition

High resolution structural T1 MRI data were acquired with the following acquisition parameters: Matrix size 512x512; 180 contiguous axial slices; slice thickness of 1 mm, slice gap of 0 mm; voxel resolution 0.47x0.47x1 mm^3; echo time (TE) = 3.93 ms, repetition time (TR) = 2000 ms and inversion time (TI) = 710 ms; flip angle 15º.

3.5.1.2. Brain volume analysis

Calculation of the total volume of GM and WM brain volume (normalised for participant's head size) was performed with SIENAX (Smith, 2002), part of FSL -FMRIB Software Library, Oxford www.fmrib.ox.ac.uk/fsl/- (Smith *et al.*, 2004).

Lateral ventricle volume (also normalised for participant's head size) was computed via the FreeSurfer software -http://surfer.nmr.mgh.harvard.edu/fswiki/ (Dale *et al.*, 1999). The reliability of this method has been shown to be comparable to that between two manual raters (Fischl *et al.*, 2002).

The brain volume measures were compared using parametric statistics (ANOVA and independent two-sample t-test), since all data were interval and were checked to follow a normal distribution.

3.5.1.3. VBM analysis

Structural data were analyzed with FSL-VBM, an optimized VBM style analysis (Ashburner and Friston, 2000; Good *et al.*, 2001) carried out with FSL tools; this yields a measure of difference in local GM volume. First, structural

images were brain-extracted (Smith, 2002). Next, tissue-type segmentation was carried out. The resulting GM partial volume images were then linearly aligned to MNI 152 standard space (Jenkinson and Smith, 2001; Jenkinson *et al.*, 2002), followed by nonlinear registration. The resulting images were averaged to create a study-specific template, to which the native GM images were then non-linearly re-registered. The registered partial volume images were then modulated by dividing by the Jacobian of the warp field. The modulated segmentated images were then smoothed with an isotropic Gaussian kernel with a sigma of 4mm (technical details are shown in www.fmrib.ox.ac.uk/fsl/fslvbm/).

All comparisons were carried out with permutation-based non-parametric tests. These were made with the randomise function implemented in FSL, using the recently developed threshold-free cluster-enhancement method with 10000 iterations.

A VBM analysis of WM volume was also carried out. Since the VBM analysis in FSL has only been validated for GM, the VBM5 (http://dbm.neuro.uni-jena.de/vbm/vbm5-for-spm5/), a toolbox based on the Statistical Parametric Mapping (SPM) software package (SPM5 version), was used. The following standard pre-processing steps were carried out: tissue-type segmentation; normalisation (warping) to standard space of the obtained WM images; and modulation. The resulting images were then smoothed with an isotropic Gaussian kernel with a sigma of 4 mm. Statistical analyses were carried out using the general linear model (GLM) with correction using the theory of Gaussian random fields.

All statistical tests in the VBM analyses were performed with a statistical threshold of $p<0.05$, corrected for multiple comparisons.

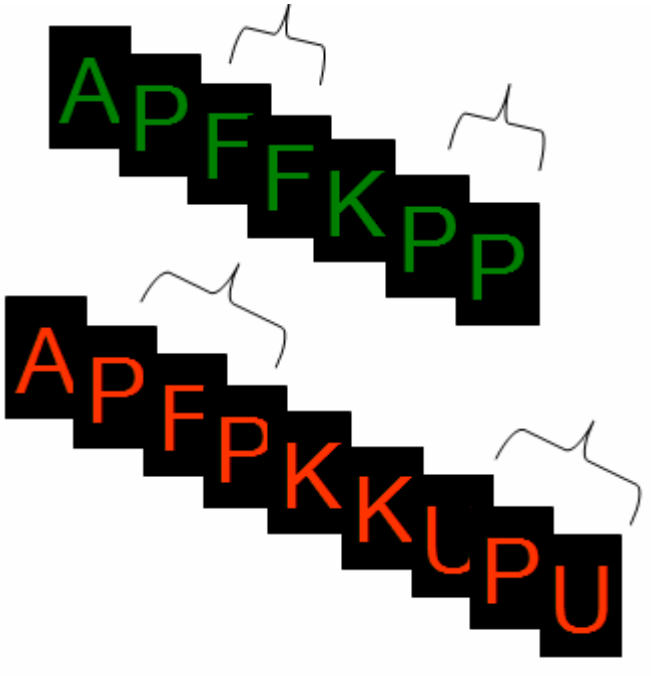
3.5.2. Functional neuroimaging

3.5.2.1. 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 (Lezak *et al.*, 2004). 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 letters in-between, whereas in the 2-back task there was one letter between the model and the goal letter (see Figure 6).

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



Each block consisted of 24 letters which were shown every two seconds (1 second on, one second off) and all blocks contained five repetitions (1-back and 2-back depending on the block) located randomly within block. Individuals had to detect these repetitions and respond by pressing a button. In order to identify which task had to be performed, characters were shown in green in the 1-back blocks and in red in the 2-back blocks. 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 seconds. All individuals went through a training session before entering the scanner.

Participants' performance was measured using the signal detection theory index of sensitivity (d') of ability to discriminate targets from non-targets (Green and Swets, 1966). Higher values of d' indicate better ability to

discriminate between targets and distractors. Subjects who had 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 it, were a priori excluded from the study.

3.5.2.2. Image acquisition

In each individual scanning session 266 volumes were acquired. A gradient echo echo-planar sequence depicting the BOLD contrast was used. Each volume contained 16 axial planes acquired with the following parameters: TR = 2000 ms, TE = 20 ms, flip angle = 70 degrees, 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.

3.5.2.3. fMRI analysis

fMRI image analyses were performed with the FEAT module, included in FSL software (Smith *et al.*, 2004). Pre-processing with FSL-FEAT included: a) motion correction (Jenkinson *et al.*, 2002); b) non-brain removal (Smith *et al.*, 2002); c) isotropic 5mm-FWHM Gaussian smoothing; d) high-pass temporal filtering; e) time-series statistical analysis with local autocorrelation correction (Woolrich *et al.*, 2001); and f) registration to the MNI 152 standard space (Jenkinson and Smith, 2001; Jenkinson *et al.*, 2002). The motion correction generates movement parameters that were used as a covariate in the individual analysis. To minimize unwanted movement-related effects, participants with an estimated maximum absolute movement >3.0 mm or an average absolute movement >0.3 mm were excluded from the study.

At a first level, images were corrected for movement. The temporal derivate of the blocked experimental design was added as a covariate in order

to minimize possible movements due to the presentation of the stimuli. In addition, the motion parameters generated during the pre-processing were also added as a covariate. Images were also eventually coregistered to a common stereotaxic space (MNI template).

GLMs were fitted to generate the individual activation maps for three different contrasts. The first contrast was baseline vs 1-back; the second contrast was baseline vs 2-back; and the third contrast was 2-back vs 1-back.

Differences in fMRI activation maps between patients and controls were performed within the FEAT module, with mixed effects GLM models (Beckmann *et al.*, 2006). FEAT uses the Gaussian Random Field theory to properly account for the spatially distributed patterns when performing statistical tests. Specifically, the analyses were performed with the FLAME stage 1 with default height threshold ($z > 2.3$) (Woolrich *et al.*, 2001; Beckmann *et al.*, 2003) and a p-value < 0.05 corrected for multiple comparisons (Worsley, 2001; Woolrich *et al.*, 2004).

A supplementary analysis was carried out which examined the effect of increasing working memory load on the differences between the healthy comparison group and the cognitively preserved schizophrenia group and between both schizophrenia groups. To do this, models were fitted that assume a linear relationship through the baseline, 1-back and 2-back levels of the task, thus reporting significant differences on regression slopes between these groups.

4. Results

4.1. Structural neuroimaging findings

4.1.1. Samples characteristics of the structural neuroimaging study

All the patients and all the controls participated in this part of the study.

The three subject groups (controls and two patient samples) were comparable for age, sex and estimated premorbid cognitive functioning as measured with the TAP (see Table 5).

The cognitively impaired group had a lower current WAIS-III full scale IQ and performance IQ compared to both the cognitively preserved patients and the healthy controls. The two latter groups did not differ on any WAIS-III scale (see Table 5).

As can be seen from Table 5, the two schizophrenia groups did not differ in overall severity of illness as measured by the CGI; however cognitively impaired individuals with the disorder had significantly higher total symptom scores on the PANSS; this was due to the fact that the subsample with impaired cognition presented significantly more negative and disorganized symptomatology than the subsample with schizophrenia and no marked cognitive compromise. The former group also had a significantly longer duration of illness and showed trend level higher mean dosages of antipsychotic drugs than the latter group.

Table 5. Demographic, cognitive and psychopathological characteristics of the participants with schizophrenia and controls in the structural neuroimaging study.

	Controls (*n*=39)	Participants with schizophrenia (*n*=49)		Group statistics
		Preserved (*n*=23)	Impaired (*n*=26)	
Age	40.10 (11.58)	40.10 (10.22)	42.38 (8.23)	F=0.45 *p*=0.64
Sex (M/F)	30/9	17/6	20/6	χ^2=0.85 *p*=0.96
TAP estimated IQ[1]	102.22 (10.21)	103.54 (8.37)	98.36 (10.90)	F=1.83 *p*=0.17
Total IQ (WAIS-III)	103.49 (13.13)	100.43 (13.04)	92.73 (13.43)	F=5.26 ***p*=0.01** **I<C** (t=3.21; *p*=0.002) **I<P** (t=2.03; *p*=0.048)
Verbal IQ (WAIS-III)	104.90 (16.73)	104.00 (17.65)	96.85 (15.93)	F=1.97 *p*=0.15
Performance IQ (WAIS-III)	100.08 (17.59)	94.00 (14.61)	84.54 (16.56)	F=6.87 ***p*=0.002** **I<C** (t=3.57; *p*=0.001) **I<P** (t=2.11; *p*=0.04)
BADS profile score	-	16.04 (2.40)	10.69 (4.33)	t=5.43 ***p*<0.001**
RBMT screening score	-	9.48 (1.44)	5.17 (1.63)	t=9.58 ***p*<0.001**
Years of illness	-	18.28 (10.02)	23.76 (8.29)	t=-2.09 ***p*=0.04**
PANSS total score	-	66.57 (17.11)	76.15 (15.03)	t=-2.09 ***p*=0.04**
Positive Syndrome (PANSS)	-	15.09 (5.02)	16.15 (5.90)	t=-0.68 *p*=0.50
Negative Syndrome (PANSS)	-	13.91 (6.08)	17.46 (4.39)	t=-2.36 ***p*=0.02**
Disorganized Syndrome (PANSS)	-	7.39 (2.64)	10.42 (3.46)	t=-3.73 ***p*=0. 001**[2]
CGI score	-	4.13 (1.36)	4.58 (0.90)	M-W U=232.00 *p*=0.16
Antipsychotic dosage (CPZ equivalent mg)	-	663.41 (550.94)	985.34 (608.59)	t=-1.93 *p*=0.06

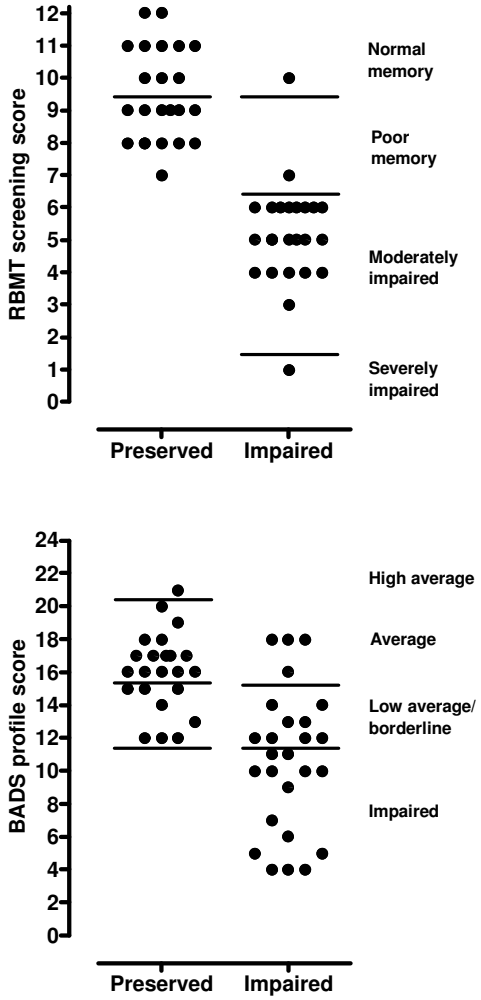
[1]One cognitively preserved patient had missing data for this analysis.

[2] After $\log^{10}$ transformation.

As expected, the two schizophrenia groups differed in their performance on the BADS and RBMT. The means and standard deviations are shown in Table 5; a scatter plot of the two groups' scores is shown in Figure 7, together with cut-offs for different levels of performance derived from the normative data

for healthy, non-elderly adults available for each test. It can be seen that all the preserved individuals fell into the 'normal' or 'poor (normal) memory' range on the RBMT and in the 'high average', 'average', 'low average' or 'borderline' ranges on the BADS. All but two of the cognitively impaired patients fell into the moderately impaired or severely impaired range on the RBMT (in accordance with the selection criteria the two patients who scored in the normal memory range in the RBMT scored in the impaired range on the BADS). The range of scores among the cognitively impaired patients on the BADS was wider, with 12/26 patients scoring in the 'average', 'low average' or 'borderline' ranges. All of these patients scored in the moderately impaired range on the RBMT.

Figure 7. Scatterplot of the cognitively preserved and cognitively impaired participants' scores on the RMBT and the BADS. Data form the subsamples of the structural MRI study.



4.1.2. Brain and lateral ventricular volume measures

All subjects of the structural neuroimaging study were included in the analysis except in the comparison of lateral ventricles, where one control had to be excluded for technical reasons (in this case, the automatic segmentation process gave a result which was not reconcilable with visual inspection).

A preliminary comparison of the whole group of schizophrenia patients with the controls revealed that the patients showed significantly reduced whole

brain volume (t=3.74, $p<0.001$), significantly reduced GM volume (t=4.19, $p<0.001$) and significantly larger lateral ventricles (t=-2.20, $p=0.03$). There was no difference in WM volume between the patients and the controls (t=1.32, $p=0.19$), although the schizophrenia patients showed a numerically smaller mean volume (see Table 6).

Table 6. Whole brain and lateral ventricular volume measures (cm^3) in the controls and in the combined schizophrenia group.

	Controls (*n*=39)	Schizophrenia group (*n*=49)	Statistics
Whole brain	1256.75 (47.69)	1485.92 (53.36)	t=3.74, ***p*<0.001**
GM	819.46 (35.339)	785.75 (39.09)	t=4.19, ***p*<0.001**
WM	707.29 (25.62)	700.17 (24.71)	t=1.32, *p*=0.19
Lateral ventricles[1]	12.58 (7.24)	16.74 (10.47)	t=-2.20, ***p*=0.03**

[1]One control was excluded from the analysis.

4.1.2.1. Controls vs cognitively preserved patients

The previously found differences in whole brain volume and GM volume remained evident when the controls were compared only to the cognitively preserved patients (whole brain: t=2.62, $p=0.01$) (GM: t=2.83, $p=0.006$) (see Table 7). The cognitively preserved patients continued to show a larger lateral ventricular volume than the controls, but the difference no longer reached significance (t =71.25, $p=0.22$).

Table 7. Whole brain and lateral ventricular volume measures (cm^3) in the controls, and in the cognitively preserved and cognitively impaired schizophrenia groups.

	Controls (*n*=39)	Preserved (*n*=23)	Impaired (*n*=26)	ANOVA
Whole brain	1526.75 (47.69)	1488.82 (65.92)	1483.35 (40.36)	F=6.98 ***p*=0.002** **P<C** (t=2.62; *p*=0.01) **I<C** (t=3.82; *p*<0.001)
GM	819.46 (35.39)	789.55 (47.52)	782.38 (30.36)	F=8.94 ***p*<0.001** **P<C** (t=2.83; *p*=0.01) **I<C** (t=4.37; *p*<0.001)
WM	707.29 (25.62)	699.27 (29.79)	700.96 (19.74)	F=0.89 *p*=0.41
Lateral ventricles[1]	12.58 (7.24)	15.95 (12.49)	17.44 (8.49)	F=2.95 *p*=0.06 **I>C** (t=-2.59; *p*=0.01)

[1]One control was excluded from the analysis.

4.1.2.2. Cognitively preserved vs cognitively impaired patients

As shown in Table 7, the differences between the two patient groups were small and non-significant on all three measures (whole brain: t=0.36, *p*=0.72; GM: t=0.62, *p*=0.54; lateral ventricular volume: t=0.92, *p*=0.36).

4.1.3. VBM

4.1.3.1. Controls vs cognitively preserved participants with schizophrenia

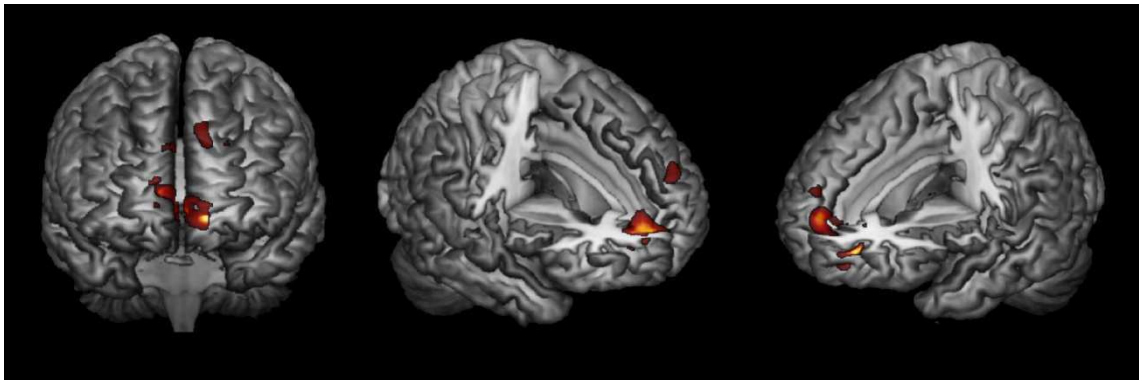
The cognitively preserved patients with schizophrenia showed significantly smaller GM volume than the controls in one cluster. This was situated anteriorly and medially, extending from the orbital and medial prefrontal cortex to the anterior cingulate gyrus [2190 voxels, *p*=0.04; peak activation in BA10, left medial orbitofrontal cortex, MNI (-12, 44, -8), z score=4.7]. Peak

values in each anatomical region are shown in Table 8, and a rendering of the cluster on a 3D brain is shown in Figure 8.

Table 8. Significant cluster and the corresponding peak values in each anatomical region where cognitively preserved individuals with schizophrenia show a significant decrease in GM volume, when compared to controls, using VBM.

Cluster 1 2190 voxels	*p*=0.04				
	BA	Z	x	y	z
Medial and orbitofrontal cortex					
Left medial orbitofrontal cortex	10	4.70	-12	44	-8
Right medial orbitofrontal cortex	10	3.12	11	50	0
Left anterior cingulate	11	3.98	-10	38	-6
Right anterior cingulate	11	2.99	6	34	-6
Left superior medial frontal cortex	10	2.90	0	62	28
Right superior medial frontal cortex	10	3.83	13	51	6

Figure 8. Brain regions showing significant GM volume reduction in cognitively preserved individuals with schizophrenia compared to healthy controls.



The appearance as separate clusters is artefactual, due to the irregular shape of the extended single cluster.

There were no regions where the cognitively preserved participants showed significantly greater volume than the controls.

No areas of significant WM volume difference were found between the controls and the cognitively preserved participants with the disorder.

4.1.3.2. Cognitively preserved vs cognitively impaired participants with schizophrenia

There were no areas of significant GM or WM volume difference between both schizophrenia groups.

4.2. Functional imaging findings

4.2.1. Sample characteristics of the fMRI study

This part of the study included 19 cognitively impaired, 18 cognitively preserved patients with schizophrenia and 34 healthy controls. Not all the study participants could be included in the fMRI part of the study, either because the images were not usable because of excessive movement (*n*=6) or because the images were not acquired for technical reasons (*n*=5). Two participants could not tolerate the fMRI procedure. Additionally, four controls were removed in order to maintain matching for age, sex and estimated premorbid intellectual functioning among the three groups (see Table 9).

Sociodemographic, psychopathological and cognitive data of the sample characteristics of the fMRI study are shown in Table 9. The cognitively impaired group had a lower current WAIS-III full scale IQ and performance IQ compared to the healthy controls. No other differences concerning IQ were statistically significant, although the IQ measures were numerically higher for the controls than for both patients' groups in all cases and for the cognitively preserved patients compared to the cognitively impaired.

As can be seen from Table 9, the two schizophrenia groups did not differ in overall severity of illness as measured by the CGI and in overall symptom scores as measured with the PANSS. However, similar to the sample as a

whole, the subsample with impaired cognition presented significantly more negative and disorganized symptomatology than the subsample without marked cognitive compromise. The two schizophrenia groups did not differ on duration of illness or on mean dosages of antipsychotic drugs.

Among the patients with schizophrenia, there were no significant differences between those who took part in this part of the study and those who did not, for age (41.07 vs 42.05; p=0.69), sex (29 male/8 female vs 8/4; p=0.41) or TAP score (22.03 vs 22.83; p=0.79).

Table 9. Mean values, standard deviations and statistical results of demographic, cognitive and psychopathological characteristics of the fMRI sample.

	Controls (*n*=34)	Participants with schizophrenia (*n*=37)		Group statistics
		Preserved (*n*=18)	Impaired (*n*=19)	
Age	40.90 (11.80)	40.49 (10.58)	41.62 (7.94)	F=0.06 *p*=0.95
Sex (M/F)	26/8	14/4	15/4	χ^2=0.04 *p*=0.98
TAP estimated IQ[1]	102.22 (10.46)	103.01 (7.75)	97.95 (9.81)	F=1.55 *p*=0.25
Total IQ (WAIS-III)	104.24 (12.47)	100.44 (13.99)	94.11 (9.37)	F=4.24 ***p*=0.02** **I<C** (t=3.08; *p*=0.003)
Verbal IQ (WAIS-III)	105.44 (16.06)	103.06 (19.07)	96.58 (10.86)	F=1.95 *p*=0.15
Performance IQ (WAIS-III)	100.85 (18.19)	94.67 (15.68)	86.74 (17.08)	F=4.09 ***p*=0.02** **I<C** (t=2.77; *p*=0.01)
BADS profile score	-	16.06 (2.69)	11.58 (4.26)	t=3.80 ***p*=0.001**
RBMT screening score	-	9.72 (1.36)	5.56 (1.46)	t=8.84 ***p*=0.001**
Years of illness	-	18.44 (10.86)	22.71 (7. 17)	t=-1.39 *p*=0.18
PANSS total score	-	67.89 (18.33)	76.79 (17.04)	t=-1.53 *p*=0.14
Positive Syndrome (PANSS)	-	15.44 (5.47)	16.37 (5.90)	t=-0.49 *p*=0.63
Negative Syndrome (PANSS)	-	14.17 (6.13)	17.89 (4.15)	t=-2.16 ***p*=0.04**
Disorganized Syndrome (PANSS)	-	7.67 (2.85)	10.74 (3.71)	t=-2.81 ***p*=0. 01**
CGI score	-	4.28 (1.41)	4.58 (1.02)	M-W U=146.50 *p*=0.44
Antipsychotic dosage (CPZ equivalent mg)	-	688.22 (603.25)	913.50 (507.21)	t=-1.23 *p*=0.23

[1]One cognitively preserved participant had missing data for this analysis.

4.2.2. Behavioural performance

The cognitively preserved individuals were significantly impaired compared to the controls on the 1-back version of the task (mean d'=3.77, SD=0.91 vs mean d'=4.40, SD=0.65; t=2.90, *p*=0.01) and on the 2-back version (mean d'=2.67, SD=0.87 vs mean d'=3.27, SD=0.96; t=2.22, *p*=0.03). The cognitively impaired patients were also impaired compared to the controls in both versions of the task (1-back: mean d'=3.07, SD=1.16 vs mean d'=4.40, SD=0.65; t=5.36, *p*<0.001; 2-back: mean d'=1.89, SD=0.68 vs mean d'=3.27, SD=5.57; t=2.22, *p*<0.001).

The cognitively impaired participants with schizophrenia were marginally significantly impaired compared to the cognitively preserved ones on the 1-back task (mean d'=3.07, SD=1.16 vs mean d'=3.77, SD=0.91; t=2.03, *p*=0.05), and significantly impaired on the 2-back task (mean d'=1.89, SD=0.68 vs mean d'=2.67, SD=0.87; t=3.06, *p*=0.004).

4.2.3. fMRI findings: controls vs cognitively preserved patients

The cognitively preserved participants showed no areas of significantly reduced activation relative to the controls in the 1-back vs baseline contrast. In the 2-back vs baseline contrast the controls activated more than the cognitively preserved individuals only in the cerebellum [1606 voxels, $p=8.27 \times 10^{-5}$; peak activation in vermis, MNI (1, -53, -28), z score=4.52] (see Table 10). No areas of significant difference were seen in the 2-back vs 1-back contrast.

Table 10. Significant clusters and corresponding peak values in each anatomical region in the 2-back versus baseline contrast.

Control>Preserved						
Cluster 1	1606 voxels	p=8.27x10^{-5}				
Cerebellum			Z	x	y	z
Vermis			4.52	1	-53	-28
Right cerebellum			4.48	12	-58	-24
Left cerebellum			3.93	-20	-62	-28
Preserved>Control						
Cluster 1	3878 voxels	p=1.72x10^{-9}				
Medial and orbitofrontal cortex		BA	Z	x	y	z
Left gyrus rectus		11	4.52	0	26	-14
Right gyrus rectus		11	3.93	3	33	-14
Left anterior cingulate		11	4.49	-2	32	-6
Right anterior cingulate		11	4.07	1	32	-6
Left medial orbitofrontal cortex		11	3.64	-11	53	-8
Right medial orbitofrontal cortex		11	4.40	0	32	-8
Cluster 2	629 voxels	p=0.0425				
		BA	Z	x	y	z
Right insula		48	4.13	42	-8	-6
Temporal lobe						
Right middle temporal gyrus (Temporal pole)		36	3.57	30	10	-40
Right superior temporal gyrus (Temporal pole)		20	3.34	38	10	-28
Right hippocampus		20	3.19	34	-11	-19
Preserved>Impaired						
Cluster 1	1749 voxels	p=2.94x10^{-5}				
		BA	Z	x	y	z
Right DLPFC						
Right inferior frontal gyrus (Pars triangularis)		48	3.93	38	28	26
Right middle prefrontal cortex		46	3.27	38	29	34
Right inferior frontal gyrus (Pars opercularis)		6	3.57	56	12	12
Right perirolandic regions						
Right rolandic operculum		6	3.47	58	6	12
Right precentral gyrus		6	3.39	49	0	24

In this analysis, there were also areas where the cognitively preserved patients showed higher activation relative to the controls. These clusters were seen in both the 2-back vs baseline and the 2-back vs 1-back contrasts. In the 2-back vs baseline contrast, there were two clusters of significant difference: one involved parts of the medial and inferior orbital prefrontal cortex, extending to the anterior cingulate cortex [3878 voxels, p=1.72x10^{-9}; peak activation in BA11, left gyrus rectus, MNI (0, 26, -14), z score=4.52]; the other was located in the right insula, in the hippocampus and in the right superior temporal gyrus [629 voxels, p=0.04; peak activation in BA48, right insula, MNI (42, -8, -6), z

score=4.13] (see Table 10). In the 2-back vs 1-back contrast, there was a large cluster of significantly greater relative activation in the patients which included the medial and inferior orbital prefrontal cortex, left basal ganglia and anterior regions of left temporal cortex spreading to both amygdala and the hippocampus [5748 voxels, p=8.66x10^{-13}; peak activation in BA38, left middle temporal pole, MNI (-40, 18, -34), z score=4.49]. Another cluster affected parts of the right basal ganglia, the right insula, the anterior temporal cortex and the right amygdala-hippocampus complex [2235 voxels, p=2.56x10^{-6}; peak activation in BA35, right parahippocampal gyrus, MNI (26, 2, -34), z score=4.56]. The findings for this contrast are summarized in Table 11 and shown graphically in Figure 9.

Figure 9. Brain regions where the cognitively preserved individuals with schizophrenia showed significant failure to de-activate compared the controls in the 2-back vs 1-back contrast.

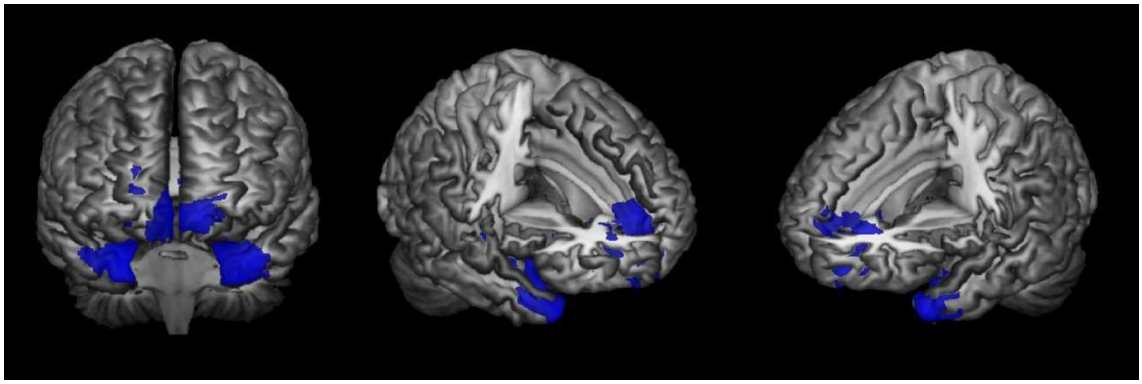


Table 11. Significant clusters and the corresponding peak values of increased activation in each anatomical region in the cognitively preserved schizophrenia group compared to the control group in the 2-back versus 1-back contrast.

Cluster 1 5748 voxels	p=8.66x10^{-13}				
	BA	Z	x	y	z
Left amygdala-hipppocampal complex					
Left amygdala	36	3.08	-30	1	-24
Left hippocampus	36	3.11	-24	-6	-25
Left parahippocampal gyrus	28	3.66	-23	2	-30
Left temporal lobe					
Left fusiform gyrus	36	3.63	-33	2	-33
Left inferior temporal gyrus	20	3.93	-32	8	-40
Left middle temporal gyrus (Temporal pole)	38	4.49	-40	18	-34
Left superior temporal gyrus (Temporal pole)	36	3.80	-29	5	-33
Leftt basal ganglia					
Left caudate nucleus	25	3.20	-5	9	-11
Left putamen	48	3.16	-18	8	-7
Medial and orbitofrontal cortex					
Left gyrus rectus	11	3.62	-6	50	-16
Right gyrus rectus	11	3.47	2	48	-15
Left olfactory tract	25	3.89	-2	21	-11
Right olfactory tract	25	3.93	3	21	-11
Left superior orbitofrontal cortex	11	3.09	-10	55	-19
Left medial orbitofrontal cortex	11	3.33	-3	41	-11
Right medial orbitofrontal cortex	10	3.06	4	51	-5
Left anterior cingulate	32	3.63	-9	40	9
Right anterior cingulate	11	3.02	9	41	1
Cluster 2 2235 voxels	p=8.66x10^{-13}				
	BA	Z	x	y	z
Right amygdala-hipppocampal complex					
Right amygdala	36	3.42	29	1	-25
Right hippocampus	20	4.00	28	-12	-22
Right parahippocampal gyrus	35	4.56	26	2	-34
Right temporal lobe					
Right fusiform gyrus	36	3.99	31	1	-31
Right middle temporal gyrus (Temporal pole)	36	4.34	28	10	-34
Right insula	48	3.10	39	6	-12
Right basal ganglia					
Right putamen	48	2.81	20	8	-4
Right pallidum	-	2.93	17	10	0

As described in the introduction (section 1522), this relatively greater activation in the cognitively preserved schizophrenic patients could have represented either hyperactivation or failure of de-activation. To establish which of these possibilities applied, an ROI of boxplots of the averaged values in the ROI of the cluster in the medial frontal cortex is shown in Figures 10 and 11 respectively for the 2-back vs baseline and for the 2-back vs 1-back contrasts

and indicate that the differences represented failure of de-activation: the controls showed a clearly negative activation whereas the patients showed a mean value close to 0.

Figure 10. Boxplot of the averaged level of activation from the cognitively preserved patients and the healthy control groups in the medial frontal cluster of significant difference in the 2-back vs baseline contrast.

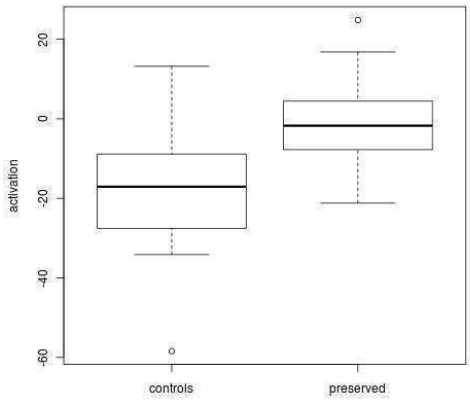
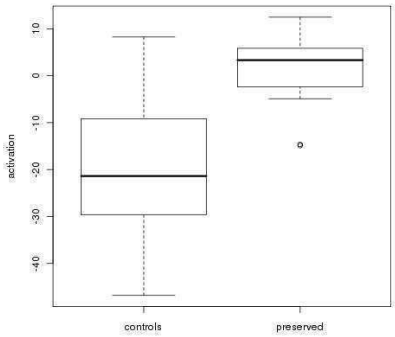


Figure 11. Boxplot of the averaged level of activation from the cognitively preserved patients and the healthy control groups in the medial frontal cluster of significant difference in the 2-back vs 1-back contrast.



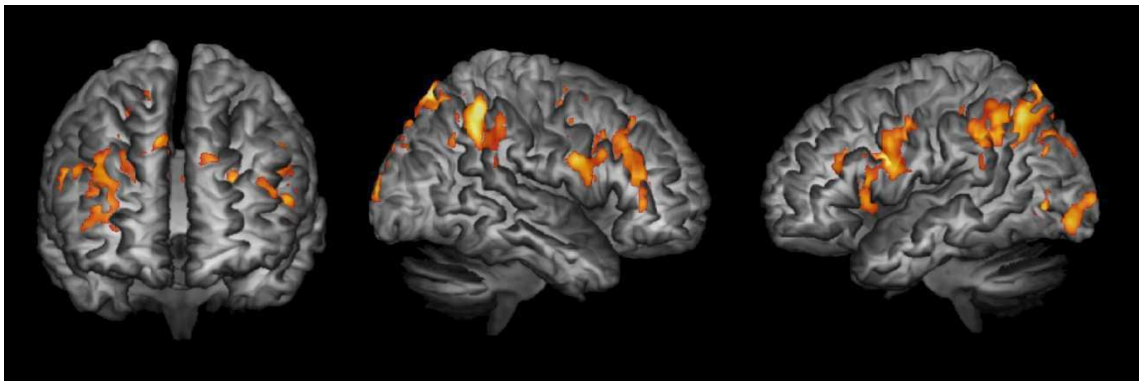
4.2.4. fMRI findings: cognitively preserved vs cognitively impaired participants with schizophrenia

There were no areas of significant difference between the schizophrenia groups in the 1-back vs baseline contrast. The 2-back vs baseline contrast revealed significantly reduced activation in the cognitively impaired individuals in an area which included the right DLPFC and right perirolandic regions [1749 voxels, p=2.94x10^{-5}; peak activation in BA48-, pars triangularis of the right frontal inferior gyrus, MNI (38, 28, 26), z score=3.93] (see Table 10).

Areas of significantly reduced activation were also evident in the 2-back vs 1-back contrast. Here, the cognitively impaired patients showed significantly reduced activation in two large clusters in the DLPFC bilaterally. On the right, this included the DLPFC and extended to the precentral gyrus posteriorly and to the superior middle frontal cortex anteriorly [2494 voxels, p=1.19x10^{-7}; peak activation in BA42, right superior frontal gyrus, MNI (12, 24, 46), z score=3.88]. The corresponding cluster on the left included the DLPFC and extended to the basal ganglia, the insula and the precentral gyrus [1786 voxels, p=5.96x10^{-6}; peak activation in BA6, left precentral gyrus, MNI (-40, -6, 40), z score=3.74]. Two more clusters were located in regions of the right parietal and occipital lobes [1962 voxels, p=2.09x10^{-6}; peak activation in BA40, right inferior parietal gyrus, MNI (38, -46, 50), z score=4.25] and in roughly similar regions on the left [1785 voxels, p=6.02x10^{-6}; peak activation in BA7, left superior parietal gyrus, MNI (-32, -64, 48), z score=3.91]. Two further smaller clusters were found in both thalami [608 voxels, p=0.02; peak activation in the left thalamus, MNI (-9, -21, 19), z score=3.41], and in the left inferior occipital cortex [603 voxels,

p=0.03; peak activation in BA19, left inferior occipital gyrus, MNI (-52, -76, -2), z score=4.04]. The findings are shown in Figure 12 and Table 12.

Figure 12. Brain regions where the cognitively impaired schizophrenia group activated significantly less than the cognitively preserved group in the 2-back vs 1-back contrast.



There were no areas in which the cognitively impaired individuals with schizophrenia activated more than the cognitively preserved ones.

Table 12. Significant clusters and corresponding peak values of significantly decreased activation in each anatomical region in the cognitively impaired schizophrenia group when compared to the cognitively preserved group in the 2-back versus 1-back contrast.

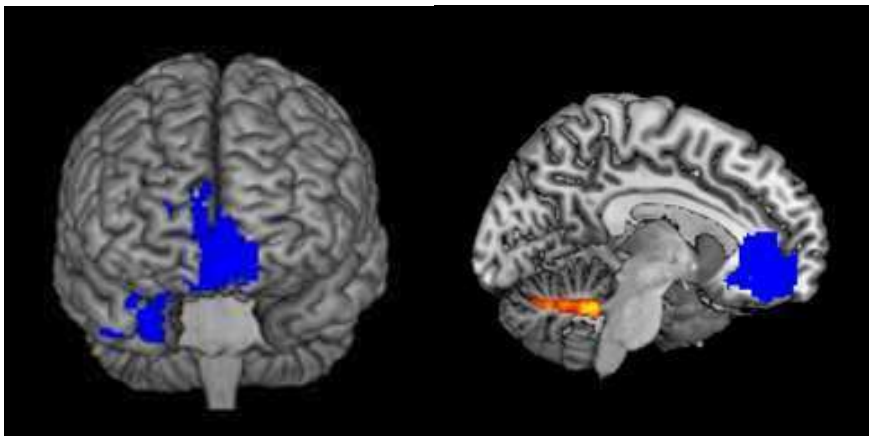
Cluster 1	2494 voxels	p=1.19x10^{-7}				
		BA	Z	x	Y	Z
Right medial cortex						
	Right middle cingulate	32	3.29	12	20	40
	Right superior medial frontal gyrus	32	3.00	8	30	42
Right DLPFC						
	Right superior frontal gyrus	32	3.88	12	25	46
	Right middle frontal gyrus	45	3.12	38	36	16
	Right inferior frontal gyrus (Pars triangulars)	46	3.49	37	27	30
	Right inferior frontal gyrus (Pars opercularis)	48	3.62	32	6	29
Right prerolandic region						
	Right precentral gyrus	6	3.81	54	2	26
	Right rolandic operculum	6	3.30	55	8	16
Cluster 2	1786 voxels	p=5.96x10^{-6}				
		BA	Z	X	y	z
Left DLPFC						
	Left inferior frontal gyrus (Pars opercularis)	48	3.56	-50	16	14
	Left inferior frontal gyrus (Pars triangulars)	48	3.19	-41	33	22
Leftt prerolandic region						
	Left rolandic operculum	6	3.61	-47	2	19
	Left precentral gyrus	6	3.74	-40	-6	40
Left insula		48	3.14	-33	18	8
Left basal ganglia						
	Left putamen	48	3.35	-24	17	4
	Left caudate	-	2.61	-13	12	4
Cluster 3	1962 voxels	p=2.09x10^{-6}				
		BA	Z	X	y	z
Right parietal cortex						
	Right supramarginal gyrus	40	3.07	54	-37	43
	Right angular gyrus	40	3.68	46	-48	38
	Right inferior parietal gyrus	40	4.26	38	-46	50
	Right superior parietal gyrus	7	3.84	20	-66	52
Right occipital cortex						
	Right precuneus	7	4.14	6	-72	60
	Right cuneus	19	3.17	10	-84	46
Cluster 4	1785 voxels	p=6.02x10^{-6}				
		BA	Z	x	y	Z
Left parietal cortex						
	Left superior parietal gyrus	7	3.91	-32	-64	48
	Left inferior parietal gyrus	7	3.73	-32	-61	39
Left occipital cortex						
	Left cuneus	18	3.37	-18	-78	35
Left superior occipital gyrus		19	3.29	-23	-75	31
Cluster 5	608 voxels	p=0.025				
			Z	x	y	Z
Left thalamus			3.41	-9	-21	20
Right thalamus			2.86	6	-8	19
Cluster 6	603 voxels	p=0.0261				
Left occipital cortex		BA	Z	x	y	z
	Left middle occipital gyrus	17	3.47	-24	-100	4
	Left inferior occipital gyrus	19	4.04	-52	-76	-2
	Left lingual gyrus	18	3.13	-28	-89	-12

4.2.5. fMRI analysis by working memory load

This analysis -where models were fitted that assume a linear relationship through the baseline, 1-back and 2-back levels of the task- had broadly similar findings to those in the preceding sections.

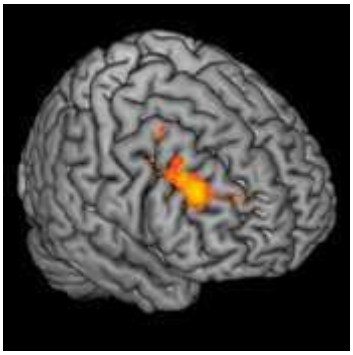
In the analysis comparing the cognitively preserved schizophrenic patients to the healthy controls, the patients showed a cluster of significantly reduced activation in the cerebellum [1411 voxels, p=0.000246; peak activation in vermis, MNI (6, -60, -26), z score=4.45]. As previously, the cognitively preserved participants also showed clusters where they showed a significant failure to de-activate relative to the controls. One of these affected parts of the medial and inferior orbital prefrontal cortex, extending to the anterior cingulate cortex [3681 voxels, p=3.75x10^{-9}; peak activation in BA11, left anterior cingulate, MNI (-2, 32, -6), z score=4.48]. The other, smaller cluster was located in the right insula, hippocampus and parahippocampus extending marginally to the right superior temporal gyrus [1173 voxels, p=0.00103; peak activation in BA48, right insula, MNI (42, -8, -6), z score=4.1]. The findings for these contrasts are shown graphically in Figure 13.

Figure 13. Brain regions where the cognitively preserved individuals with schizophrenia showed significant failure to de-activate compared the controls in the working memory load contrast.



When the cognitively impaired and cognitively preserved patients were compared using working memory load, the former showed a single area of significantly reduced activation in the right DLPFC [892 voxels, *p*=0.00546; peak activation in BA48, pars triangulars of the right inferior frontal gyrus, MNI (36, 28, 26), z score=3.58] when compared to the latter. There were no areas where the cognitively impaired group activated significantly more than the cognitively preserved group. The findings for this contrast are shown graphically in Figure 14.

Figure 14. Brain regions where the cognitively impaired schizophrenia group activated significantly less than the cognitively preserved group in the working memory load contrast.



5. Discussion

5.1. Summary of findings

The aim of this study was to examine the brain structural and functional correlates of cognitive impairment in schizophrenia. A design which compared groups of patients preselected for showing and not showing substantial levels of cognitive deficit was employed. This was principally because previous studies using a correlational approach had not had consistent findings, which may have reflected difficulties controlling for other factors which can affect brain structure and function in this type of study, such as age and IQ.

In terms of brain structure, while the schizophrenic patients as a group showed a range of areas of reduced volume compared to controls, the patients with cognitive impairment showed no more abnormality than those without cognitive impairment. In contrast, differences were found between the two patient groups on functional brain imaging. Specifically, the cognitively impaired patients showed reduced activation compared to the cognitively preserved patients in a series of brain regions encompassing the DLPFC, pre- and postcentral regions, parieto-occipital areas and the thalamus.

The functional imaging part of the study also revealed differences between the healthy controls and the cognitively preserved schizophrenic patients. The most conspicuous finding here, which was seen in all analyses performed, was failure of de-activation in the cognitively preserved patients. This affected the medial frontal cortex and adjacent areas of the inferior frontal lobe, the insula, temporal-hippocampal regions and the basal ganglia. Additionally, the cognitively preserved patients showed an area of reduced activation compared to the healthy controls in parts in the cerebellum, although this was less consistent across the analyses.

These findings are discussed in more detail below.

5.2. Structural neuroimaging findings in relation to previous studies

As a group, the schizophrenic in this study showed reduced brain volume, reduced GM volume and lateral ventricular enlargement compared to the healthy controls. These are the typical structural imaging findings associated with schizophrenia (e.g. see the meta-analysis of MRI studies by Wright *et al.* (2000) presented in section 1511). This pattern remained evident in both the cognitively preserved patients and the cognitively impaired patients when they were considered separately (the difference in lateral ventricular volume between the controls and cognitively preserved patients was no longer significant, which might be attributable to the smaller sample size in this analysis).

In contrast, there was no statistically significant difference in whole brain volume or GM volume between the cognitively preserved and cognitively impaired patients with schizophrenia. It could be argued that this negative finding could simply have reflected lack of power -there were in fact differences in whole brain and GM volume between the two groups of patients of 0.4% and 0.9% respectively, both in the direction of smaller volume in the cognitively impaired patients. Against this, it can be pointed out that two groups of 769 participants would be required to make the differences found in whole brain volume between cognitively impaired and cognitive preserved groups significant, and 239 for each group would be needed to do so for the differences in GM volume.

VBM analysis comparing controls to schizophrenic patients with relatively preserved cognitive function revealed a pattern of volume reduction quite similar to that found in meta-analyses of studies comparing unselected schizophrenic patients and controls. Specifically, they showed a cluster of reduced volume in medial and orbital frontal GM compared to healthy controls. This area overlaps with an area found to be affected in Fornito *et al*. (2009) meta-analysis of 37 studies, and the overlap was greater in the larger and more recent meta-analysis of 52 studies carried out by Bora *et al*. (2011b). However, applying this technique to the schizophrenic patients with and without cognitive impairment again failed to reveal clusters of significant volume difference between them.

This finding of lack of structural imaging differences between cognitively preserved and cognitively impaired schizophrenia is in line with those of a number of correlational studies reviewed in the introduction, which found only weak and conflicting evidence for an association between cognitive impairment and lateral ventricular size, whole brain volume and regional cortical volumes (see section 171). However, as noted in the introduction (section 173), a small number of previous studies which examined separate groups of patients with and without cognitive impairment had more mixed findings. Thus, while Wexler *et al*. (2009) found no significant differences in lateral ventricular volume and GM volume between 54 cognitively impaired and 21 cognitively near-normal schizophrenic patient groups, they did find differences in WM volume in two of eight regions examined (sensorimotor and parietal-occipital), with a trend towards significant reduction in a third (inferior occipital). Applying VBM to a region limited to the frontal lobe cortex bilaterally, Rüsch *et al*. (2007) found clusters of reduced volume in the DLPFC and the anterior cingulate cortex in 21

cognitively impaired compared to 30 cognitively preserved patients. Using cortical thickness analysis, Cobia *et al*. (2011) found no clusters of significant difference between 34 cognitively impaired and 45 cognitively preserved patients. However, clusters emerged when no correction for multiple comparisons was used.

The findings of the present study also need to be considered in relation to studies which have divided schizophrenia into subgroups on the basis of measures which show an association with cognitive function. One subdivision of this type is the distinction between deficit and non-deficit schizophrenia. Deficit schizophrenia, differently to non-deficit schizophrenia, is characterised by mainly negative symptoms that are stable over time and by a poor functional outcome (Kirkpatrick *et al.*, 2001). As expected, these patients have been found to show more severe cognitive impairment than non-deficit cases (Cohen *et al*., 2007). Galderisi and Maj (2009) reviewed six studies comparing brain structure in patients meeting criteria for these two forms of schizophrenia. They concluded that there was no evidence for larger lateral ventricles in the former group, and measures of regional cortical volumes and volumes of subcortical structures failed to identify clear morphological correlates of the deficit syndrome. However, it should be noted that a subsequent study (Fischer *et al*., 2012) comparing 20 deficit and 36 demographically well-matched non-deficit schizophrenia patients found diminished volume in the superior prefrontal and superior and middle temporal gyrus bilaterally in the former group. Nevertheless, there were no differences between the two groups in other brain regions, including the dorsolateral prefrontal cortex, the inferior parietal cortex,

the thalamus, the caudate nucleus, the orbitofrontal cortex, superior temporal gyrus and the amygdala-hippocampus.

Another, closely related division is that between 'Kraepelinian' and 'non-Kraepelinian' types of schizophrenia. Kraepelinian patients are characterised by poor outcome; they typically require long-term hospitalization or equivalent levels of supervision in the community and many show ongoing severe active psychotic symptoms (Keefe *et al.*, 1987). Non-Kraepelinian patients show a bettter outcome between episodes of illness and are able to live independently long periods, with hospitalization not exceeding five years. Outcome in this sense and cognitive function are related, with cognitive impairment having been found to be the most important predictor of poor functional outcome in the disorder (Green, 1996; Green and Nuechterlein, 1999; Green *et al.*, 2000; Fett *et al.*, 2011). Mitelman *et al.* (2007) compared 51 good outcome and 53 poor outcome schizophrenic patients. There were no differences in whole brain volume between the groups. With respect to GM volume, they found significant volume reductions in the poor outcome patients compared to the good outcome patients in 18 out of approximately 92 cortical areas examined. Most or all of these would not have survived controlling for multiple comparisons. WM volume showed a pattern of both reductions and increases in the poor outcome patients relative to the good outcome patients, with differences in either direction being present in eight brain areas (again uncorrected for multiple comparisons). Lateral ventricular volume did not differ between good and poor outcome groups (Mitelman *et al.*, 2010).

The failure to find a relationship between structural brain abnormality and cognitive impairment in schizophrenia in the present study is also in keeping

with a well-established neuropathological finding in the disorder. This is that, while severe cognitive impairment is prevalent among elderly institutionalized people with schizophrenia -more than 70% have MMSE scores in the demented range (Harvey *et al.*, 1995)-, post-mortem studies have revealed no more Alzheimer-type or other brain pathology than in age-matched controls in samples of elderly people with schizophrenia with a dementia-like functional status (Powchik *et al.*, 1998; Harrison, 1999; Religa *et al.*, 2003). In the same direction, two CSF biomarkers which are diminished in Alzheimer's disease, tau and Aβ42, were found not to be altered in elderly patients with schizophrenia (Frisoni *et al.*, 2011).

5.3. Functional imaging findings in relation to previous studies

In contrast to the lack of positive findings with structural imaging, clear differences between cognitively impaired and cognitively preserved participants with schizophrenia on functional imaging were found. Specifically, in the 2-back vs baseline and 2-back vs 1-back contrasts the cognitively impaired group with schizophrenia showed reduced activation in the DLPFC and other areas. These areas became bilateral and extended more widely in the 2-back vs 1-back contrast.

As noted in the introduction, previous studies have not consistently found associations between the degree of hypofrontality in schizophrenia and cognitive task performance. Thus, two meta-analyses of 14 studies (Hill *et al.*, 2004) and 20 studies (Van Snellenberg *et al.*, 2006) found that the ES for differences in prefrontal activation were moderated by impairment on task performance differences only at trend level (p=0.06 and p=0.09 respectively). The findings reported in this thesis suggest a stronger association, to the point

that most of the task-related hypoactivation found appeared to be attributable to cognitive impairment -in the comparison between cognitively preserved participants with schizophrenia and controls reduced activation was seen only in the cerebellum.

One possible reason why this study had stronger findings than previously is that, rather than using correlational methods, it compared groups which differed in cognitive function but which were matched for other factors that might influence task performance, for example age and premorbid IQ. In this respect, it may be relevant that Van Snellenberg *et al*. (2006) found in their meta-analysis, this time using 24 studies, that age significantly moderated differences in left-hemisphere activation between patients and controls. However, gender and two measures of premorbid intellectual function (years of education and NART score) did not significantly influence activation in frontal regions. Other more recent studies have also failed to find a relationship between premorbid IQ or educational level with frontal activation in schizophrenia during performance of executive tasks (e.g Wolf *et al*., 2007; Pae *et al*., 2008; Karlsgodt *et al*., 2009).

There appears to be only one study which has examined the brain functional correlates of cognitive impairment in schizophrenia using groups preselected for showing and not showing this. Fletcher *et al*. (1998) examined brain function during a word list recall task in two groups of patients with (*n*=6) and without (*n*=6) memory impairment, as defined on the basis of scores on the RBMT. They found that the pattern of activation with increasing memory difficulty differed qualitatively from those in both groups of schizophrenic subjects: whereas the controls (*n*=7) responded to increasing word list length

with an increasing degree of left prefrontal activation, both schizophrenic groups showed a tailing off of activation during longer lists. However, there was no difference between the memory impaired and memory preserved patients. Fletcher *et al*. (1998) also found task-related de-activations in their study. These were seen in temporo-parietal regions bilaterally in the controls and both patient groups, and in the medial frontal cortex in the controls and the unimpaired schizophrenic subjects, but not in the impaired schizophrenic patients, implying that a failure of de-activation was associated with cognitive impairment.

The findings of the present study differ from those of Fletcher *et al*. (1998) both in terms of activations and de-activations. Reduced activation in the present study was related to cognitive function, whereas Fletcher *et al*. (1998) found no association with cognitive impairment. Failure of de-activation was not associated with cognitive impairment, being seen only in the comparison between the cognitively preserved patients and the controls, whereas Fletcher *et al*. (1998) found this only in the cognitively impaired patients. One obvious reason for the differences between the two studies is their respective sample sizes. Fletcher *et al*. (1998) only compared six patients with and six patients without cognitive impairment and seven controls.

As described in the introduction, studies by Weinberger and co-workers (Callicott *et al*., 2000; Callicott *et al*., 2003; Tan *et al*., 2006) and others (Manoach *et al*., 1999; Ojeda *et al*., 2002; MacDonald *et al*., 2005), have found that, during performance of the working memory tasks, schizophrenic patients show not only hypofrontality but also hyperfrontality. The finding of task-related hyperfrontality in schizophrenia has also been supported by two meta-analyses, one of studies using the n-back (Glahn *et al*., 2005) and other using a range of

different executive tasks (Minzenberg *et al.*, 2009). According to Weinberger and co-workers (Weinberger *et al.*, 2001; Callicott *et al.*, 2003; Tan *et al.*, 2007), the findings of hypofrontality and hyperfrontality are both related to cognitive function. In healthy subjects, increasing task demands are first associated with increasing activation, but this then falls off after the subject's working memory capacity is exceeded, producing a u-shaped activation curve. Due to reduced efficiency of prefrontal cortical processing, patients with schizophrenia show more activation than healthy subjects -or hyperfrontality- at low task demands, as they 'work harder to keep up'. As task demands increase, however, they then reach their limit of performance sooner than healthy subjects, and thereafter show a fall-off of activation, or hypofrontality. In other words the U-shaped curve is shifted to the left in schizophrenia. Their argument is described in detail in the introduction (Figure 5 in section 172 in page 40).

The study did not find any evidence of hyperfrontality in the comparison between cognitively preserved and cognitively impaired patients. Nor did the cognitively impaired patients show hyperactivation compared to the cognitively preserved patients on the easy (i.e. 1-back) version of the n-back task, which might also be expected on the basis of Weinberger's reduced cortical efficiency/working harder to keep up hypothesis. The study of Karlsgodt *et al.* (2009) described in the introduction (section 172), also failed to find a simple relationship between hyperfrontality and cognitive function in schizophrenia. During performance of the Sternberg working memory task, both 14 patients and 18 controls showed a pattern of increasing activation in the left DLPFC, with increasing working memory load, which then decreased slightly at the highest levels. However, there was no clear evidence that the curve was shifted

to the left in the patients, as the model of Weinberger's group suggested. Results were similar when the patient group was split into high- and low-performing groups.

In addition to reduced activation related to cognitive function, the study described in this thesis found failure of de-activation in the medial prefrontal cortex among other regions, which was only seen in the comparison between the controls and the cognitively preserved cases. This finding is similar to those of other recent studies (Pomarol-Clotet *et al.*, 2008; Whitfield-Gabrieli *et al.*, 2009; Milanovic *et al.*, 2011), comparing unselected groups of schizophrenic patients with controls. In two of these studies (Pomarol-Clotet *et al.*, 2008; Whitfield-Gabrieli *et al.*, 2009), the medial frontal failure of de-activation remained after controlling for the difference in n-back task performance between the patients and controls, suggesting it was not a function of cognitive impairment. This fits with the finding of the present study, where failure of de-activation was found in the comparison between controls and cognitively preserved patients but not in that between cognitively preserved and cognitively impaired patients.

Pomarol-Clotet *et al.* (2008) have argued that failure of de-activation might account for some of the apparent hyperfrontality found in schizophrenia - which can give the appearance of hyperactivation as a result of 'reverse subtraction' from a high baseline. Their argument is described in detail in the introduction (Figure 3 in section 1522 in page 27). It may be relevant in this respect that failure of de-activation found in the present study and in other studies (Pomarol-Clotet *et al.*, 2008; Whitfield-Gabrieli *et al.*, 2009; Milanovic *et al.*, 2011) involves the medial frontal cortex. This cortical region has also been

found to be one of the main areas where hyperfrontality has been found. Thus, in their meta-analysis of studies using the n-back task, Glahn *et al*. (2005) identified the anterior cingulate and left frontal pole regions as showing consistently increased activation across studies. Interestingly, Glahn *et al*. (2005) also noted that the dorsomedial prefrontal region was not activated by either patients alone or controls alone, making inferences about this region difficult. In the larger meta-anlaysis of Minzenberg *et al*. (2009), hyperactivation was found in lateral and medial frontal regions, but also in some other frontal regions, as well as in right temporal and limbic regions and the left inferior parietal gyrus.

Failure of de-activation in the medial frontal cortex in schizophrenia has been interpreted as indicating that there is DMN dysfunction in schizophrenia (Pomarol-Clotet *et al.*, 2008; Broyd *et al.*, 2009; Whitfield-Gabrieli *et al.*, 2009). The DMN is a series of interconnected brain regions, with two prominent midline 'hubs' in the medial frontal cortex anteriorly and the posterior cingulate cortex/precuneus posteriorly. This circuitry of brain regions is activated when a person focuses into internal information (such as remembering past events, anticipating the future, and considering others' perspectives) instead of external perceptions (Buckner *et al.*, 2008). It is currently a focus of considerable research interest in schizophrenia, with reviewed studies finding evidence of changes in task-related de-activation (in both directions), as well as abnormal connectivity at rest (Broyd *et al.*, 2009). Among other things, it has been suggested that failure of de-activation in the network might account for the cognitive impairment associated with the schizophrenia (Pomarol-Clotet *et al.*, 2008; Whitfield-Gabrieli *et al.*, 2009). The results of the present study suggest

that failure of de-activation in the DMN in schizophrenia is a feature of schizophrenia, but is unrelated to the cognitive impairment associated with the disorder, and so do not support this view.

It is very interesting to compare the results just discussed with the results of the VBM comparison between the controls and the cognitively preserved group. Volume reductions were clustered in a medial frontal cortex region in the VBM comparison, where failure of de-activation was also seen in the fMRI study. The overlapping of structural and functional change in the anterior node of the DMN in this study has already been found previously. Members of Benito Menni's research group have previously examined this overlap in more detail. Pomarol-Clotet *et al*. (2010), and Salgado-Pineda *et al*. (2011) found failure of both de-activation and volume reductions along the length of the cingulate gyrus. Another study had comparable findings; Camchong *et al*. (2011) found functional connectivity abnormality in the anterior node of the DMN, plus WM changes in subjacent regions on DTI.

5.4. Implications of the findings for understanding cognitive impairment in schizophrenia

One of the two main findings of the study reported in this thesis was a failure to find a relationship between cognitive impairment in schizophrenia and brain structural change. Specifically, cognitively impaired patients did not show significantly reduced brain volume, GM volume or WM volume, or have larger lateral ventricles, compared to cognitively preserved patients. Nor were did clusters of significant volume difference appear with VBM. Structural brain abnormality in schizophrenia appeared to be a function of having the disorder, but not the cognitive impairment that accompanies it.

This finding could be considered counter-intuitive, but it is in accordance with those of a considerable number of other structural imaging studies in schizophrenia, which have generally failed to find consistent evidence of significant correlations between overall or regional brain volumes and cognitive test scores. It is also in line with findings from post-mortem studies, which have uniformly failed to find that elderly chronically hospitalized schizophrenic patients, who have a high rate of dementia, show no more evidence of dementia-related pathology at post-mortem than age matched healthy controls.

The main significance of this finding is that it implies that cognitive impairment in schizophrenia might be based on different mechanisms than cognitive impairment in other diseases. Thus, in neurological disorders such as dementia and brain injury, cognitive deficits result from structural brain changes and a relationship between the degree of structural change in different areas and the pattern neuropsychological test impairment can often be demonstrated (McDonald *et al.*, 2002; Whitwell, 2010).

It is interesting to note that, in a few neurological disorders, cognitive impairment is present but this is related to disturbed brain function and structural changes are absent or slight. The leading example here is delirium, where brain function is affected by factors such as infection or drug toxicity. In this disorder, unlike dementia and brain damage, complete recovery takes place if the underlying cause can be treated. Another example is Parkinson's disease, where patients in the early stages of the disorder have been found to show impaired executive function. This has been argued to be due to a neurochemical (dopaminergic) disturbance in frontostriatal circuits, and there is evidence suggesting that it improves with L-dopa treatment (Owen, 2004). This

may be particularly relevant to cognitive impairment in schizophrenia, given the role of dopamine in both disorders.

5.5. Implications of the findings for treatment

The findings of this study suggest that cognitive impairment is related to brain functional but not structural changes. If so, it may be potentially reversible, as in neurological disorders like delirium or in Parkinson. In fact, cognitive impairment is increasingly considered a treatment goal in the disorder (Goldberg *et al.*, 2010), partly because of the finding that it has a greater impact on functional outcome than psychotic symptoms (Green *et al.*, 2000; Penadés *et al.*, 2001). An effective intervention in cognitive impairment could therefore significantly decrease the burden of schizophrenia.

It has been known for some time that treatment with conventional or first-generation neuroleptics is associated with a small improvement in cognitive performance (Mishara and Goldberg, 2004; Goldberg *et al.*, 2010). After the introduction of atypical or second-generation neuroleptics, a number of studies suggested that they produced a greater degree of improvement (Meltzer and McGurk, 1999; Harvey and Keefe, 2001; Harvey *et al.*, 2005). However, recent rigorous studies (Goldberg *et al.*, 2007; Keefe *et al.*, 2007; Goldberg *et al.*, 2010) indicate that the improvements in test scores found are simply due to practice effects. Other pharmacological treatments, such as cholinergic, GABAergic and glutamate agonists, have been considered for targeting cognitive impairment in schizophrenia. However, so far none of these have been found to show evidence of effectiveness (Coyle *et al.*, 2010; Burdick *et al.*, 2011).

Starting in the 1990s, a number of studies have also examined the effectiveness of cognitive remediation in schizophrenia. A recent meta-analysis, which included 40 controlled studies (2104 participants) (Wykes *et al.*, 2011) found a pooled effect size of 0.45 for improvement, in the 'medium' range, and the treatment was also associated with improved social functioning. However, it should be noted that most studies did not control for the nonspecific effects of intervention (Goff *et al.*, 2011), and one large, well-conducted study that did so had negative findings (Dickinson *et al.*, 2010).

5.6. Limitations

This study is one of the largest to have examined the brain structural correlates of schizophrenic cognitive impairment, and the largest to examine its correlates in brain function. It also had other methodological strengths, especially the use of groups of predetermined groups of patients meeting criteria for being cognitively impaired and cognitively preserved. Nevertheless, the study has a number of limitations which need to be pointed out.

Perhaps the most important limitation was the relatively small numbers of schizophrenic patients. The sample sizes of 26 cognitively impaired and 23 cognitively preserved patients respectively are towards the lower end of the range that have been used in both conventional MRI and VBM studies of schizophrenia and other major psychiatric disorders, and so there is potential for false negative findings. Nevertheless, as noted in the discussion, very large numbers (over 750 in each group for whole brain volume and over 200 in each group for GM volume) would be necessary to detect differences, if they are present, based on the magnitude of differences found between the cognitively impaired and cognitively preserved patients in this study.

Another limitation is that, since the cognitively preserved patients were defined only as having memory and executive function above the 5th percentile cut-offs on the RBMT and the BADS, they were not completely free of cognitive impairment; some of them fell into the poor normal memory range on the RBMT and the low average/borderline categories in the BADS. Therefore, this study should be regarded as having compared cognitively impaired and relatively cognitively preserved, or cognitively near-normal patients.

Concerning the functional imaging findings, interpretation of the differences in the degree of prefrontal activation between the cognitively impaired and cognitively preserved patients is complicated by a methodological factor. This is the fact that there were also differences in the level of n-back task performance between the two groups. It is difficult to exclude the possibility that differences in task performance accounted for the differences in activation, because the n-back task is itself a cognitive task and the groups were preselected on the basis that they differed in cognitive function. Therefore, entering n-back performance as a covariate in the analysis would violate the principle that the covariate should not be affected by the group factor. This issue in fact forms part of a wider debate about what drives task-related hypofrontality in schizophrenia: are both poor task performance and reduced brain activation manifestations of an underlying intrinsic cortical dysfunction? Or does the reduced activation merely index the fact that the patients are performing the task more poorly and so activating their frontal lobes to a correspondingly lesser extent (Fletcher *et al.*, 1998)?

Finally, the thickness of slices of 7mm in the fMRI study is on the large side by contemporary standards. In general, the amount of signal delivered by

the images depends on the volume of tissue that is sampled (i.e. volume of the voxel). A rather high in-plane resolution of 3x3 mm^2 was used in the study. Since the study used a 1.5 T scanner, the 7 mm thickness was to compensate for these relatively small sizes in the X-Y plane, keeping the total volume of the voxel large enough to ensure a good signal-to-noise ratio in the BOLD images.

6. Conclusions

1. This study found that patients with schizophrenia and no marked cognitive impairment showed a significant decrease in total brain volume and GM volume as well as a significant lateral ventricle enlargement compared to healthy controls. However, these MRI parameters did not distinguish patients with and without moderate or severe degrees of cognitive impairment.
2. Using VBM, a cluster of reduced GM volume in the orbital medial frontal cortex was found in the group of schizophrenia with no marked cognitive impairment compared to matched healthy controls. However, volume differences in these or other clusters were not found to distinguish between patients with and without significant degrees of cognitive impairment. These and the abovementioned findings suggest that cognitive impairment in schizophrenia is not a function of the brain structural changes seen in the disorder.
3. Patients with schizophrenia showed a greater degree of reduced activation in the DLPFC than the cognitively preserved schizophrenic during performance of the n-back working memory task. This finding suggests that cognitive impairment in schizophrenia is closely related to hypofrontality, one of the main functional imaging abnormalities associated with the disorder.
4. Patients with schizophrenia without cognitive impairment showed a failure of de-activation in the medial prefrontal cortex. However, the cognitively impaired schizophrenic patients did not show a greater degree of failure of de-activation than the cognitively preserved patients. This finding does not

support the view that de-activation abnormality, and consequently DMN dysfunction, underlies the cognitive impairment seen in schizophrenia.

7. Resum

Els correlats neurals del dèficit cognitiu en l'esquizofrènia

Introducció

Característiques generals de l'esquizofrènia

L'esquizofrènia és un trastorn psiquiàtric molt sever, incapacitant i costós (p.e. Mueser i McGurk, 2004; Oliva-Moreno *et al.*, 2006), que afecta vora l'un per cent de la població mundial (Jablensky, 2010). En la majoria de casos, es manifesta per primer cop al final de l'adolescència o al començament de l'edat adulta (Delisi, 2008b). La simptomatologia de l'esquizofrènia inclou els *símptomes psicòtics o positius* (deliris i al·lucinacions), els *símptomes negatius* (com ara pèrdua o disminució de la voluntat, la producció lingüística i/o l'expressió emocional), els trastorns del moviment, el *discurs incoherent* i la *manca de consciència de malaltia* (per exemple Tandon *et al.*, 2009). Les *alteracions cognitives* són un altre símptoma característic de l'esquizofrènia i conformen el tema de la tesi.

L'esquizofrènia és molt heterogènia en la forma de manifestar-se, tant en els símptomes que es presenten, com en el curs que aquests segueixen o en el grau d'autonomia que manté la persona, que pot variar entre una autonomia pràcticament total i, en la immensa majoria dels casos, un grau de dependència de lleu a sever (McKenna, 2007; Tandon *et al.*, 2009).

La intervenció d'elecció per l'esquizofrènia són els fàrmacs neurolèptics. Són efectius, en la majoria de casos, en el tractament de símptomes psicòtics i en la seva prevenció; la seva eficàcia en la millora dels símptomes negatius i

dels dèficits cognitius és, tanmateix, baixa (Edlinger *et al.*, 2005; Buchanan *et al.*, 2010; Kane i Correll, 2010). De forma general, es recomana les intervencions psicosocials de forma complementària al tractament farmacològic de l'esquizofrènia (Dixon *et al.*, 2010).

L'etiologia de l'esquizofrènia és desconeguda en bona part (Macher, 2010). Se sap, però, de la importància de diferents factors genètics, neuroquímics i del neurodesenvolupament.

La predisposició genètica n'és el factor de risc amb més evidència. En general, la probabilitat que té una persona de desenvolupar esquizofrènia augmenta progressivament quan més propers són els familiars que pateixen el trastorn (Gottesman, 1991; Cardno i Gottesman, 2000). La presència dels gens DISC 1, neuroregulina o disbindina incrementa lleument la susceptibilitat a l'esquizofrènia (per exemple Balu i Coyle, 2011). Així mateix, en una percentatge petit dels casos, certes mutacions genètiques augmenten de forma important la probabilitat de patir el trastorn (Tiwari *et al.*, 2010).

Pel que fa als factors neuroquímics, les dues hipòtesis més esteses són la teoria d'un excés de dopamina cerebral i, en segon lloc, la d'una disminució de la transmissió glutamatèrgica cerebral. Tanmateix, l'evidència científica respecte a ambdues propostes és inconsistent (Pomarol-Clotet *et al.*, 2006; Howes i Kapur, 2009).

Segons la hipòtesi del neurodesenvolupament, un dany cerebral en l'embaràs o els primers temps de vida produiria una maduració aberrant del cervell que podria dur a l'aparició progressiva dels símptomes de l'esquizofrènia. Al respecte, l'evidència científica mostra una major freqüència de problemes en el part i de disfuncions menors cognitives, conductuals i

d'altres tipus en nens que després desenvoluparan el trastorn, en comparació amb els nens que no el desenvoluparan (p.e. Done *et al.*, 1994; Cannon *et al.*, 2002; McKenna, 2007).

Bases neurals de l'esquizofrènia

Gran part del nostre coneixement actual sobre els canvis cerebrals de l'esquizofrènia es deu als estudis amb neuroimatge estructural i cerebral.

Els primers estudis de tomografia axial computeritzada (CT) van trobar de forma consistent un augment del volum dels ventricles laterals en més d'un 25% en persones amb esquizofrènia respecte a subjectes sans (Andreasen *et al.*, 1990). Les revisions i les metaanàlisis dels estudis de regions d'interès (ROI) amb ressonància magnètica (MRI) van augmentar el coneixement sobre els canvis estructurals en l'esquizofrènia (Wright *et al.*, 2000; Steen *et al.*, 2006). S'hi va trobar una disminució del volum cerebral total en un 2%, que seria més important en la substància grisa que en la substància blanca. Altres canvis evidenciats hi són disminucions volumètriques al lòbul frontal i al gir de Heschl de l'escorça temporal, així com a l'hipocamp, tàlem i amígdala.

La tècnica més recent de morfometria basada en el vòxel (VBM) ha permès un augment de la sensibilitat per detectar petites diferències cerebrals estructurals. La literatura científica actual hi evidencia disminucions volumètriques de substància grisa en regions corticals frontals bilaterals mediales i inferiors, així com a l'ínsula, el gir temporal superior esquerre i el tàlem en esquizofrènia (Bora *et al.*, 2011b). També s'hi ha trobat disminucions en substància blanca a la càpsula interna de forma bilateral i al lòbul temporal dret (Bora *et al.*, 2011a).

La imatge per tensor de difusió (DTI) és una altra tècnica de neuroimatge estructural desenvolupada recentment que permet detectar canvis en la difusió cerebral de l'aigua i, d'aqueta manera, en els tractes de substància blanca. Malgrat la diversitat metodològica i de resultats, les revisions i metaanàlisis de DTI en esquizofrènia indiquen alteracions al cos callós i en tractes temporals i frontals (Kanaan *et al.*, 2005; Kyriakopoulos *et al.*, 2008; Bora *et al.*, 2011a).

Pel que respecta als canvis en neuroimatge funcional en l'esquizofrènia, des de l'estudi pioner d'Ingvar i Franzén (1974), la recerca va girar bàsicament al voltant de confirmar o no la menor activació en àrees cerebral frontals en persones amb esquizofrènia respecte a controls sans.

Els estudis més recents de neuroimatge funcional en esquizofrènia, a partir de 1999, progressivament han anat fent ús de la ressonància magnètica funcional (fMRI) i n'han abandonat altres tècniques més agressives. Al mateix temps, han adoptat tècniques d'anàlisi de les dades d'imatge basades en el vòxel, deixant de banda les anàlisis de ROI. Aquests estudis més recents i sensibles han confirmat, durant la realització de tasques executives, una menor activació en àrees prefrontals dorsolaterals (hipofrontalitat) i, a més, han trobat un augment d'activació en àrees frontals medials (hiperfrontalitat) en comparació amb subjectes sans (p.e. Minzenberg *et al.*, 2009).

Més recentment, s'ha evidenciat que aquesta hiperactivació frontal medial aparent seria, almenys en part, una alteració en la desactivació del node anterior de la xarxa neural per defecte (DMN) durant la realització de tasques de rendiment cognitiu (Pomarol-Clotet *et al.*, 2008). La DMN és una xarxa d'àrees cerebrals que s'activa quan les persones no realitzem activitats

cognitives que impliquen focalització externa sinó interna de l'atenció (Gusnard i Raichle, 2001).

Dèficits cognitius de l'esquizofrènia

El progrés en el coneixement científic de l'esquizofrènia ha posat de manifest la importància del dèficits cognitius en aquest trastorn. El rendiment cognitiu i intel·lectual general de les persones amb esquizofrènia és, de forma mitjana, una desviació típica més baix que el de la població general. Així mateix, el deteriorament no és igual de pronunciat en totes les funcions cognitives, de forma que els dèficits en memòria declarativa a llarg termini, en els processos atencionals i en les funcions executives són especialment marcats i altres processos com el llenguatge, la percepció, la memòria implícita i la memòria a curt termini estan relativament menys afectats (per exemple Reichenberg, 2010). En qualsevol cas, el grau dels dèficits cognitius i el seu perfil són heterogenis entre les persones que pateixen el trastorn i fins i tot no està clar fins a quin punt els dèficits cognitius estan presents en tots els casos d'esquizofrènia (Palmer *et al.*, 1997; Kremen *et al.*, 2000; Weickert *et al.*, 2000; Keefe *et al.*, 2005).

Així mateix, se sap que les alteracions cognitives, i en particular les amnèsiques i disexecutives, es relacionen amb la simptomatologia negativa i desorganitzada pròpia del trastorn però no amb els símptomes psicòtics (Mckenna i Oh, 2005; Dibben *et al.*, 2009). Al mateix temps, els dèficits cognitius semblen ser la principal característica clínica que permet predir el funcionament en l'esquizofrènia (p.e. Green *et al.*, 2000).

Bases neurals del dèficits cognitius en l'esquizofrènia

Malgrat l'evidència que l'esquizofrènia cursa amb dèficits cognitius en tots o gairebé tots els casos, poc se sap de la relació d'aquests dèficits amb les alteracions cerebrals tant estructurals com funcionals que caracteritzen el trastorn. De fet, els resultats de la majoria d'estudis, que han emprat anàlisis correlacionals, no són consistents.

Diferents estudis i revisions han intentar aprofundir en el coneixement de la relació entre els canvis cerebrals estructurals i els dèficits cognitius propis de l'esquizofrènia. Els resultats, tanmateix, no n'han segut concloents, independentment de la forma d'adquisició (CT o MRI) i del tipus d'anàlisi de neuroimatge realitzat (ROI o VBM) (per exemple Crespo-Facorro *et al.*, 2007; Bonilha *et al.*, 2008; Minatogawa-Chang *et al.*, 2009).

Manquen també resultats consistents per conèixer la relació entre l'activació cerebral i el rendiment cognitiu en l'esquizofrènia. N'hi ha indicis, però, d'una relació entre un menor rendiment cognitiu i una major hipoactivació prefrontal en tasques de memòria de treball (Hill *et al.*, 2004; Van Snellenberg *et al.*, 2006).

Una metodologia alternativa, emprada per uns pocs estudis per aprofundir en l'estudi de les bases neurals dels dèficits cognitius en l'esquizofrènia, consisteix en comparar la neuroimatge estructural de dos grups de persones amb esquizofrènia, un dels quals tindria un rendiment cognitiu relativament preservat i l'altre el tindria clarament alterat. Aquesta estratègia té l'avantatge afegit que permet separar els canvis cerebrals estructurals i funcionals associats amb l'esquizofrènia dels canvis associats amb el dèficit cognitiu propi del trastorn. Aquests estudis, per ara, mostren possibles indicis

de canvis estructurals cerebrals subtils associats amb un baix rendiment cognitiu en l'esquizofrènia (Rüsch *et al.*, 2007; Wexler *et al.*, 2009; Cobia *et al.*, 2011).

Hipòtesi i objectius

Es treballa sota la hipòtesi que els dèficits cognitius de l'esquizofrènia poden estar reflectint anomalies cerebrals estructurals i funcionals.

L'objectiu d'aquest estudi era aprofundir en el coneixement dels correlats cerebrals estructurals i funcionals del dèficits cognitiu en l'esquizofrènia utilitzant un disseny que permetés comparar grups amb esquizofrènia preseleccionats per mostrar o no una alteració cognitiva marcada. En concret, els objectius eren:

1. Investigar la relació entre les alteracions cerebrals estructurals pròpies de l'esquizofrènia i l'alteració cognitiva pròpia del trastorn.
2. Determinar si l'alteració cognitiva de l'esquizofrènia s'associa específicament amb disfuncions cerebrals evidenciables mitjançant fMRI.

Mètode

Vam seleccionar una mostra de 26 participants amb esquizofrènia que presentaven alteracions cognitives severes i 23 que en presentaven una cognició relativament preservada, així com 39 controls sans. Tots tres grups eren comparables en edat, sexe i QI premòrbid estimat.

El criteri per dividir les persones amb esquizofrènia en un o altre grup va ser la seva puntuació en el RBMT (Wilson *et al.*, 1985) i la BADS (Wilson *et al.*, 1996). El RBMT i la BADS són dues bateries neuropsicològiques que valoren

respectivament el rendiment en memòria i en funcions executives mitjançant tasques amb més validesa ecològica que les proves neuropsicològiques clàssiques. El criteri d'inclusió al grup d'esquizofrènia sense alteració cognitiva significativa era un rendiment superior al percentil cinc en ambdues proves, mentre que, pel grup d'esquizofrènia i alteració cognitiva marcada, calia un rendiment menor del percentil ú en almenys una de les dues proves. Un estudi complementari realitzat va mostrar que aquests criteris de separació eren sensibles al rendiment cognitiu general (veure annex 2). El grup d'esquizofrènia sense rendiment alterat en la BADS i el RBMT presentava un rendiment numèricament més baix que el grup control en una sèrie de proves de rendiment en diferents àrees cognitives, però en gairebé cap d'aquestes comparacions la diferència va ser estadísticament significativa. Pel contrari, el grup d'esquizofrènia amb un rendiment alterat en almenys una de les dues bateries va puntuar significativament més baix que el grup control i que el grup d'esquizofrènia i rendiment cognitiu preservat en gairebé totes les àrees cognitives avaluades, més enllà de les funcions mnèsiques i executives.

Es va valorar la psicopatologia dels dos grups d'esquizofrènia mitjançant la PANSS (Peralta i Cuesta, 1994) i la CGI (NIMH, 1976). Així mateix, es va administrar a tots els participants el TAP (Del Ser *et al.*, 1997) -per tal d'estimar el rendiment cognitiu premòrbid- i una selecció de quatre proves del WAIS-III (Wechsler, 2001), per avaluar el rendiment intel·lectual actual.

Es va adquirir neuroimatge estructural mitjançant MRI de tots els participants. Es va realitzar anàlisis del volum cerebral total, de la substància grisa i la substància blanca total i dels ventricles laterals. Així mateix es va realitzar VBM per comparar els grups.

També es va adquirir imatges de fMRI de 19 dels participants amb esquizofrènia i alteració cognitiva i 18 dels que no en presentaven una alteració cognitiva marcada, així com de 34 controls. Durant l'adquisició de les imatges de fMRI, van executar la tasca n-back, un paradigma de memòria de treball.

El principal focus de les anàlisis cerebrals estructurals i funcionals se centrava en dues comparacions específiques. En primer lloc, vam comparar el grup de cognició preservada amb el grup control, per tal de determinar els canvis cerebrals atribuïbles a l'esquizofrènia, sense el factor confusional afegit de l'alteració cognitiva. En segon lloc, vam comparar els grups preservat i alterat en cognició per conèixer la possible contribució dels canvis cerebrals a l'alteració cognitiva pròpia del trastorn.

Resultats

Característiques de les mostres

Les mostres dels dos grups d'esquizofrènia (cognició alterada i cognició preservada) i les del grup control, tant en les anàlisis de neuroimatge estructural com en les de neuroimatge funcional, eren comparables en quant a edat, gènere i rendiment cognitiu premòrbid estimat. Així mateix, en totes dues anàlisis, els participants amb cognició alterada presentaven un rendiment intel·lectual actual significativament menor tant en el quocient intel·lectual (IQ) total com en el IQ manipulatiu respecte als altres dos grups. També hi havia diferències significatives entre ambdós grups de participants amb esquizofrènia en quant a la puntuació en simptomatologia negativa i en desorganitzada, de manera que el grup amb rendiment cognitiu més deficitari hi presentava una major puntuació.

Neuroimatge estructural

L'anàlisi estructural va mostrar que els participants amb esquizofrènia de forma conjunta mostraven una disminució del volum cerebral total i del volum de la substància grisa i un augment del volum dels ventricles laterals en comparació amb els controls. Així mateix, es va trobar disminució del volum cerebral total i del volum de la substància grisa en el grup d'esquizofrènia i cognició preservada en comparació amb el grup control.

No es va, però, trobar diferències entre els participants amb cognició preservada i els que presentaven alteracions cognitives en el volum dels ventricles laterals ni tampoc en el volum cerebral total ni tampoc en el volum de la substància grisa ni blanca.

Pel que fa als resultats de VBM, el participants amb esquizofrènia i una cognició relativament preservada van presentar un àrea de disminució volumètrica significativa a la substància grisa de regions prefrontals medials i del cingulat anterior en comparació amb els controls sans. No vam trobar, però, àrees d'augment de volum en el grup de cognició preservada en relació als controls. Així mateix, no vam trobar diferències entre ambdós grups en volum de substància blanca.

En comparar els grups d'esquizofrènia amb diferent rendiment cognitiu, no van aparèixer clústers amb diferències significatives en el volum de substància blanca i grisa.

Neuroimatge funcional

Pel que fa al rendiment en la tasca n-back de memòria de treball, els participants amb esquizofrènia i cognició alterada van tenir, de forma general, un rendiment més baix que els altres dos grups i, al mateix temps, els

participants amb esquizofrènia i cognició relativament preservada van presentar un pitjor rendiment que els controls sans.

La troballa més consistent en la comparació de neuroimatge funcional entre els controls i els participants amb esquizofrènia i cognició preservada va ser un dèficit en desactivar parts de l'escorça prefrontal medial, el cingulat anterior, l'ínsula, el complex amígdala-hipocamp i l'escorça temporal durant la realització de la tasca n-back.

Així mateix, els participants amb alteració cognitiva van presentar hipoactivació en l'escorça prefrontal dorsolateral, entre d'altres regions, en relació als participants amb cognició relativament preservada.

Discussió

Els resultats d'aquest estudi no relacionen els dèficits cognitius propis de l'esquizofrènia amb les alteracions estructurals cerebrals que sovint acompanyen el trastorn. Aquesta manca de resultats positius difícilment es podria relacionar amb la grandària de les mostres utilitzades, donat que caldria mostres de centenars de subjectes perquè els resultats assolissin significació estadística.

De fet, la literatura existent no mostra evidència consistent d'una relació entre els canvis estructurals i les alteracions cognitives en l'esquizofrènia, ni en estudis correlacionals (per exemple Crespo-Facorro *et al.*, 2007) ni en estudis que comparen grups de persones amb esquizofrènia dividides en funció del seu rendiment cognitiu (Rüsch *et al.*, 2007; Wexler *et al.*, 2009; Cobia *et al.*, 2011). La manca d'una relació clara entre el dèficits cognitius i l'esquizofrènia també es posa de manifest en estudis que divideixen els pacients en funció de

característiques relacionades indirectament amb una major alteració cognitiva, com ara l'esquizofrènia deficitària (Galderisi i Maj, 2009) o l'esquizofrènia kraepeliniana (Mitelman *et al.*, 2007; Mitelman *et al.*, 2010). En la mateixa línia, tampoc hi ha evidència d'una major presència d'alteracions histopatològiques associades amb les demències en persones grans amb esquizofrènia que en la població general, malgrat que moltes persones grans amb esquizofrènia tenen un rendiment cognitiu molt deficitari, comparable fins i tot al de les persones amb demència (p.e. Harrison, 1999).

En contrast amb la manca de resultats positius en neuroimatge estructural, vam trobar diferències significatives en neuroimatge funcional entre els participants amb esquizofrènia dividits en funció del seu rendiment cognitiu. Aquestes diferències es van manifestar en una menor activació de l'escorça prefrontal dorsolateral i altres àrees cerebrals en el grup amb rendiment alterat respecte al grup relativament preservat en rendiment cognitiu.

Els resultats d'aquest estudi mostren de forma clara que gran part de la hipofrontalitat detectada en l'esquizofrènia podria estar relacionada amb l'alteració cognitiva de la malaltia. En aquest sentit, aquests resultats poden ser més contundents que els de dues metaanàlisis prèvies (Hill *et al.*, 2004; Van Snellenberg *et al.*, 2006), que havien trobat una correlació estadísticament no significativa (p=0.06 i 0.09 respectivament) entre la hipofrontalitat i el dèficit cognitiu. El fet que aquest estudi hagi controlat que el grups fossin comparables en variables potencialment confusionals (edat, l sexe i nivell cognitiu premòrbid) pot haver facilitat la major robustesa de les dades.

Com ja s'ha comentat a la introducció, diferents metaanàlisis (Glahn *et al.*, 2005; Minzenberg *et al.*, 2009) mostren una major activació en àrees

cerebrals frontals en persones amb esquizofrènia en comparació a controls sans durant la realització de tasques executives. El grup de Weinberger (p.e. Weinberger *et al.*, 2001) ho ha interpretat com un intent de compensació de la menor activació prefrontal dorsolateral per intentar mantenir el rendiment cognitiu. Els resultats d'aquesta tesi, però, no avalen la hipòtesi del grup de Weinberger.

En canvi, aquesta tesi ha mostrat resultats a favor de dèficits de desactivació a l'escorça prefrontal medial de les persones amb esquizofrènia i una cognició preservada. Altres estudis ja han posat de manifest aquest canvi cerebral funcional en l'esquizofrènia, que, fins i tot, romandria després de controlar les diferències en rendiment cognitiu (Pomarol-Clotet *et al.*, 2008; Whitfield-Gabrieli *et al.*, 2009). Tot plegat suggereix que els problemes de desactivació de l'escorça prefrontal medial estarien associats a patir esquizofrènia i serien independents de les alteracions cognitives pròpies de la malaltia. Al mateix temps, aquest dèficit de desactivació, que s'ha interpretat com una alteració en la xarxa neural per defecte (p.e. Whitfield-Gabrieli *et al.*, 2009), podria explicar almenys part de l'aparent hiperactivació trobada en l'esquizofrènia (Pomarol-Clotet *et al.*, 2008). Cal destacar que l'escorça prefrontal medial, on apareix el clúster amb un dèficit en la desactivació, és bàsicament la mateixa àrea en què s'han trobat diferències en la comparació de VBM entre el grup amb esquizofrènia i cognició preservada i el grup control.

La hipoactivació frontal associada amb els dèficit cognitius en l'esquizofrènia pot tenir un paral·lelisme amb l'alteració cerebral funcional trobada en els estats confusionals o amb la relacionada amb la disfunció executiva en fases inicials de la malaltia de Parkinson. En aquests casos, la

disfunció cognitiva pot ser reversible. Continuant amb el paral·lelisme, la disfunció cognitiva en l'esquizofrènia també podria ser reversible, encara que ara per ara ni els tractaments farmacològics ni la intervenció neurocognitiva s'hi han mostrat clarament eficaços.

Pel que fa a les limitacions que manifesta aquest estudi, són de destacar la grandària de la mostra i el fet que el criteri d'inclusió per al grup amb esquizofrènia i cognició preservada no exclogui totalment la possibilitat que els subjectes d'aquest grup tinguin un rendiment cognitiu límit. Al mateix temps, cal tenir en compte que el rendiment cognitiu entre els 3 grups difereix en la tasca de n-back. Tanmateix, els grups van ser triats en funció del seu rendiment cognitiu, de forma que no es podria afegir el rendiment cognitiu com a covariable a l'anàlisi perquè aquest n'està considerat com a factor de separació dels grups. Una altra limitació n'és la grossor dels talls a l'estudi de neuroimatge funcional (7mm), relativament gran pels estàndards actuals. L'objectiu d'això és mantenir el volum total dels vòxels amb una grandària que permeti mantenir una bona relació entre senyal i soroll en les imatges BOLD.

Conclusions

1. L'estudi va trobar que els participants amb esquizofrènia sense alteració cognitiva marcada presentaven una disminució significativa en el volum cerebral total i en el volum de substància grisa així com un eixamplament dels ventricles laterals en comparació amb el grup control. Tanmateix, aquests canvis no van distingir entre els pacients amb i sense una alteració cognitiva moderada o severa.

2. En utilitzar VBM, es va trobar un clúster de reducció de volum a la substància grisa de l'escorça frontal orbitomedial en el grup d'esquizofrènia sense alteració cognitiva marcada en comparació amb el grup control. Tanmateix, no s'hi van trobar diferències volumètriques en aquest o altres clústers entre els grups d'esquizofrènia amb i sense alteració cognitiva marcada. Aquests resultats i els esmentats anteriorment recolzen que l'alteració cognitiva en l'esquizofrènia no seria una funció dels canvis cerebrals estructurals presents en el trastorn.

3. Les persones amb esquizofrènia i dèficit cognitiu van mostrar un nivell més gran de reducció de l'activació a l'escorça prefrontal dorsolateral que els pacients amb preservació cognitiva durant la realització de la tasca n-back de memòria de treball. Aquest resultat suggereix que l'alteració cognitiva en l'esquizofrènia està molt relacionada amb la hipofrontalitat, una de les principals alteracions de neuroimatge funcional trobades en el trastorn.

4. Els pacients amb esquizofrènia sense alteració cognitiva van presentar una desactivació insuficient de l'escorça prefrontal medial. Tanmateix, els pacients amb esquizofrènia i alteració cognitiva moderada o severa no van presentar un major fracàs en la desactivació que els pacients amb preservació cognitiva. Aquest resultat no recolza la visió que l'alteració en la desactivació, i, en conseqüència, la disfunció en la xarxa neural per defecte estiguin en la base de l'alteració cognitiva pròpia de l'esquizofrènia.

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8. References

Aleman A, Kahn RS, Selten JP. Sex differences in the risk of schizophrenia: evidence from meta-analysis. *Arch Gen Psychiatry* 2003; 60(6): 565-71.

Allen DN, Goldstein G, Warnick E. A consideration of neuropsychologically normal schizophrenia. *J Int Neuropsychol Soc* 2003; 9(1): 56-63.

Andreasen NC, Olsen S. Negative v positive schizophrenia. Definition and validation. *Arch Gen Psychiatry* 1982; 39(7): 789-94.

Andreasen NC, Swayze VW, 2nd, Flaum M, Yates WR, Arndt S, McChesney C. Ventricular enlargement in schizophrenia evaluated with computed tomographic scanning. Effects of gender, age, and stage of illness. *Arch Gen Psychiatry* 1990; 47(11): 1008-15.

Andreasen NC, Arndt S, Alliger R, Miller D, Flaum M. Symptoms of schizophrenia. Methods, meanings, and mechanisms. *Arch Gen Psychiatry* 1995; 52(5): 341-51.

Andreasen NC. A unitary model of schizophrenia: Bleuler's "fragmented phrene" as schizencephaly. *Arch Gen Psychiatry* 1999; 56(9): 781-7.

Antonova E, Sharma T, Morris R, Kumari V. The relationship between brain structure and neurocognition in schizophrenia: a selective review. *Schizophr Res* 2004; 70(2-3): 117-45.

APA. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington DC: American Psychiatric Association; 1994.

Ariel RN, Golden CJ, Berg RA, Quaife MA, Dirksen JW, Forsell T, Wilson J, Graber B. Regional cerebral blood flow in schizophrenics. Tests using the xenon Xe 133 inhalation method. *Arch Gen Psychiatry* 1983; 40(3): 258-63.

Ashburner J, Friston KJ. Voxel-based morphometry--the methods. *Neuroimage* 2000; 11(6 Pt 1): 805-21.

Balu DT, Coyle JT. Neuroplasticity signaling pathways linked to the pathophysiology of schizophrenia. *Neurosci Biobehav Rev* 2011; 35(3): 848-70.

Basso MR, Nasrallah HA, Olson SC, Bornstein RA. Neuropsychological correlates of negative, disorganized and psychotic symptoms in schizophrenia. *Schizophr Res* 1998; 31(2-3): 99-111.

Baxter RD, Liddle PF. Neuropsychological deficits associated with schizophrenic syndromes. *Schizophr Res* 1998; 30(3): 239-49.

Beckmann CF, Jenkinson M, Smith SM. General multilevel linear modeling for group analysis in FMRI. *Neuroimage* 2003; 20(2): 1052-63.

Beckmann CF, Jenkinson M, Woolrich MW, Behrens TE, Flitney DE, Devlin JT, Smith SM. Applying FSL to the FIAC data: model-based and model-free analysis of voice and sentence repetition priming. *Hum Brain Mapp* 2006; 27(5): 380-91.

Bell MD, Lysaker PH, Beam-Goulet JL, Milstein RM, Lindenmayer JP. Five-component model of schizophrenia: assessing the factorial invariance of the positive and negative syndrome scale. *Psychiatry Res* 1994a; 52(3): 295-303.

Bell MD, Lysaker PH, Milstein RM, Beam-Goulet JL. Concurrent validity of the cognitive component of schizophrenia: relationship of PANSS scores to neuropsychological assessments. *Psychiatry Res* 1994b; 54(1): 51-8.

Blanchard JJ, Neale JM. The neuropsychological signature of schizophrenia: generalized or differential deficit? *Am J Psychiatry* 1994; 151(1): 40-8.

Bohnen NI, Albin RL. The cholinergic system and Parkinson disease. *Behav Brain Res* 2011; 221(2): 564-73.

Bonilha L, Molnar C, Horner MD, Anderson B, Forster L, George MS, Nahas Z. Neurocognitive deficits and prefrontal cortical atrophy in patients with schizophrenia. *Schizophr Res* 2008; 101(1-3): 142-51.

Bora E, Fornito A, Raduà J, Walterfang M, Seal M, Wood SJ, Yücel M, Velakoulis D, Pantelis C. Neuroanatomical abnormalities in schizophrenia: a multimodal voxelwise meta-analysis and meta-regression analysis. *Schizophr Res* 2011a; 127(1-3): 46-57.

Bora E, Fornito A, Yücel M, Pantelis C. The effects of gender on grey matter abnormalities in major psychoses: a comparative voxelwise meta-analysis of schizophrenia and bipolar disorder. *Psychol Med* 2011b; 1-13. [Published online ahead of print August 2011]

Breier A, Su TP, Saunders R, Carson RE, Kolachana BS, de Bartolomeis A, Weinberger DR, Weisenfeld N, Malhotra AK, Eckelman WC, Pickar D. Schizophrenia is associated with elevated amphetamine-induced synaptic dopamine concentrations: evidence from a novel positron emission tomography method. *Proc Natl Acad Sci U S A* 1997; 94(6): 2569-74.

Brekke JS, Raine A, Thomson C. Cognitive and psychophysiological correlates of positive, negative, and disorganized symptoms in the schizophrenia spectrum. *Psychiatry Res* 1995; 57(3): 241-50.

Brown KW, White T. Syndromes of chronic schizophrenia and some clinical correlates. *Br J Psychiatry* 1992; 161: 317-22.

Broyd SJ, Demanuele C, Debener S, Helps SK, James CJ, Sonuga-Barke EJ. Default-mode brain dysfunction in mental disorders: a systematic review. *Neurosci Biobehav Rev* 2009; 33(3): 279-96.

Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci* 2008; 1124: 1-38.

Buchanan RW, Javitt DC, Marder SR, Schooler NR, Gold JM, McMahon RP, Heresco-Levy U, Carpenter WT. The Cognitive and Negative Symptoms in Schizophrenia Trial (CONSIST): the efficacy of glutamatergic agents for negative symptoms and cognitive impairments. *Am J Psychiatry* 2007; 164(10): 1593-602.

Buchanan RW, Kreyenbuhl J, Kelly DL, Noel JM, Boggs DL, Fischer BA, Himelhoch S, Fang B, Peterson E, Aquino PR, Keller W. The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. *Schizophr Bull* 2010; 36(1): 71-93.

Buchsbaum MS, DeLisi LE, Holcomb HH, Cappelletti J, King AC, Johnson J, Hazlett E, Dowling-Zimmerman S, Post RM, Morihisa J, et al. Anteroposterior gradients in cerebral glucose use in schizophrenia and affective disorders. *Arch Gen Psychiatry* 1984; 41(12): 1159-66.

Buka SL, Tsuang MT, Lipsitt LP. Pregnancy/delivery complications and psychiatric diagnosis. A prospective study. *Arch Gen Psychiatry* 1993; 50(2): 151-6.

Burdick KE, Gopin CB, Malhotra AK. Pharmacogenetic approaches to cognitive enhancement in schizophrenia. *Harv Rev Psychiatry* 2011; 19(3): 102-8.

Cadenhead KS, Geyer MA, Butler RW, Perry W, Sprock J, Braff DL. Information processing deficits of schizophrenia patients: relationship to clinical ratings, gender and medication status. *Schizophr Res* 1997; 28(1): 51-62.

Callicott JH, Bertolino A, Mattay VS, Langheim FJ, Duyn J, Coppola R, Goldberg TE, Weinberger DR. Physiological dysfunction of the dorsolateral prefrontal cortex in schizophrenia revisited. *Cereb Cortex* 2000; 10(11): 1078-92.

Callicott JH, Mattay VS, Verchinski BA, Marenco S, Egan MF, Weinberger DR. Complexity of prefrontal cortical dysfunction in schizophrenia: more than up or down. *Am J Psychiatry* 2003; 160(12): 2209-15.

Camchong J, Macdonald AW, 3rd, Bell C, Mueller BA, Lim KO. Altered Functional and Anatomical Connectivity in Schizophrenia. *Schizophr Bull* 2011; 37(3): 640-50.

Cameron AM, Oram J, Geffen GM, Kavanagh DJ, McGrath JJ, Geffen LB. Working memory correlates of three symptom clusters in schizophrenia. *Psychiatry Res* 2002; 110(1): 49-61.

Cannon M, Jones PB, Murray RM. Obstetric complications and schizophrenia: historical and meta-analytic review. *Am J Psychiatry* 2002; 159(7): 1080-92.

Cannon TD, Bearden CE, Hollister JM, Rosso IM, Sanchez LE, Hadley T. Childhood cognitive functioning in schizophrenia patients and their unaffected siblings: a prospective cohort study. *Schizophr Bull* 2000; 26(2): 379-93.

Cardno AG, Gottesman, II. Twin studies of schizophrenia: from bow-and-arrow concordances to star wars Mx and functional genomics. *Am J Med Genet* 2000; 97(1): 12-7.

Clark O, O'Carroll RE. An examination of the relationship between executive function, memory and rehabilitation status in schizophrenia. *Neuropsychol Rehabil* 1998; 8: 229-41.

Cobia DJ, Csernansky JG, Wang L. Cortical thickness in neuropsychologically near-normal schizophrenia. *Schizophr Res* 2011; 133(1-3): 68-76.

Cohen AS, Saperstein AM, Gold JM, Kirkpatrick B, Carpenter WT, Jr., Buchanan RW. Neuropsychology of the deficit syndrome: new data and meta-analysis of findings to date. *Schizophr Bull* 2007; 33(5): 1201-12.

Collins PY, Patel V, Joestl SS, March D, Insel TR, Daar AS, Anderson W, Dhansay MA, Phillips A, Shurin S, Walport M, Ewart W, Savill SJ, Bordin IA, Costello EJ, Durkin M, Fairburn C, Glass RI, Hall W, Huang Y, Hyman SE, Jamison K, Kaaya S, Kapur S, Kleinman A, Ogunniyi A, Otero-Ojeda A, Poo MM, Ravindranath V, Sahakian BJ, Saxena S, Singer PA, Stein DJ. Grand challenges in global mental health. *Nature* 2011; 475(7354): 27-30.

Coyle JT, Balu D, Benneyworth M, Basu A, Roseman A. Beyond the dopamine receptor: novel therapeutic targets for treating schizophrenia. *Dialogues Clin Neurosci* 2010; 12(3): 359-82.

Crawford JR, Garthwaite PH, Slick DJ. On percentile norms in neuropsychology: proposed reporting standards and methods for quantifying the uncertainty over the percentile ranks of test scores. *Clin Neuropsychol* 2009; 23(7): 1173-95.

Crespo-Facorro B, Barbadillo L, Pelayo-Terán JM, Rodríguez-Sánchez JM. Neuropsychological functioning and brain structure in schizophrenia. *Int Rev Psychiatry* 2007; 19(4): 325-36.

Cuesta MJ, Peralta V. Cognitive disorders in the positive, negative, and disorganization syndromes of schizophrenia. *Psychiatry Res* 1995; 58(3): 227-35.

Cunningham Owens DG. A guide to the extrapyramidal side-effects of neurleptic drugs. Cambridge: Cambridge University Press; 1999.

Chan RC, Chen EY, Cheung EF, Chen RY, Cheung HK. The components of executive functioning in a cohort of patients with chronic schizophrenia: a multiple single-case study design. *Schizophr Res* 2006; 81(2-3): 173-89.

Chapman LJ, Chapman JP. Disordered Thought in Schizophrenia. New York: Apple-Century-Crofts; 1973.

Chua SE, McKenna PJ. Schizophrenia--a brain disease? A critical review of structural and functional cerebral abnormality in the disorder. *Br J Psychiatry* 1995; 166(5): 563-82.

Daban C, Amado I, Baylé F, Gut A, Willard D, Bourdel MC, Loo H, Olié JP, Millet B, Krebs MO, Poirier MF. Correlation between clinical syndromes and neuropsychological tasks in unmedicated patients with recent onset schizophrenia. *Psychiatry Res* 2002; 113(1-2): 83-92.

Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis. I. Segmentation and surface reconstruction. *Neuroimage* 1999; 9(2): 179-94.

Davatzikos C. Why voxel-based morphometric analysis should be used with great caution when characterizing group differences. *Neuroimage* 2004; 23(1): 17-20.

David GB. The pathological anatomy of the shizophrenias. In *Schizophrenia: Somatic aspects* (ed. D. Richter): 93-130. Oxford: Pergamon; 1957.

Davis JM. Antipsychotic drugs. In *Comprehensive textbook of psychiatry* (ed. H. I. Kaplan and B. J. Sadok): 1481-512. Baltimore, MD: Williams and Wilkins; 1985.

de Vries PJ, Honer WG, Kemp PM, McKenna PJ. Dementia as a complication of schizophrenia. *J Neurol Neurosurg Psychiatry* 2001; 70(5): 588-96.

Del Ser T, González-Montalvo JI, Martínez-Espinosa S, Delgado-Villapalos C, Bermejo F. Estimation of premorbid intelligence in Spanish people with the Word Accentuation Test and its application to the diagnosis of dementia. *Brain Cogn* 1997; 33(3): 343-56.

DeLisi LE, Buchsbaum MS, Holcomb HH, Dowling-Zimmerman S, Pickar D, Boronow J, Morihisa JM, van Kammen DP, Carpenter W, Kessler R, et al. Clinical correlates of decreased anteroposterior metabolic gradients in positron emission tomography (PET) of schizophrenic patients. *Am J Psychiatry* 1985; 142(1): 78-81.

DeLisi LE. Reviewing the "facts about schizophrenia": a possible or impossible task? *Schizophr Res* 2008a; 102(1-3): 19-20.

Delisi LE. The Concept of Progressive Brain Change in Schizophrenia: Implications for Understanding Schizophrenia. *Schizophr Bull* 2008b; 106(2-3): 115-24.

Dibben CR, Rice C, Laws K, McKenna PJ. Is executive impairment associated with schizophrenic syndromes? A meta-analysis. *Psychol Med* 2009; 39(3): 381-92.

Dickinson D, Tenhula W, Morris S, Brown C, Peer J, Spencer K, Li L, Gold JM, Bellack AS. A randomized, controlled trial of computer-assisted cognitive remediation for schizophrenia. *Am J Psychiatry* 2010; 167(2): 170-80.

Dixon LB, Lehman AF, Levine J. Conventional antipsychotic medications for schizophrenia. *Schizophr Bull* 1995; 21(4): 567-77.

Dixon LB, Dickerson F, Bellack AS, Bennett M, Dickinson D, Goldberg RW, Lehman A, Tenhula WN, Calmes C, Pasillas RM, Peer J, Kreyenbuhl J. The 2009 schizophrenia PORT psychosocial treatment recommendations and summary statements. *Schizophr Bull* 2010; 36(1): 48-70.

Done DJ, Johnstone EC, Frith CD, Golding J, Shepherd PM, Crow TJ. Complications of pregnancy and delivery in relation to psychosis in adult life: data from the British perinatal mortality survey sample. *BMJ* 1991; 302(6792): 1576-80.

Done DJ, Crow TJ, Johnstone EC, Sacker A. Childhood antecedents of schizophrenia and affective illness: social adjustment at ages 7 and 11. *BMJ* 1994; 309(6956): 699-703.

Donohoe G, Hayden J, McGlade N, O'Grada C, Burke T, Barry S, Behan C, Dinan TG, O'Callaghan E, Gill M, Corvin AP. Is "clinical" insight the same as "cognitive" insight in schizophrenia? *J Int Neuropsychol Soc* 2009; 15(3): 471-5.

Duffy L, O'Carroll R. Memory impairment in schizophrenia--a comparison with that observed in the Alcoholic Korsakoff syndrome. *Psychol Med* 1994; 24(1): 155-65.

Eckman PS, Shean GD. Impairment in test performance and symptom dimensions of schizophrenia. *J Psychiatr Res* 2000; 34(2): 147-53.

Edlinger M, Baumgartner S, Eltanaihi-Furtmuller N, Hummer M, Fleischhacker WW. Switching between second-generation antipsychotics: why and how? *CNS Drugs* 2005; 19(1): 27-42.

Fett AK, Viechtbauer W, Domínguez MD, Penn DL, van Os J, Krabbendam L. The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: a meta-analysis. *Neurosci Biobehav Rev* 2011; 35(3): 573-88.

Fioravanti M, Carlone O, Vitale B, Cinti ME, Clare L. A meta-analysis of cognitive deficits in adults with a diagnosis of schizophrenia. *Neuropsychol Rev* 2005; 15(2): 73-95.

Fischer BA, Keller WR, Arango C, Pearlson GD, McMahon RP, Meyer WA, Francis A, Kirkpatrick B, Carpenter WT, Buchanan RW. Cortical structural abnormalities in deficit versus nondeficit schizophrenia. *Schizophr Res* 2012; 136 (1-3): 51-4.

Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, van der Kouwe A, Killiany R, Kennedy D, Klaveness S, Montillo A, Makris N, Rosen B, Dale AM. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron* 2002; 33(3): 341-55.

Fletcher PC, McKenna PJ, Frith CD, Grasby PM, Friston KJ, Dolan RJ. Brain activations in schizophrenia during a graded memory task studied with functional neuroimaging. *Arch Gen Psychiatry* 1998; 55(11): 1001-8.

Fornito A, Yücel M, Patti J, Wood SJ, Pantelis C. Mapping grey matter reductions in schizophrenia: an anatomical likelihood estimation analysis of voxel-based morphometry studies. *Schizophr Res* 2009; 108(1-3): 104-13.

Frisoni GB, Prestia A, Geroldi C, Adorni A, Ghidoni R, Amicucci G, Bonetti M, Soricelli A, Rasser PE, Thompson PM, Giannakopoulos P. Alzheimer's CSF markers in older schizophrenia patients. *Int J Geriatr Psychiatry* 2011; 26(6): 640-8.

Frith CD, Leary J, Cahill C, Johnstone EC. Performance on psychological tests. Demographic and clinical correlates of the results of these tests. *Br J Psychiatry Suppl* 1991; (13): 26-9, 44-6.

Frith CD, Friston KJ, Herold S, Silbersweig D, Fletcher P, Cahill C, Dolan RJ, Frackowiak RS, Liddle PF. Regional brain activity in chronic schizophrenic patients during the performance of a verbal fluency task. *Br J Psychiatry* 1995; 167(3): 343-9.

Galderisi S, Maj M. Deficit schizophrenia: an overview of clinical, biological and treatment aspects. *Eur Psychiatry* 2009; 24(8): 493-500.

Gershon ES, Alliey-Rodriguez N, Liu C. After GWAS: searching for genetic risk for schizophrenia and bipolar disorder. *Am J Psychiatry* 2011; 168(3): 253-6.

Gevins A, Cutillo B. Spatiotemporal dynamics of component processes in human working memory. *Electroencephalogr Clin Neurophysiol* 1993; 87(3): 128-43.

Glahn DC, Ragland JD, Abramoff A, Barrett J, Laird AR, Bearden CE, Velligan DI. Beyond hypofrontality: a quantitative meta-analysis of functional neuroimaging studies of working memory in schizophrenia. *Hum Brain Mapp* 2005; 25(1): 60-9.

Glahn DC, Laird AR, Ellison-Wright I, Thelen SM, Robinson JL, Lancaster JL, Bullmore E, Fox PT. Meta-Analysis of Gray Matter Anomalies in Schizophrenia: Application of Anatomic Likelihood Estimation and Network Analysis. *Biol Psychiatry* 2008; 64(9): 774-81.

Goff DC, Cather C, Evins AE, Henderson DC, Freudenreich O, Copeland PM, Bierer M, Duckworth K, Sacks FM. Medical morbidity and mortality in schizophrenia: guidelines for psychiatrists. *J Clin Psychiatry* 2005; 66(2): 183-94; quiz 47, 273-4.

Goff DC, Hill M, Barch D. The treatment of cognitive impairment in schizophrenia. *Pharmacol Biochem Behav* 2011; 99(2): 245-53.

Goldberg SC, Klerman GL, Cole JO. Changes in Schizophrenic Psychopathology and Ward Behaviour as a Function of Phenothiazine Treatment. *Br J Psychiatry* 1965; 111: 120-33.

Goldberg TE, Weinberger DR, Berman KF, Pliskin NH, Podd MH. Further evidence for dementia of the prefrontal type in schizophrenia? A controlled study of teaching the Wisconsin Card Sorting Test. *Arch Gen Psychiatry* 1987; 44(11): 1008-14.

Goldberg TE, Goldman RS, Burdick KE, Malhotra AK, Lencz T, Patel RC, Woerner MG, Schooler NR, Kane JM, Robinson DG. Cognitive improvement after treatment with second-generation antipsychotic medications in first-episode schizophrenia: is it a practice effect? *Arch Gen Psychiatry* 2007; 64(10): 1115-22.

Goldberg TE, Keefe RS, Goldman RS, Robinson DG, Harvey PD. Circumstances under which practice does not make perfect: a review of the practice effect literature in schizophrenia and its relevance to clinical treatment studies. *Neuropsychopharmacology* 2010; 35(5): 1053-62.

Goldstein G. Cognitive and perceptual differences between schizophrenics and organics. *Schizophr Bull* 1978; 4(2): 160-85.

Gomar JJ, Ortiz-Gil J, McKenna PJ, Salvador R, Sans-Sansa B, Sarró S, Guerrero A, Pomarol-Clotet E. Validation of the Word Accentuation Test (TAP) as a means of estimating premorbid IQ in Spanish speakers. *Schizophr Res* 2011; 128(1-3): 175-6.

González-Suárez B, Gomar JJ, Pousa E, Ortiz-Gil J, García A, Salvador R, Sans-Sansa B, Pomarol-Clotet E, McKenna PJ. Awareness of cognitive impairment in schizophrenia and its relationship to insight into illness. *Schizophr Res* 2011; 133(1-3): 187-92.

Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage* 2001; 14(1 Pt 1): 21-36.

Gottesman II. Schizophrenia genesis: The origins of madness. New York: Freeman; 1991.

Green DM, Swets JA. Signal Detection Theory and Psychophysics. New york, USA: Krieger; 1966.

Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia? *Am J Psychiatry* 1996; 153(3): 321-30.

Green MF, Nuechterlein KH. Should schizophrenia be treated as a neurocognitive disorder? *Schizophr Bull* 1999; 25(2): 309-19.

Green MF, Kern RS, Braff DL, Mintz J. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? *Schizophr Bull* 2000; 26(1): 119-36.

Guillem F, Bicu M, Bloom D, Wolf MA, Desautels R, Lalinec M, Kraus D, Debruille JB. Neuropsychological impairments in the syndromes of schizophrenia: a comparison between different dimensional models. *Brain Cogn* 2001; 46(1-2): 153-9.

Gur RE, Skolnick BE, Gur RC, Caroff S, Rieger W, Obrist WD, Younkin D, Reivich M. Brain function in psychiatric disorders. I. Regional cerebral blood flow in medicated schizophrenics. *Arch Gen Psychiatry* 1983; 40(11): 1250-4.

Gur RE, Gur RC, Skolnick BE, Caroff S, Obrist WD, Resnick S, Reivich M. Brain function in psychiatric disorders. III. Regional cerebral blood flow in unmedicated schizophrenics. *Arch Gen Psychiatry* 1985; 42(4): 329-34.

Gusnard DA, Raichle ME. Searching for a baseline: functional imaging and the resting human brain. *Nat Rev Neurosci* 2001; 2(10): 685-94.

Häfner H, an der Heiden W, Behrens S, Gattaz WF, Hambrecht M, Löffler W, Maurer K, Munk-Jorgensen P, Nowotny B, Riecher-Rössler A, Stein A. Causes and consequences of the gender difference in age at onset of schizophrenia. *Schizophr Bull* 1998a; 24(1): 99-113.

Häfner H, Maurer K, Löffler W, an der Heiden W, Munk-Jorgensen P, Hambrecht M, Riecher-Rössler A. The ABC Schizophrenia Study: a preliminary overview of the results. *Soc Psychiatry Psychiatr Epidemiol* 1998b; 33(8): 380-6.

Harrison PJ. The neuropathology of schizophrenia. A critical review of the data and their interpretation. *Brain* 1999; 122 (Pt 4)593-624.

Harrison PJ, Freemantle N, Geddes JR. Meta-analysis of brain weight in schizophrenia. *Schizophr Res* 2003; 64(1): 25-34.

Harrison PJ, Weinberger DR. Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. *Mol Psychiatry* 2005; 10(1): 40-68; image 5.

Harvey PD, Lombardi J, Kincaid MM, Parrella M, White L, Powchik P, Davidson M. Cognitive functioning in chronically hospitalized schizophrenic patients: age-related changes and age disorientation as a predictor of impairment. *Schizophr Res* 1995; 17(1): 15-24.

Harvey PD, Keefe RS. Studies of cognitive change in patients with schizophrenia following novel antipsychotic treatment. *Am J Psychiatry* 2001; 158(2): 176-84.

Harvey PD, Rabinowitz J, Eerdekens M, Davidson M. Treatment of cognitive impairment in early psychosis: a comparison of risperidone and haloperidol in a large long-term trial. *Am J Psychiatry* 2005; 162(10): 1888-95.

Heaton RK, Baade LE, Johnson KL. Neuropsychological test results associated with psychiatric disorders in adults. *Psychol Bull* 1978; 85(1): 141-62.

Heinrichs RW, Zakzanis KK. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. *Neuropsychology* 1998; 12(3): 426-45.

Hill K, Mann L, Laws KR, Stephenson CM, Nimmo-Smith I, McKenna PJ. Hypofrontality in schizophrenia: a meta-analysis of functional imaging studies. *Acta Psychiatr Scand* 2004; 110(4): 243-56.

Hill SK, Ragland JD, Gur RC, Gur RE. Neuropsychological profiles delineate distinct profiles of schizophrenia, an interaction between memory and executive function, and uneven distribution of clinical subtypes. *J Clin Exp Neuropsychol* 2002; 24(6): 765-80.

Himelhoch S, Taylor SF, Goldman RS, Tandon R. Frontal lobe tasks, antipsychotic medication, and schizophrenia syndromes. *Biol Psychiatry* 1996; 39(3): 227-9.

Holthausen EA, Wiersma D, Cahn W, Kahn RS, Dingemans PM, Schene AH, van den Bosch RJ. Predictive value of cognition for different domains of outcome in recent-onset schizophrenia. *Psychiatry Res* 2007; 149(1-3): 71-80.

Howell DC. Statistical Methods for Psychology. 4th ed. Belmont, CA: Duxbury Press; 1997.

Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: version III--the final common pathway. *Schizophr Bull* 2009; 35(3): 549-62.

Howes OD, Montgomery AJ, Asselin MC, Murray RM, Valli I, Tabraham P, Bramon-Bosch E, Valmaggia L, Johns L, Broome M, McGuire PK, Grasby PM. Elevated striatal dopamine function linked to prodromal signs of schizophrenia. *Arch Gen Psychiatry* 2009; 66(1): 13-20.

Ingvar DH, Franzén G. Abnormalities of cerebral blood flow distribution in patients with chronic schizophrenia. *Acta Psychiatr Scand* 1974; 50(4): 425-62.

Jablensky A. The diagnostic concept of schizophrenia: its history, evolution, and future prospects. *Dialogues Clin Neurosci* 2010; 12(3): 271-87.

Jastak S, Wilkinson GS. The Wide Range Achievement Test–Revised Administration Manual. Wilmington. Del: Jastak Associates; 1984.

Javitt DC, Zukin SR. Recent advances in the phencyclidine model of schizophrenia. *Am J Psychiatry* 1991; 148(10): 1301-8.

Jenkinson M, Smith S. A global optimisation method for robust affine registration of brain images. *Med Image Anal* 2001; 5(2): 143-56.

Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage* 2002; 17(2): 825-41.

Jeste DV, Wolkowitz OM, Palmer BW. Divergent trajectories of physical, cognitive, and psychosocial aging in schizophrenia. *Schizophr Bull* 2011; 37(3): 451-5.

John JP, Halahalli HN, Vasudev MK, Jayakumar PN, Jain S. Regional brain activation/deactivation during word generation in schizophrenia: fMRI study. *Br J Psychiatry* 2011; 198(3): 213-22.

Johnstone EC, Crow TJ, Frith CD, Husband J, Kreel L. Cerebral ventricular size and cognitive impairment in chronic schizophrenia. *Lancet* 1976; 2(7992): 924-6.

Johnstone M, Thomson PA, Hall J, McIntosh AM, Lawrie SM, Porteous DJ. DISC1 in schizophrenia: genetic mouse models and human genomic imaging. *Schizophr Bull* 2011; 37(1): 14-20.

Jones P, Rodgers B, Murray R, Marmot M. Child development risk factors for adult schizophrenia in the British 1946 birth cohort. *Lancet* 1994; 344(8934): 1398-402.

Jones PB, Rantakallio P, Hartikainen AL, Isohanni M, Sipila P. Schizophrenia as a long-term outcome of pregnancy, delivery, and perinatal complications: a 28-year follow-up of the 1966 north Finland general population birth cohort. *Am J Psychiatry* 1998; 155(3): 355-64.

Joyce EM, Collinson SL, Crichton P. Verbal fluency in schizophrenia: relationship with executive function, semantic memory and clinical alogia. *Psychol Med* 1996; 26(1): 39-49.

Kanaan RA, Kim JS, Kaufmann WE, Pearlson GD, Barker GJ, McGuire PK. Diffusion tensor imaging in schizophrenia. *Biol Psychiatry* 2005; 58(12): 921-9.

Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry* 1988; 45(9): 789-96.

Kane JM, Correll CU. Pharmacologic treatment of schizophrenia. *Dialogues Clin Neurosci* 2010; 12(3): 345-57.

Karlsgodt KH, Sanz J, van Erp TG, Bearden CE, Nuechterlein KH, Cannon TD. Re-evaluating dorsolateral prefrontal cortex activation during working memory in schizophrenia. *Schizophr Res* 2009; 108(1-3): 143-50.

Kay SR, Opler LA, Fiszbein A. Significance of positive and negative syndromes in chronic schizophrenia. *Br J Psychiatry* 1986; 149: 439-48.

Keefe RS, Mohs RC, Losonczy MF, Davidson M, Silverman JM, Kendler KS, Horvath TB, Nora R, Davis KL. Characteristics of very poor outcome schizophrenia. *Am J Psychiatry* 1987; 144(7): 889-95.

Keefe RS, Eesley CE, Poe MP. Defining a cognitive function decrement in schizophrenia. *Biol Psychiatry* 2005; 57(6): 688-91.

Keefe RS, Bilder RM, Davis SM, Harvey PD, Palmer BW, Gold JM, Meltzer HY, Green MF, Capuano G, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Davis CE, Hsiao JK, Lieberman JA. Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. *Arch Gen Psychiatry* 2007; 64(6): 633-47.

Kenny JT, Meltzer HY. Attention and higher cortical functions in schizophrenia. *J Neuropsychiatry Clin Neurosci* 1991; 3(3): 269-75.

Keshavan MS, Tandon R, Boutros NN, Nasrallah HA. Schizophrenia, "just the facts": what we know in 2008 Part 3: neurobiology. *Schizophr Res* 2008; 106(2-3): 89-107.

King DJ. The effect of neuroleptics on cognitive and psychomotor function. *Br J Psychiatry* 1990; 157: 799-811.

Kirkpatrick B, Buchanan RW, Ross DE, Carpenter WT, Jr. A separate disease within the syndrome of schizophrenia. *Arch Gen Psychiatry* 2001; 58(2): 165-71.

Kremen WS, Seidman LJ, Faraone SV, Toomey R, Tsuang MT. The paradox of normal neuropsychological function in schizophrenia. *J Abnorm Psychol* 2000; 109(4): 743-52.

Kubicki M, Westin CF, McCarley RW, Shenton ME. The application of DTI to investigate white matter abnormalities in schizophrenia. *Ann N Y Acad Sci* 2005; 1064: 134-48.

Kubicki M, McCarley R, Westin CF, Park HJ, Maier S, Kikinis R, Jolesz FA, Shenton ME. A review of diffusion tensor imaging studies in schizophrenia. *J Psychiatr Res* 2007; 41(1-2): 15-30.

Kyriakopoulos M, Bargiotas T, Barker GJ, Frangou S. Diffusion tensor imaging in schizophrenia. *Eur Psychiatry* 2008; 23(4): 255-73.

Laruelle M, Abi-Dargham A, van Dyck CH, Gil R, D'Souza CD, Erdos J, McCance E, Rosenblatt W, Fingado C, Zoghbi SS, Baldwin RM, Seibyl JP, Krystal JH, Charney DS, Innis RB. Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug-free schizophrenic subjects. *Proc Natl Acad Sci U S A* 1996; 93(17): 9235-40.

Laruelle M. Imaging dopamine transmission in schizophrenia. A review and meta-analysis. *Q J Nucl Med* 1998; 42(3): 211-21.

Laruelle M, Abi-Dargham A, Gil R, Kegeles L, Innis R. Increased dopamine transmission in schizophrenia: relationship to illness phases. *Biol Psychiatry* 1999; 46(1): 56-72.

Lee KH, Harris AW, Loughland CM, Williams LM. The five symptom dimensions and depression in schizophrenia. *Psychopathology* 2003; 36(5): 226-33.

Leucht S, Kissling W, Davis JM. Second-generation antipsychotics for schizophrenia: can we resolve the conflict? *Psychol Med* 2009; 39(10): 1591-602.

Lewine RR, Fogg L, Meltzer HY. Assessment of negative and positive symptoms in schizophrenia. *Schizophr Bull* 1983; 9(3): 368-76.

Lewis SW. Computerised tomography in schizophrenia 15 years on. *Br J Psychiatry Suppl* 1990; (9): 16-24.

Lezak MD, Howieson DB, Loring DW, Hannay HJ, Fischer JS. Neuropsychological Assessment. 4th ed. New York: Oxford University Press; 2004.

Liddle PF. Schizophrenic syndromes, cognitive performance and neurological dysfunction. *Psychol Med* 1987a; 17(1): 49-57.

Liddle PF. The symptoms of chronic schizophrenia. A re-examination of the positive-negative dichotomy. *Br J Psychiatry* 1987b; 151: 145-51.

Liddle PF, Morris DL. Schizophrenic syndromes and frontal lobe performance. *Br J Psychiatry* 1991; 158: 340-5.

Lindenmayer JP, Bernstein-Hyman R, Grochowski S, Bark N. Psychopathology of Schizophrenia: initial validation of a 5-factor model. *Psychopathology* 1995; 28(1): 22-31.

Lynch D, Laws KR, McKenna PJ. Cognitive behavioural therapy for major psychiatric disorder: does it really work? A meta-analytical review of well-controlled trials. *Psychol Med* 2010; 40(1): 9-24.

MacDonald AW, 3rd, Carter CS, Kerns JG, Ursu S, Barch DM, Holmes AJ, Stenger VA, Cohen JD. Specificity of prefrontal dysfunction and context processing deficits to schizophrenia in never-medicated patients with first-episode psychosis. *Am J Psychiatry* 2005; 162(3): 475-84.

MacLullich AM, Beaglehole A, Hall RJ, Meagher DJ. Delirium and long-term cognitive impairment. *Int Rev Psychiatry* 2009; 21(1): 30-42.

Macher JP. Schizophrenia. *Dialogues Clin Neurosci* 2010; 12(3): 265.

Malec J. Neuropsychological assessment of schizophrenia versus brain damage: a review. *J Nerv Ment Dis* 1978; 166(7): 507-16.

Malla A, Payne J. First-episode psychosis: psychopathology, quality of life, and functional outcome. *Schizophr Bull* 2005; 31(3): 650-71.

Manoach DS, Press DZ, Thangaraj V, Searl MM, Goff DC, Halpern E, Saper CB, Warach S. Schizophrenic subjects activate dorsolateral prefrontal cortex during a working memory task, as measured by fMRI. *Biol Psychiatry* 1999; 45(9): 1128-37.

Mathew RJ, Duncan GC, Weinman ML, Barr DL. Regional cerebral blood flow in schizophrenia. *Arch Gen Psychiatry* 1982; 39(10): 1121-4.

McDonald BC, Flashman LA, Saykin AJ. Executive dysfunction following traumatic brain injury: neural substrates and treatment strategies. *NeuroRehabilitation* 2002; 17(4): 333-44.

McEvoy JP. The costs of schizophrenia. *J Clin Psychiatry* 2007; 68 Suppl 144-7.

Mckenna PJ, Ornstein T, Baddeley AD. Schizophrenia. In *Handbook of Memory Disorders* (ed. A. D. Baddeley, B. A. Wilson and M. Kopelman). Chichester, UK; 2002.

Mckenna PJ, Oh TM. Thought disorder as a dysexecutive phenomenon. In *Schizophrenic Speech*: 123-45. Cambridge, U.K.: Cambridge University Press; 2005.

McKenna PJ. Schizophrenia and related syndromes. 2nd ed. Hove; New York: Taylor & Francis; 2007.

Mechelli A, Price CJ, Friston KJ, Ashburner J. Voxel-Based Morphometry of the Human Brain: Methods and Applications. *Current Medical Imaging Reviews* 2005; 1(2): 105-13.

Medalia A, Lim RW. Self-awareness of cognitive functioning in schizophrenia. *Schizophr Res* 2004; 71(2-3): 331-8.

Medalia A, Thysen J. Insight into neurocognitive dysfunction in schizophrenia. *Schizophr Bull* 2008; 34(6): 1221-30.

Meltzer HY, McGurk SR. The effects of clozapine, risperidone, and olanzapine on cognitive function in schizophrenia. *Schizophr Bull* 1999; 25(2): 233-55.

Milanovic SM, Thermenos HW, Goldstein JM, Brown A, Gabrieli SW, Makris N, Tsuang MT, Buka SL, Seidman LJ. Medial prefrontal cortical activation during working memory differentiates schizophrenia and bipolar psychotic patients: a pilot FMRI study. *Schizophr Res* 2011; 129(2-3): 208-10.

Minatogawa-Chang TM, Schaufelberger MS, Ayres AM, Duran FL, Gutt EK, Murray RM, Rushe TM, McGuire PK, Menezes PR, Scazufca M, Busatto GF. Cognitive performance is related to cortical grey matter volumes in early stages of schizophrenia: a population-based study of first-episode psychosis. *Schizophr Res* 2009; 113(2-3): 200-9.

Mintz AR, Dobson KS, Romney DM. Insight in schizophrenia: a meta-analysis. *Schizophr Res* 2003; 61(1): 75-88.

Minzenberg MJ, Laird AR, Thelen S, Carter CS, Glahn DC. Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. *Arch Gen Psychiatry* 2009; 66(8): 811-22.

Mishara AL, Goldberg TE. A meta-analysis and critical review of the effects of conventional neuroleptic treatment on cognition in schizophrenia: opening a closed book. *Biol Psychiatry* 2004; 55(10): 1013-22.

Mitelman SA, Brickman AM, Shihabuddin L, Newmark RE, Hazlett EA, Haznedar MM, Buchsbaum MS. A comprehensive assessment of gray and white matter volumes and their relationship to outcome and severity in schizophrenia. *Neuroimage* 2007; 37(2): 449-62.

Mitelman SA, Canfield EL, Brickman AM, Shihabuddin L, Hazlett EA, Buchsbaum MS. Progressive ventricular expansion in chronic poor-outcome schizophrenia. *Cogn Behav Neurol* 2010; 23(2): 85-8.

Mohamed S, Paulsen JS, O'Leary D, Arndt S, Andreasen N. Generalized cognitive deficits in schizophrenia: a study of first-episode patients. *Arch Gen Psychiatry* 1999; 56(8): 749-54.

Moritz S, Andresen B, Jacobsen D, Mersmann K, Wilke U, Lambert M, Naber D, Krausz M. Neuropsychological correlates of schizophrenic syndromes in patients treated with atypical neuroleptics. *Eur Psychiatry* 2001; 16(6): 354-61.

Mortimer AM. Cognitive function in schizophrenia--do neuroleptics make a difference? *Pharmacol Biochem Behav* 1997; 56(4): 789-95.

Mozaz T. Test conductual de memoria de Rivermead. Madrid: TEA; 1991.

Mueser KT, McGurk SR. Schizophrenia. *Lancet* 2004; 363(9426): 2063-72.

Nelson HE, Willis JR. The Revised National Adult Reading Test. Windsor, Berks, UK: NFER-Nelson; 1991.

NIMH. Clinical Global Impressions. In *ECDEU Assessment for Psychopharmacology, Rev* (ed. E. Guy). Rockville, MD: National Institute of Mental Health; 1976.

Norman RM, Malla AK, Morrison-Stewart SL, Helmes E, Williamson PC, Thomas J, Cortese L. Neuropsychological correlates of syndromes in schizophrenia. *Br J Psychiatry* 1997; 170: 134-9.

O'Leary DS, Flaum M, Kesler ML, Flashman LA, Arndt S, Andreasen NC. Cognitive correlates of the negative, disorganized, and psychotic symptom dimensions of schizophrenia. *J Neuropsychiatry Clin Neurosci* 2000; 12(1): 4-15.

Ojeda N, Ortuño F, Arbizu J, López P, Martí-Climent JM, Peñuelas I, Cervera-Enguix S. Functional neuroanatomy of sustained attention in schizophrenia: contribution of parietal cortices. *Hum Brain Mapp* 2002; 17(2): 116-30.

Oliva-Moreno J, López-Bastida J, Osuna-Guerrero R, Montejo-González AL, Duque-González B. The costs of schizophrenia in Spain. *Eur J Health Econ* 2006; 7(3): 182-88.

Owen AM. Cognitive dysfunction in Parkinson's disease: the role of frontostriatal circuitry. *Neuroscientist* 2004; 10(6): 525-37.

Pae CU, Juh R, Yoo SS, Choi BG, Lim HK, Lee C, Paik IH, Jeun SS, Lee CU. Verbal working memory dysfunction in schizophrenia: an FMRI investigation. *Int J Neurosci* 2008; 118(10): 1467-87.

Palmer BW, Heaton RK, Paulsen JS, Kuck J, Braff D, Harris MJ, Zisook S, Jeste DV. Is it possible to be schizophrenic yet neuropsychologically normal? *Neuropsychology* 1997; 11(3): 437-46.

Palmer BW, Dawes SE, Heaton RK. What do we know about neuropsychological aspects of schizophrenia? *Neuropsychol Rev* 2009; 19(3): 365-84.

Pantelis C, Velakoulis D, McGorry PD, Wood SJ, Suckling J, Phillips LJ, Yung AR, Bullmore ET, Brewer W, Soulsby B, Desmond P, McGuire PK. Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. *Lancet* 2003; 361(9354): 281-8.

Payne RW. Cognitive abnomalities. In *Handbook of Abnormal Psychology* (ed. H. J. Eysenck). London: Pitman; 1973.

Penadés R, Gastó C, Boget T, Catalán R, Salamero M. Deficit in schizophrenia: the relationship between negative symptoms and neurocognition. *Compr Psychiatry* 2001; 42(1): 64-9.

Peralta V, Cuesta MJ. Psychometric properties of the positive and negative syndrome scale (PANSS) in schizophrenia. *Psychiatry Res* 1994; 53(1): 31-40.

Pérez M, Godoy J. Comparison between a "traditional" memory test and a "behavioral" memory battery in Spanish patients. *J Clin Exp Neuropsychol* 1998; 20(4): 496-502.

Pomarol-Clotet E, Honey GD, Murray GK, Corlett PR, Absalom AR, Lee M, McKenna PJ, Bullmore ET, Fletcher PC. Psychological effects of ketamine in healthy volunteers. Phenomenological study. *Br J Psychiatry* 2006; 189: 173-9.

Pomarol-Clotet E, Salvador R, Sarró S, Gomar J, Vila F, Martínez Á, Guerrero A, Ortiz-Gil J, Sans-Sansa B, Capdevila A, Cebamanos JM, McKenna PJ. Failure to deactivate in the prefrontal cortex in schizophrenia: dysfunction of the default mode network? *Psychol Med* 2008; 38(8): 1185-93.

Pomarol-Clotet E, Canales-Rodríguez EJ, Salvador R, Sarró S, Gomar JJ, Vila F, Ortiz-Gil J, Iturria-Medina Y, Capdevila A, McKenna PJ. Medial prefrontal cortex pathology in schizophrenia

as revealed by convergent findings from multimodal imaging. *Mol Psychiatry* 2010; 15(8): 823-30.

Poulton R, Caspi A, Moffitt TE, Cannon M, Murray R, Harrington H. Children's self-reported psychotic symptoms and adult schizophreniform disorder: a 15-year longitudinal study. *Arch Gen Psychiatry* 2000; 57(11): 1053-8.

Powchik P, Davidson M, Haroutunian V, Gabriel SM, Purohit DP, Perl DP, Harvey PD, Davis KL. Postmortem studies in schizophrenia. *Schizophr Bull* 1998; 24(3): 325-41.

Reichenberg A. The assessment of neuropsychological functioning in schizophrenia. *Dialogues Clin Neurosci* 2010; 12(3): 383-92.

Religa D, Laudon H, Styczynska M, Winblad B, Naslund J, Haroutunian V. Amyloid beta pathology in Alzheimer's disease and schizophrenia. *Am J Psychiatry* 2003; 160(5): 867-72.

Rico B, Marín O. Neuregulin signaling, cortical circuitry development and schizophrenia. *Curr Opin Genet Dev* 2011; 21(3): 262-70.

Robert PH, Lafont V, Medecin I, Berthet L, Thauby S, Baudu C, Darcourt G. Clustering and switching strategies in verbal fluency tasks: comparison between schizophrenics and healthy adults. *J Int Neuropsychol Soc* 1998; 4(6): 539-46.

Roncone R, Falloon IR, Mazza M, De Risio A, Pollice R, Necozione S, Morosini P, Casacchia M. Is theory of mind in schizophrenia more strongly associated with clinical and social functioning than with neurocognitive deficits? *Psychopathology* 2002; 35(5): 280-8.

Rosen WG, Mohs RC, Johns CA, Small NS, Kendler KS, Horvath TB, Davis KL. Positive and negative symptoms in schizophrenia. *Psychiatry Res* 1984; 13(4): 277-84.

Rosso IM, Bearden CE, Hollister JM, Gasperoni TL, Sanchez LE, Hadley T, Cannon TD. Childhood neuromotor dysfunction in schizophrenia patients and their unaffected siblings: a prospective cohort study. *Schizophr Bull* 2000; 26(2): 367-78.

Rowe EW, Shean G. Card-sort performance and syndromes of schizophrenia. *Genet Soc Gen Psychol Monogr* 1997; 123(2): 197-209.

Ruiz Garzón R. Las voces del laberinto. Barcelona: Plaza & Janés; 2005.

Rüsch N, Spoletini I, Wilke M, Bria P, Di Paola M, Di Iulio F, Martinotti G, Caltagirone C, Spalletta G. Prefrontal-thalamic-cerebellar gray matter networks and executive functioning in schizophrenia. *Schizophr Res* 2007; 93(1-3): 79-89.

Salgado-Pineda P, Fakra E, Delaveau P, McKenna PJ, Pomarol-Clotet E, Blin O. Correlated structural and functional brain abnormalities in the default mode network in schizophrenia patients. *Schizophr Res* 2011; 125(2-3): 101-9.

Salvador R, Sarró S, Gomar JJ, Ortiz-Gil J, Vila F, Capdevila A, Bullmore E, McKenna PJ, Pomarol-Clotet E. Overall brain connectivity maps show cortico-subcortical abnormalities in schizophrenia. *Hum Brain Mapp* 2010; 31(12): 2003-14.

Saykin AJ, Gur RC, Gur RE, Mozley PD, Mozley LH, Resnick SM, Kester DB, Stafiniak P. Neuropsychological function in schizophrenia. Selective impairment in memory and learning. *Arch Gen Psychiatry* 1991; 48(7): 618-24.

Saykin AJ, Shtasel DL, Gur RE, Kester DB, Mozley LH, Stafiniak P, Gur RC. Neuropsychological deficits in neuroleptic naive patients with first-episode schizophrenia. *Arch Gen Psychiatry* 1994; 51(2): 124-31.

Schmahmann J, Pandya D. Fiber Pathways of the Brain. Oxford: Oxford University Press; 2006.

Schneider FC, Royer A, Grosselin A, Pellet J, Barral FG, Laurent B, Brouillet D, Lang F. Modulation of the default mode network is task-dependant in chronic schizophrenia patients. *Schizophr Res* 2011; 125(2-3): 110-7.

Schultz SK, Andreasen NC. Schizophrenia. *Lancet* 1999; 353(9162): 1425-30.

Seaton BE, Allen DN, Goldstein G, Kelley ME, van Kammen DP. Relations between cognitive and symptom profile heterogeneity in schizophrenia. *J Nerv Ment Dis* 1999; 187(7): 414-9.

Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, Reiss AL, Greicius MD. Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci* 2007; 27(9): 2349-56.

Seppi K, Schocke MF. An update on conventional and advanced magnetic resonance imaging techniques in the differential diagnosis of neurodegenerative parkinsonism. *Curr Opin Neurol* 2005; 18(4): 370-5.

Shallice T, Evans ME. The involvement of the frontal lobes in cognitive estimation. *Cortex* 1978; 14(2): 294-303.

Shotbolt P, Stokes PR, Owens SF, Toulopoulou T, Picchioni MM, Bose SK, Murray RM, Howes OD. Striatal dopamine synthesis capacity in twins discordant for schizophrenia. *Psychol Med* 2011; 41(11): 2331-8.

Smith SM. Fast robust automated brain extraction. *Hum Brain Mapp* 2002; 17(3): 143-55.

Smith SM, Zhang Y, Jenkinson M, Chen J, Matthews PM, Federico A, De Stefano N. Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. *Neuroimage* 2002; 17(1): 479-89.

Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, Bannister PR, De Luca M, Drobnjak I, Flitney DE, Niazy RK, Saunders J, Vickers J, Zhang Y, De Stefano N, Brady JM, Matthews PM. Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage* 2004; 23 Suppl 1S208-19.

Steen RG, Mull C, McClure R, Hamer RM, Lieberman JA. Brain volume in first-episode schizophrenia: systematic review and meta-analysis of magnetic resonance imaging studies. *Br J Psychiatry* 2006; 188: 510-8.

Stephan KE, Baldeweg T, Friston KJ. Synaptic plasticity and dysconnection in schizophrenia. *Biol Psychiatry* 2006; 59(10): 929-39.

Stilo SA, Murray RM. The epidemiology of schizophrenia: replacing dogma with knowledge. *Dialogues Clin Neurosci* 2010; 12(3): 305-15.

Tabarés R, Sanjuán J, Gómez-Beneyto M, Leal C. Correlates of symptom dimensions in schizophrenia obtained with the Spanish version of the Manchester scale. *Psychopathology* 2000; 33(5): 259-64.

Tai S, Turkington D. The evolution of cognitive behavior therapy for schizophrenia: current practice and recent developments. *Schizophr Bull* 2009; 35(5): 865-73.

Tan HY, Sust S, Buckholtz JW, Mattay VS, Meyer-Lindenberg A, Egan MF, Weinberger DR, Callicott JH. Dysfunctional prefrontal regional specialization and compensation in schizophrenia. *Am J Psychiatry* 2006; 163(11): 1969-77.

Tan HY, Callicott JH, Weinberger DR. Dysfunctional and compensatory prefrontal cortical systems, genes and the pathogenesis of schizophrenia. *Cereb Cortex* 2007; 17 Suppl 1i: 171-81.

Tandon R, Keshavan MS, Nasrallah HA. Schizophrenia, "just the facts" what we know in 2008. 2. Epidemiology and etiology. *Schizophr Res* 2008; 102(1-3): 1-18.

Tandon R, Nasrallah HA, Keshavan MS. Schizophrenia, "just the facts" 4. Clinical features and conceptualization. *Schizophr Res* 2009; 110(1-3): 1-23.

Thompson PA, Meltzer HY. Positive, negative, and disorganisation factors from the Schedule for Affective Disorders and Schizophrenia and the Present State Examination. A three-factor solution. *Br J Psychiatry* 1993; 163: 344-51.

Tiwari AK, Zai CC, Muller DJ, Kennedy JL. Genetics in schizophrenia: where are we and what next? *Dialogues Clin Neurosci* 2010; 12(3): 289-303.

Tuominen HJ, Tiihonen J, Wahlbeck K. Glutamatergic drugs for schizophrenia: a systematic review and meta-analysis. *Schizophr Res* 2005; 72(2-3): 225-34.

Van der Does AJ, Dingemans PM, Linszen DH, Nugter MA, Scholte WF. Symptom dimensions and cognitive and social functioning in recent-onset schizophrenia. *Psychol Med* 1993; 23(3): 745-53.

Van Snellenberg JX, Torres IJ, Thornton AE. Functional neuroimaging of working memory in schizophrenia: task performance as a moderating variable. *Neuropsychology* 2006; 20(5): 497-510.

Vargas ML, Sanz JC, Marín JJ. Behavioral assessment of the dysexecutive syndrome battery (BADS) in schizophrenia: a pilot study in the Spanish population. *Cogn Behav Neurol* 2009; 22(2): 95-100.

Wechsler D. Wechsler Abbreviated Scale of Intelligence (WASI). Wechsler Abbreviated. San Antonio, TX: The Psychological Corporation; 1999.

Wechsler D. Escala de inteligencia de Wechsler para adultos. WAIS-III. Madrid: TEA; 2001.

Weickert TW, Goldberg TE, Gold JM, Bigelow LB, Egan MF, Weinberger DR. Cognitive impairments in patients with schizophrenia displaying preserved and compromised intellect. *Arch Gen Psychiatry* 2000; 57(9): 907-13.

Weinberger DR, Berman KF, Zec RF. Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia. I. Regional cerebral blood flow evidence. *Arch Gen Psychiatry* 1986; 43(2): 114-24.

Weinberger DR, Egan MF, Bertolino A, Callicott JH, Mattay VS, Lipska BK, Berman KF, Goldberg TE. Prefrontal neurons and the genetics of schizophrenia. *Biol Psychiatry* 2001; 50(11): 825-44.

Wexler BE, Zhu H, Bell MD, Nicholls SS, Fulbright RK, Gore JC, Colibazzi T, Amat J, Bansal R, Peterson BS. Neuropsychological near normality and brain structure abnormality in schizophrenia. *Am J Psychiatry* 2009; 166(2): 189-95.

White T, Nelson M, Lim KO. Diffusion tensor imaging in psychiatric disorders. *Top Magn Reson Imaging* 2008; 19(2): 97-109.

Whitfield-Gabrieli S, Thermenos HW, Milanovic S, Tsuang MT, Faraone SV, McCarley RW, Shenton ME, Green AI, Nieto-Castanon A, LaViolette P, Wojcik J, Gabrieli JD, Seidman LJ. Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. *Proc Natl Acad Sci U S A* 2009; 106(4): 1279-84.

Whitwell JL. Progression of atrophy in Alzheimer's disease and related disorders. *Neurotox Res* 2010; 18(3-4): 339-46.

Wilk CM, Gold JM, McMahon RP, Humber K, Iannone VN, Buchanan RW. No, it is not possible to be schizophrenic yet neuropsychologically normal. *Neuropsychology* 2005; 19(6): 778-86.

Wilson BA, Cockburn J, Baddeley AD. The Rivermead Behavioural Memory Test (RBMT). Reading, UK: Thames Valley Test Co; 1985.

Wilson BA, Alderman N, Burgess PW, Emslie H, Evans JJ. Behavioural Assessment of the Dysexecutive Syndrome (BADS). Reading, UK: Thames Valley Test Co; 1996.

Williams HJ, Owen MJ, O'Donovan MC. Schizophrenia genetics: new insights from new approaches. *Br Med Bull* 2009; 91: 61-74.

Wolf RC, Vasic N, Hose A, Spitzer M, Walter H. Changes over time in frontotemporal activation during a working memory task in patients with schizophrenia. *Schizophr Res* 2007; 91(1-3): 141-50.

Wolf RC, Höse A, Frasch K, Walter H, Vasic N. Volumetric abnormalities associated with cognitive deficits in patients with schizophrenia. *Eur Psychiatry* 2008; 23(8): 541-8.

Woodward TS, Ruff CC, Thornton AE, Moritz S, Liddle PF. Methodological considerations regarding the association of Stroop and verbal fluency performance with the symptoms of schizophrenia. *Schizophr Res* 2003; 61(2-3): 207-14.

Woolrich MW, Ripley BD, Brady M, Smith SM. Temporal autocorrelation in univariate linear modeling of FMRI data. *Neuroimage* 2001; 14(6): 1370-86.

Woolrich MW, Behrens TE, Beckmann CF, Jenkinson M, Smith SM. Multilevel linear modelling for FMRI group analysis using Bayesian inference. *Neuroimage* 2004; 21(4): 1732-47.

Worsley KJ. Statistical analysis of activation images. In *Functional MRI: an introduction to methods* (ed. P. Jezzard, P. M. Matthews and S. M. Smith). Oxford: Oxford University Press; 2001.

Wright IC, Rabe-Hesketh S, Woodruff PW, David AS, Murray RM, Bullmore ET. Meta-analysis of regional brain volumes in schizophrenia. *Am J Psychiatry* 2000; 157(1): 16-25.

Wykes T, Steel C, Everitt B, Tarrier N. Cognitive behavior therapy for schizophrenia: effect sizes, clinical models, and methodological rigor. *Schizophr Bull* 2008; 34(3): 523-37.

Wykes T, Huddy V, Cellard C, McGurk SR, Czobor P. A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. *Am J Psychiatry* 2011; 168(5): 472-85.

Zakzanis KK, Heinrichs RW. Schizophrenia and the frontal brain: a quantitative review. *J Int Neuropsychol Soc* 1999; 5(6): 556-66.

Zimmermann G, Favrod J, Trieu VH, Pomini V. The effect of cognitive behavioral treatment on the positive symptoms of schizophrenia spectrum disorders: a meta-analysis. *Schizophr Res* 2005; 77(1): 1-9.

Annex 1

Ortiz-Gil J, Pomarol-Clotet E, Salvador R, Canales-Rodríguez EJ, Sarró S, Gomar JJ, Guerrero A, Sans-Sansa B, Capdevila A, Junqué C, McKenna PJ.

Neural correlates of cognitive impairment in schizophrenia.

British Journal of Psychiatry 2011 Sep; 199(3):202-10.

2011 JCR Impact factor: 5.947 (1st decile in Psychiatry)

BJPsych | The British Journal of Psychiatry (2011) 199, 202–210. doi: 10.1192/bjp.bp.110.083600

Neural correlates of cognitive impairment in schizophrenia

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Background

Cognitive impairment is an established feature of schizophrenia. However, little is known about its relationship to the structural and functional brain abnormalities that characterise the disorder.

Aims

To identify structural and/or functional brain abnormalities associated with schizophrenic cognitive impairment.

Method

We carried out structural magnetic resonance imaging (MRI) and voxel-based morphometry in 26 participants who were cognitively impaired and 23 who were cognitively preserved, all with schizophrenia, plus 39 matched controls. Nineteen of those who were cognitively impaired and 18 of those who were cognitively preserved plus 34 controls also underwent functional MRI during performance of a working memory task.

Results

No differences were found between the participants who were cognitively intact and those who were cognitively impaired in lateral ventricular volume or whole brain volume. Voxel-based morphometry also failed to reveal clusters of significant difference in grey and white matter volume between these two groups. However, during performance of the n-back task, the participants who were cognitively impaired showed hypoactivation compared with those who were cognitively intact in the dorsolateral prefrontal cortex among other brain regions.

Conclusions

Cognitive impairment in schizophrenia is not a function of the structural brain abnormality that accompanies the disorder but has correlates in altered brain function.

Declaration of interest

None.

One of the most important changes in the concept of schizophrenia in recent years has been the recognition that cognitive impairment is part of the disorder. Although not a defining characteristic – some individuals are neurocognitively normal or near-normal[1] – deficits similar in magnitude to those seen in central nervous system disease are common,[2] and in a small number of cases may attain a severity comparable with dementia.[3] Impairment is present in most or all areas of cognitive function but appears to be particularly marked in executive function and long-term memory.[4] There are unanswered questions about the course of schizophrenic cognitive impairment, but the available evidence suggests that affected individuals show an IQ disadvantage compared with the rest of the population before they become ill; that a further decline in cognitive function takes place around illness onset; but that the level then remains stable, except in chronically hospitalised individuals in whom there may be a further decline in old age.[5]

Although cognitive impairment implies brain damage or dysfunction, little is known about the relationship between schizophrenic cognitive impairment and the structural and functional brain abnormalities that also characterise the disorder. Early computed tomography (CT) studies did not point consistently to an association with lateral ventricular enlargement.[6] Reviewing magnetic resonance imaging (MRI) studies, Antonova *et al*[7] found some evidence that whole brain, lateral ventricular and frontal and temporal lobe volume reductions were associated with general intellectual impairment and/or specific neuropsychological deficits, although there were conflicting findings in all cases. The findings were further complicated by gender differences in the associations found, and also by the existence of correlations between some volume measures and IQ in controls but not in participants with schizophrenia.

Techniques such as voxel-based morphometry (VBM), which map clusters of significant difference between groups of participants throughout the brain without the necessity of preselecting regions of interest, might have more power to detect small and/or localised volume differences related to cognitive impairment. Such studies have suggested that grey matter volume reductions are more extensive in individuals with chronic schizophrenia than in those with a first-episode,[8,9] possibly in keeping with the finding that the former group typically show greater degrees of cognitive impairment than the latter.[10,11] However, to date these techniques have not been used to examine the relationship between brain volume and cognitive impairment directly.

Investigation of the brain functional correlates of cognitive impairment in schizophrenia has been limited. In the first study to carry out functional imaging during performance of an executive task in schizophrenia, Weinberger *et al*[12] found that the degree of hypofrontality correlated with the impairment the participants showed on the Wisconsin Card Sorting Test. However, such an association was not found in two later studies that used executive[13] and memory[14] tasks. Two meta-analyses of hypofrontality in schizophrenia have also examined the influence of task performance on prefrontal activation,[15,16] and both found only trend-level correlations.

According to recent findings, schizophrenia is characterised not only by hypofrontality but also hyperfrontality, increased task-related activation in areas of the prefrontal cortex, which has been documented during performance of working memory[17] and other executive tasks.[18] Weinberger and colleagues[19,20] have explicitly linked this latter finding to cognitive function, arguing that people with schizophrenia have to 'work harder to keep up' with task demands and so engage greater and/or more widespread

cortical metabolic activity than those without schizophrenia when they try to do so. Nevertheless, a number of studies have compared participants with schizophrenia who are low- and high-performing on working memory tasks and their findings suggest that the relationship between hyperfrontality and cognitive impairment is quite complicated.[21–23]

To date, two studies have adopted a strategy of examining predefined groups of individuals with cognitive impairment. de Vries *et al*[24] found that eight participants with schizophrenia and cognitive impairment amounting to dementia had no more ventricular enlargement or sulcal widening than that seen in schizophrenia as a whole. In contrast, most of the participants showed resting perfusion deficits on single photon emission computed tomography. Wexler *et al*[25] found that 54 cognitively impaired people with schizophrenia showed similar degrees of lateral ventricular enlargement and grey matter volume reduction to 21 neuropsychologically near-normal individuals with the disorder. However, the cognitively impaired group had significantly smaller white matter volumes in two out of eight regions examined. This study did not investigate whether there were functional imaging differences between the two groups.

Method

Participants

Two groups of people with schizophrenia participated, one ($n=26$) with and one ($n=23$) without substantial degrees of cognitive impairment (the cognitively impaired group and cognitively preserved group respectively). Both these groups were recruited from long-stay wards ($n=14$), acute and subacute units ($n=26$) and out-patients/day hospital ($n=9$). They all met DSM-IV[26] criteria for schizophrenia based on interview by two psychiatrists. Individuals were excluded if they were younger than 18 or older than 65, had a history of brain trauma or neurological disease, or had shown alcohol/substance misuse within the 12 months prior to participation. Individuals were also excluded if they had a history of learning disability; this was based on attendance at a special school, or on an interview with relatives, for example if the estimated premorbid IQ measure was found to be low. All participants were taking antipsychotic medication (atypical $n=28$, typical $n=7$, both kinds $n=14$), and all were in a relatively stable clinical condition at the time of testing. The groups were selected to be matched for age, gender and premorbid IQ, as estimated using the Word Accentuation Test (TAP).[27] This is conceptually similar to the National Adult Reading Test (NART)[28] and requires pronunciation of low-frequency Spanish words whose accents have been removed.

Presence of cognitive impairment was defined on the basis of performance on two well-standardised tests of memory and executive function, the Rivermead Behavioural Memory Test (RBMT)[29] and the Behavioural Assessment of the Dysexecutive Syndrome (BADS).[30] The RBMT consists of 12 subtests examining verbal recall, recognition, orientation, remembering a route and three measures of prospective memory, the ability to remember to do things. The BADS contains six subtests covering cognitive estimation, rule shifting, planning, problem-solving and decision-making under multiple task demands. The cognitively preserved group scored above the fifth percentile for normal adults on both tests (screening score of $\geqslant 8$ on the RBMT and profile score of $\geqslant 12$ on the BADS). The cognitively impaired group were required to score below the first percentile on either the RBMT (screening score of <7) or the BADS (profile score of <8).

The control group consisted of 39 healthy individuals recruited from the community. They met the same exclusion criteria and were selected to be matched to both the groups with schizophrenia in terms of age, gender and premorbid IQ. Controls were recruited from non-medical staff working in the hospital, their relatives and acquaintances, plus independent sources in the community. They were questioned and excluded if they reported a history of mental illness and/or treatment with psychotropic medication.

All participants were right-handed. They gave written informed consent and the study was approved by the local research ethics committee.

Procedure

All participants underwent structural and functional MRI (fMRI) scanning using the same 1.5 Tesla GE Signa scanner (General Electric Medical Systems, Milwaukee, USA).

Structural imaging

High-resolution structural T_1 MRI data were acquired with the following acquisition parameters: matrix size 512×512; 180 contiguous axial slices; voxel resolution $0.47 \times 0.47 \times 1\ mm^3$; echo time (TE) = 3.93 ms, repetition time (TR) = 2000 ms and inversion time (TI) = 710 ms; flip angle 15°.

Calculation of the total volume of brain tissues (normalised for participant's head size) was performed with SIENAX, part of FSL (FMRIB Software Library, Oxford; www.fmrib.ox.ac.uk/fsl/).[31,32] This tool additionally generates separate measures of grey and white matter volume. We compared lateral ventricle volume (also normalised for participant's head size) between groups using FreeSurfer (http://surfer.nmr.mgh.harvard. edu/fswiki), for which interrater reliability with manual segmentation has been shown.[33]

Structural data were further analysed with FSL-VBM, an optimised voxel-based morphometry style analysis[34,35] carried out with FSL tools, which yields a measure of differences in local grey matter volume. First, structural images were brain-extracted. Next, tissue-type segmentation was carried out. The resulting grey matter partial volume images were then aligned to Montreal Neurologic Institute (MNI)152 standard space, followed by non-linear registration. The resulting images were averaged to create a study-specific template, to which the native grey matter images were then non-linearly re-registered. The registered partial volume images were then modulated by dividing by the Jacobian of the warp field. The modulated segmentated images were then smoothed with an isotropic Gaussian kernel with a sigma of 4 mm (for technical details see www.fmrib.ox.ac.uk/fsl/fslvbm/). Group comparisons were carried out with permutation-based non-parametric tests. These were made with the randomise function implemented in FSL, using the recently developed threshold-free cluster-enhancement method with 10 000 iterations, for proper statistical inference of spatially distributed patterns (corrected for multiple comparisons).

We also carried out a VBM analysis of white matter volume. Since the VBM analysis in FSL has only been validated for grey matter, we used VBM5 (http://dbm.neuro.uni-jena.de/vbm/vbm5-for-spm5/), performed with SPM5 tools for this analysis. The following standard pre-processing steps were carried out: tissue-type segmentation; normalisation (warping) to standard space of the obtained white matter images; and modulation. The resulting images were then smoothed with an isotropic Gaussian kernel with a sigma of 4 mm. Statistical analyses were carried out using the general linear model (GLM) with correction

for multiple comparisons using the theory of Gaussian random fields.

fMRI

The paradigm used has been described by Pomarol-Clotet *et al*.[36] Scanning was carried out while participants performed a sequential-letter version of the n-back task.[37] 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 5 repetitions (1-back and 2-back depending on the block) located randomly within block. Participants had to indicate repetitions by pressing a button. Four 1-back and four 2-back blocks were presented in an interleaved way, and between these a baseline stimulus (an asterisk flashing with the same frequency as the letters) was presented for 16 s. In order 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.

Performance was measured using the signal detection theory index of sensitivity (d′).[38] Any participants who had 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 it, were excluded from the study.

In each individual scanning session 266 volumes were acquired. A gradient echo-planar imaging (EPI) sequence depicting the blood oxygen level-dependent (BOLD) contrast was used. Each volume contained 16 axial planes acquired with the following parameters: TR = 2000 ms, TE = 20 ms, flip angle 70°, section thickness 7 mm, section skip 0.7 mm, in-plane resolution $3 \times 3\ mm^2$. The first ten volumes were discarded to avoid T_1 saturation effects.

Functional MRI analyses were performed with the FEAT module included in FSL software.[32] At a first level, images were corrected for movement and coregistered to a common stereotaxic space (MNI template), and spatially filtered with a Gaussian filter (smoothing of full width at half maximum (FWHM) 5.0 mm). To minimise unwanted movement-related effects, individuals with an estimated maximum absolute movement over 3.0 mm, or an average absolute movement higher than 0.3 mm were discarded from the study. Finally, group comparisons were performed using the same FEAT module, by means of mixed-effects GLM models. A z-threshold of 2.3 (the default in FSL) was used to generate the initial set of clusters. To properly account for the spatially distributed patterns, FEAT uses the Gaussian random field theory when performing statistical tests.

Data analysis

The main focus in the structural and functional brain analyses was on two specific comparisons. First, we contrasted the cognitively preserved group with the control group. This was in order to determine changes in brain structure and function attributable to schizophrenia, without the complicating factor of cognitive impairment. Second, in order to assess the possible contribution of cognitive impairment itself, we contrasted the cognitively preserved and cognitively impaired groups. All statistical tests in the VBM and fMRI analyses were performed with a statistical threshold of $P<0.05$, corrected for multiple comparisons.

Results

Sample characteristics

There were no differences between the three groups in age, gender and TAP-estimated premorbid IQ (Table 1). The two groups with schizophrenia did not differ in overall severity of illness as measured by the Clinical Global Impression (CGI);[40] however, the cognitively impaired group had significantly higher total symptom scores on the Positive and Negative Syndrome Scale (PANSS).[41] They also had a significantly longer duration of illness than the cognitively preserved group and showed trend level higher mean dosages of antipsychotic drugs.

As expected, the two groups with schizophrenia differed significantly in their performance on the BADS and RBMT. The distributions of their scores are shown in Fig. 1. The cognitively impaired group also had lower scores on current IQ than the

Table 1 Demographic, neurocognitive and psychopathological characteristics of the participants with schizophrenia and controls

		Participants with schizophrenia ($n=49$)		Group statistics								
	Control group ($n=39$)	Cognitively preserved group ($n=23$)	Cognitively impaired group ($n=26$)	I<C		I<P						
				t	P	t	P	F	χ^2	t	U	P
Age, years: mean (s.d.)	40.10 (11.58)	40.10 (10.22)	42.38 (8.23)					0.45				0.64
Gender, male/female: *n*	30/9	17/6	20/6						0.85			0.96
TAP correct words, mean (s.d.)	23.00 (5.29)	23.68 (4.34)	21.00 (5.65)					1.83				0.17
IQ (WAIS-III), mean (s.d.)												
Full-scale IQ	103.49 (13.13)	100.43 (13.04)	92.73 (13.43)	3.21	0.002	2.03	0.05	5.26				0.01
Verbal IQ	104.90 (16.73)	104.00 (17.65)	96.85 (15.93)					1.97				0.15
Performance IQ	100.08 (17.59)	94.00 (14.61)	84.54 (16.56)	3.57	0.001	2.11	0.04	6.87				0.002
BADS score, mean (s.d.)		16.04 (2.40)	10.69 (4.33)							5.43		<0.001
RBMT screening score, mean (s.d.)		9.48 (1.44)	5.17 (1.63)							9.58		<0.001
Years of illness, mean (s.d.)		18.28 (10.02)	23.76 (8.29)							−2.09		0.04
PANSS total score, mean (s.d.)		66.57 (17.11)	76.15 (15.03)							−2.09		0.04
CGI score, mean (s.d.)		4.13 (1.36)	4.58 (0.90)								232.00	0.16
Antipsychotic dosage (chlorpromazine equivalent, mg), mean (s.d.)		663.41 (550.94)	985.34 (608.59)							−1.93		0.06

I<C, cognitively impaired group<control group; I<P, cognitively impaired group<cognitively preserved group; TAP, Word Accentuation Test; WAIS-III, Wechsler Adult Intelligence Scale (3rd edn);[39] BADS, Behavioural Assessment of the Dysexecutive Syndrome; RBMT, Rivermead Behavioural Memory Test; PANSS, Positive and Negative Syndrome Scale; CGI, Clinical Global Impression.

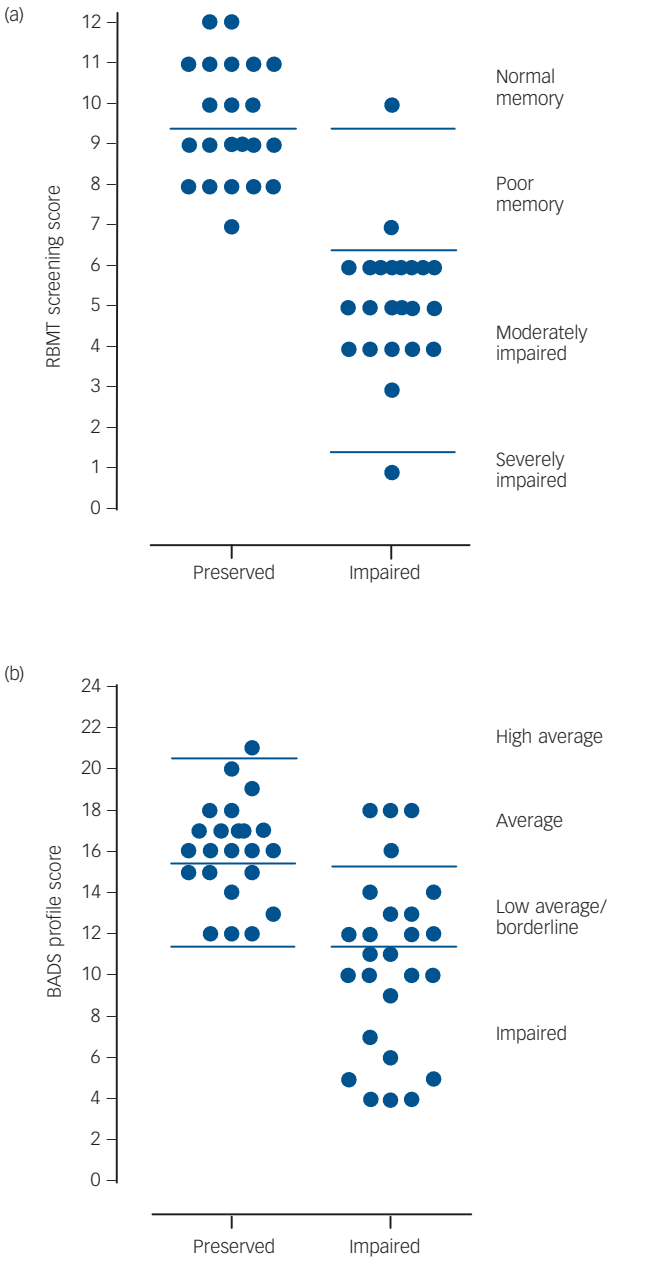

Fig 1 Scatter plots of the cognitively preserved and cognitively impaired groups' scores on the (a) Rivermead Behavioural Memory Test (RBMT) and (b) the Behavioural Assessment of the Dysexecutive Syndrome (BADS).

cognitively preserved group, but this only reached significance for performance IQ.

Brain and lateral ventricular volume measures

All participants were included in the analysis except in the comparison of lateral ventricles, where one control had to be excluded for technical reasons. Comparing all participants with schizophrenia with the controls, they showed reduced whole brain volume (1526.75 cm^3 (s.d. = 47.69) *v.* 1485.91 cm^3 (s.d. = 53.36), $t = 3.74$, $P < 0.001$, effect size (ES) = 0.80), reduced grey matter volume (819.46 cm^3 (s.d. = 35.39) *v.* 785.75 cm^3 (s.d. = 39.09), $t = 4.19$, $P < 0.001$, ES = 0.89) and lateral ventricular enlargement (12.58 cm^3 (s.d. = 7.24) *v.* 16.74 cm^3 (s.d. = 10.47), $t = -2.20$, $P = 0.03$, ES = −0.45). However, there was no difference in white matter volume between participants with schizophrenia and controls (707.29 cm^3 (s.d. = 25.62) *v.* 700.17 cm^3 (s.d. = 24.71), $t = 1.32$, $P = 0.19$, ES = 0.28). As shown in Table 2, when the controls were compared with the cognitively preserved group the differences in whole brain and grey matter volume differences remained evident (whole brain: $t = 2.62$, $P = 0.01$, ES = 0.68; grey matter: $t = 2.83$, $P = 0.006$, ES = 0.73), although that for lateral ventricular volume no longer reached significance ($t = -1.25$, $P = 0.22$, ES = −0.35). However, the differences between the cognitively preserved and cognitively impaired groups were small and non-significant on all these measures (whole brain: $t = 0.36$, $P = 0.72$, ES = 0.10; grey matter: $t = 0.62$, $P = 0.53$, ES = 0.18; lateral ventricular volume: $t = -0.92$, $P = 0.36$, ES = −0.14).

VBM

The same participants took part in this analysis, i.e. all those in the cognitively preserved group ($n = 23$) and cognitively impaired group ($n = 26$) and the 39 controls.

Controls *v.* cognitively preserved group

The cognitively preserved group showed significantly smaller grey matter volume than the controls in one cluster. This was situated anteriorly and medially, extending from the orbital and medial prefrontal cortex to the anterior cingulate gyrus (2190 voxels, $P = 0.04$; peak in Brodmann Area (BA) 10, MNI (−12, 44, −8), z-score = 4.70). This is shown in Fig. 2 (the appearance of separate clusters is artefactual, due to the 3D rendering). There were no regions where the cognitively preserved group showed significantly greater volume than the controls.

No areas of significant white matter volume difference were found between the controls and the cognitively preserved group.

Cognitively preserved group *v.* cognitively impaired group

There were no areas of significant grey or white matter volume difference between these two groups.

fMRI

Some participants could not tolerate the fMRI procedure and in others the images were not usable because of excessive movement. Therefore, 19 participants who were cognitively impaired, 18 who were cognitively preserved and 34 controls took part in this analysis. As shown in Table 3, the groups remained matched for age, gender and TAP score. Significant differences between the two groups with schizophrenia remained evident on the BADS and the RBMT. These two groups did not differ in CGI or PANSS score, or in antipsychotic dosage. There were no significant differences between the participants with schizophrenia who took part in this part of the study and those who did not in terms of age (41.07 *v.* 42.05), gender (29/8 *v.* 8/4) or TAP score (22.03 *v.* 22.83).

Behavioural performance

The cognitively preserved group were significantly impaired compared with the controls on the 1-back version of the task (mean d′ 3.77 (s.d. = 0.91) *v.* 4.40 (s.d. = 0.65), $t = 2.90$, $P = 0.01$) and in the 2-back version (mean d′ 2.67 (s.d. = 0.87) *v.* 3.27 (s.d. = 0.96), $t = 2.22$, $P = 0.03$). The cognitively impaired group were marginally significantly impaired compared with the cognitively preserved group on the 1-back task (mean d′ 3.07 (s.d. = 1.16) *v.* 3.77 (s.d. = 0.91), $t = 2.03$, $P = 0.05$) and significantly impaired on the 2-back task (mean d′ 1.89 (s.d. = 0.68) *v.* 2.67 (s.d. = 0.87), $t = 3.06$, $P = 0.004$).

Table 2 Whole brain and lateral ventricular volume measures in the controls, cognitively preserved and cognitively impaired groups with schizophrenia

	Controls ($n=39$)	Cognitively preserved group ($n=23$)	Cognitively impaired group ($n=26$)	ANOVA							
				P<C		I<C		I>C			
				t	*P*	*t*	*P*	*t*	*P*	*F*	*P*
Whole brain	1526.75 (47.69)	1488.82 (65.92)	1483.35 (40.36)	2.62	0.01	3.82	<0.001			6.98	0.002
Grey matter	819.46 (35.39)	789.55 (47.52)	782.38 (30.36)	2.83	0.006	4.37	<0.001			8.94	<0.001
White matter	707.29 (25.62)	699.27 (29.79)	700.96 (19.74)							0.89	0.41
Lateral ventricles[a]	12.58 (7.24)	15.95 (12.49)	17.44 (8.49)					−2.59	0.01	2.95	0.06

P<C, cognitively preserved group<control group; I<C, cognitively impaired group<control group; I>C, cognitively impaired group>control group.
a. Data in this analysis were corrected for intracranial volume; results were similar without correction. One control was excluded from the analysis.

Controls *v.* cognitively preserved group

No areas of significant difference in activation were seen in the 1-back *v.* baseline contrast or in the 2-back *v.* 1-back contrast. In the 2-back *v.* baseline contrast the controls activated more than the cognitively preserved group in the right cerebellum (1606 voxels, $P=8.27\times10^{-5}$, MNI (12, –58, –24), *z*-score 4.48).

Additionally, in the 2-back *v.* baseline contrast, the cognitively preserved group showed two clusters where they failed to de-activate significantly relative to the control group. The larger of these included parts of the medial and inferior orbital prefrontal cortex, extending to the anterior cingulate cortex (3878 voxels, $P=1.72\times10^{-9}$, peak activation in BA11, MNI (0, 26,–14), *z*-score 4.52). The smaller cluster was located in the right insula and in the right superior temporal gyrus (629 voxels, $P=0.04$, peak activation in BA48, MNI (42, –8, –6), *z*-score 4.13).

This failure of de-activation was more evident in the 2-back *v.* 1-back contrast. Here, a large cluster was seen that included the medial and inferior orbital prefrontal cortex, the left basal ganglia and anterior regions of the left temporal cortex (5748 voxels, $P=8.66\times10^{-13}$, peak activation in BA38, MNI (−40, 18, −34), *z*-score 4.49). Another cluster affected parts of the right basal ganglia and anterior temporal cortex (2235 voxels, $P=2.56\times10^{-6}$; peak activation in BA35, MNI (26, 2, –34), *z*-score 4.56) (Fig. 3).

Cognitively preserved group *v.* cognitively impaired group

There were no differences between the groups in the 1-back *v.* baseline contrast. The 2-back *v.* baseline contrast revealed significantly reduced activation in the cognitively impaired group in an area that included the right dorsolateral prefrontal cortex, the inferior lateral frontal lobe and the right insula (1749 voxels, $P=2.94\times10^{-5}$, peak activation in right frontal inferior pars triangularis, MNI (38, 28, 26), *z*-score 3.93). This area of reduced

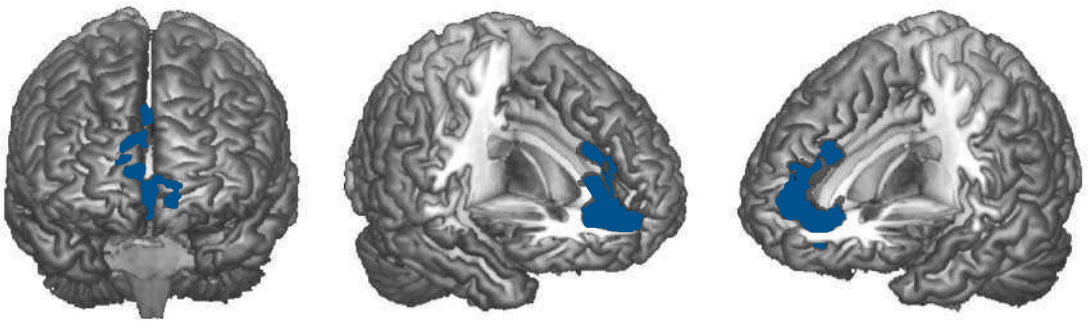

Fig. 2 Brain regions showing significant grey matter volume reduction in the cognitively preserved group with schizophrenia compared with healthy controls.

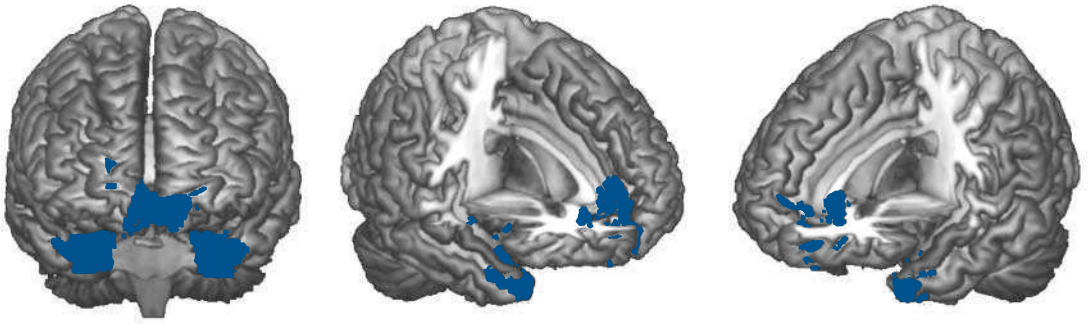

Fig. 3 Brain regions where the cognitively preserved group with schizophrenia showed significant failure to de-activate compared with the controls in the 2-back *v.* 1-back contrast.

Table 3 Mean values, standard deviations and statistical results of demographic, neurocognitive and psychopathological characteristics of the functional magnetic resonance imaging sample

		Participants with schizophrenia ($n=37$)		Group statistics								
				I<C		I<P						
	Control group ($n=34$)	Cognitively preserved group ($n=18$)	Cognitively impaired group ($n=19$)	t	P	t	P	F	χ^2	t	U	P
Age, years: mean (s.d.)	40.90 (11.80)	40.49 (10.58)	41.62 (7.94)					0.06				0.95
Gender, male/female: n	26/8	14/4	15/4						0.04			0.98
TAP correct words, mean (s.d.)	23.00 (5.42)	23.41 (4.02)	20.79 (5.08)					1.55				0.25
IQ (WAIS-III), mean (s.d.)												
Full-scale IQ	104.24 (12.47)	100.44 (13.99)	94.11 (9.37)	3.08	0.003			4.24				0.02
Verbal IQ	105.44 (16.06)	103.06 (19.07)	96.58 (10.86)					1.95				0.15
Performance IQ	100.85 (18.19)	94.67 (15.68)	86.74 (17.08)	2.77	0.01			4.09				0.02
BADS score, mean (s.d.)		16.06 (2.69)	11.58 (4.26)							3.80		0.001
RBMT screening score, mean (s.d.)		9.72 (1.36)	5.56 (1.46)							8.84		0.001
Years of illness, mean (s.d.)		18.44 (10.86)	22.71 (7.71)							−1.39		0.18
PANSS total score, mean (s.d.)		67.89 (18.33)	76.79 (17.04)							−1.53		0.14
CGI score, mean (s.d.)		4.28 (1.41)	4.58 (1.02)								146.50	0.44
Antipsychotic dosage (chlorpromazine equivalent, mg), mean (s.d.)		688.22 (603.25)	913.50 (507.21)							−1.23		0.23

I<C, cognitively impaired group<control group; I<P, cognitively impaired group<cognitively preserved group; TAP, Word Accentuation Test; WAIS-III, Wechsler Adult Intelligence Scale (3rd edn); BADS, Behavioural Assessment of the Dysexecutive Syndrome; RBMT, Rivermead Behavioural Memory Test; PANSS, Positive and Negative Syndrome Scale; CGI, Clinical Global Impression.

activation was more pronounced in the 2-back *v.* 1-back contrast: on the right, one cluster included the dorsolateral prefrontal cortex extending to the precentral gyrus posteriorly and the superior middle frontal cortex anteriorly (2494 voxels, $P=1.19\times10^{-7}$, peak activation in BA42, MNI (12, 24, 46), z-score 3.88). A similar cluster on the left included the dorsolateral prefrontal cortex and extended to the basal ganglia, the insula and the precentral gyrus (1786 voxels, $P=96\times10^{-6}$; peak activation in BA6, MNI (−30, 6, 24), z-score 4.27). Two more clusters were located in regions of the right parietal and occipital lobes (1962 voxels, $P=2.09\times10^{-6}$, peak activation in BA40, MNI (38, −46, 50), z-score 4.25) and in roughly similar regions on the left (1785 voxels, $P=6.02\times10^{-6}$, peak activation in BA7, MNI (−32, −64, 48), z-score 3.91). Two further small clusters were found in both thalami (608 voxels, $P=0.02$, peak activation in the right thalamus, MNI (6, −8, 19), z-score 2.9) and in the left inferior and middle occipital gyri (603 voxels, $P=0.03$, peak activation in BA19, MNI (−52, −76, −2), z-score 4.04). The findings are shown in Fig. 4.

There were no areas where the cognitively impaired group activated more than the cognitively preserved group.

Discussion

Structural imaging findings

As a group, the participants with schizophrenia in this study showed typical structural imaging findings associated with the disorder, namely reduced brain volume, reduced grey matter volume and lateral ventricular enlargement. However, the cognitively preserved and cognitively impaired groups did not differ from each other on these measures. When VBM was used to examine grey and white matter volume further, a cluster of grey matter volume reduction was seen in the cognitively preserved group in the medial and orbital prefrontal cortex, overlapping with areas identified in recent meta-analyses.[9,42] Once again, no clusters of significant grey or white matter volume difference emerged between the cognitively preserved and cognitively impaired groups.

Although counterintuitive, these findings are consistent with the rest of the structural imaging literature, which has documented only weak and conflicting evidence of an association between cognitive impairment and lateral ventricular size, whole brain volume and regional cortical volumes in schizophrenia.[6,7]

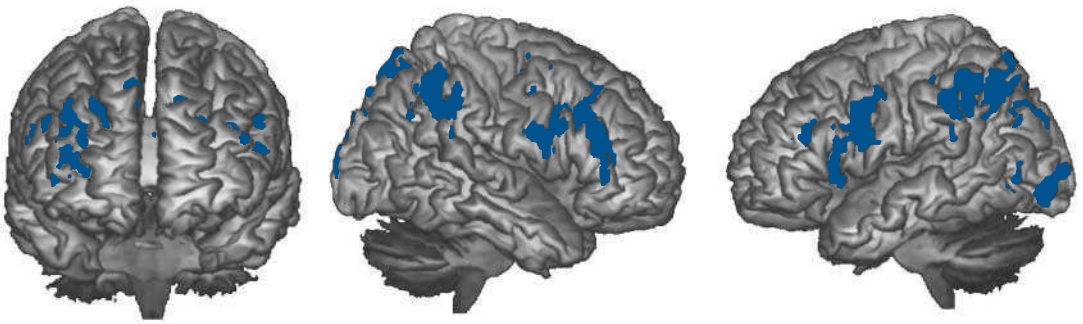

Fig. 4 Brain regions where the cognitively preserved group activated significantly more than the cognitively impaired group in the 2-back *v.* 1-back contrast.

The recent study of Wexler *et al*,[25] the only other study besides ours to explicitly compare groups of cognitively preserved and impaired individuals with schizophrenia, also failed to find significant differences in lateral ventricular volume and grey matter volume between them. Wexler *et al*[25] did find that cognitively impaired individuals showed significantly smaller white matter volume in two out of eight regions examined (sensorimotor and parietal-occipital cortex). However, these differences may not have been robust since there was no control for multiple comparisons.

Our structural imaging findings are also in keeping with a well-established neuropathological finding in schizophrenia. This is that, although severe cognitive impairment is prevalent among elderly people who are institutionalised – more than 70% have Mini-Mental State Examination (MMSE) scores in the demented range[43] – post-mortem studies have revealed no more Alzheimer-type or other brain pathology in such individuals than in age-matched controls.[3]

Nevertheless, our study does not completely exclude the possibility of small structural differences related to cognitive function. This is because in the conventional MRI analysis there were differences in whole brain volume and grey matter volume between the cognitively impaired and cognitively preserved groups of 0.4% and 0.9% respectively. Although these differences were small and non-significant, the reductions of brain volume in schizophrenia as a whole are also small, being of the order of 2% (whole brain) and 4% (grey matter) according to the meta-analysis of Wright *et al*.[44] It could therefore be argued that our study was simply underpowered to detect differences between the two groups with schizophrenia. However, it should be noted that two groups of 769 participants would be required to make the differences we found in whole brain volume between cognitively impaired and cognitive preserved groups significant, and 239 for each group would be needed to do so for the differences in grey matter volume.

A final objection to our finding of no relationship between cognitive impairment and brain volume reduction is conceptual. If, as is widely accepted,[45] structural brain abnormality in schizophrenia is neurodevelopmental in origin, then it might not be expected to show the same relationship with cognitive impairment as brain changes that are the result of brain injury or degenerative disease. When the evidence that additional brain volume reductions also take place after illness onset[46] is also taken into account, plus the fact that cognitive impairment itself follows a complex pre-, peri- and postmorbid course,[5] there is scope for a further argument, that the relationship between brain structure and cognitive impairment in schizophrenia cannot be adequately assessed in a simple cross-sectional study such as ours.

Functional imaging findings

In contrast to the brain structural findings, we found clear evidence of differences between the cognitively impaired and cognitively preserved groups on functional imaging. Specifically, in the 2-back *v.* baseline contrast the cognitively impaired group showed reduced activation compared with the cognitively preserved group in the right dorsolateral prefrontal cortex and other frontal areas, changes which became bilateral and extended more widely in the 2-back *v.* 1-back contrast. In fact, most of the task-related hypoactivation we found appeared to be attributable to cognitive impairment – in the comparison between the cognitively preserved group and the controls the cognitively preserved group showed reduced activation only in the cerebellum.

This result deviates somewhat from the rest of the literature which, as noted in the introduction, has not found evidence of a robust correlation between hypofrontality and task performance.[15,16] One possible reason for our stronger findings here is that, rather than using correlational methods, we prospectively compared groups that differed in cognitive function but which were matched for other factors that might affect task performance, especially premorbid intellectual function. The fact that the two groups were also well-separated in terms of memory and/or executive performance (i.e. one was above the fifth percentile and the other was below the first percentile) would also have tended to increase functional imaging differences between them related to this factor.

It does not seem likely that the differences we found between the cognitively impaired and cognitively preserved groups were the result of the former simply not performing the task, since we excluded *a priori* any participants who showed negative d′ scores, an indicator of failure to perform the task. At the same time, the difference in level of n-back performance between the two groups with schizophrenia has the potential to complicate the interpretation of any functional imaging differences found between them. This possibility could not be investigated in our study because the groups were preselected on the basis that they differed in cognitive function and the n-back task is itself a cognitive task. Therefore, entering n-back performance as a covariate in the analysis would have violated the principle that the covariate should not be affected by the group factor.

In fact, this issue is part of a wider debate about what drives task-related hypofrontality in schizophrenia: are both poor task performance and reduced brain activation manifestations of an underlying intrinsic cortical dysfunction? Or does the reduced activation merely index the fact that cognitively impaired individuals perform the task more poorly and so activate their frontal lobes to a correspondingly lesser extent (see Fletcher *et al*[14])? This debate has now to some extent been superseded by the finding that schizophrenia is characterised not only by hypofrontality, but also by hyperfrontality during task performance.[17,18] Nevertheless, cognitive impairment continues to play a central role in explanations of this latter functional imaging abnormality. Thus, according to Weinberger *et al*,[19,20] people with schizophrenia have reduced efficiency of prefrontal cortical processing. This causes them to show more activation than healthy individuals – i.e. hyperfrontality – at low task demands, as they 'work harder to keep up'. As task demands increase, they then reach their limit of performance sooner than healthy participants, and thereafter show a fall-off of activation, or hypofrontality. We did not find any evidence of hyperfrontality in our study, suggesting that this abnormality may not be related to cognitive function in the way predicted by Weinberger and colleagues,[19,21] a conclusion also reached by Karlsgodt *et al*.[23] However, it should be noted that we did not fully examine this question, since the theory predicts that hyperfrontality should be seen at low task difficulty in the comparison between controls and individuals who are cognitively impaired, and we did not compare these two groups directly.

In addition to reduced activation related to cognitive function, we also found failure of de-activation. This affected the medial frontal cortex among other areas and, since it was only seen in the comparison between the controls and the cognitively preserved group, it was unrelated to the presence of cognitive impairment. Failure of task-related de-activation in the medial frontal cortex in schizophrenia has now been documented several times,[36,47,48] where it has been interpreted as evidence of dysfunction in the default mode network – one of the two prominent midline nodes of which is located in the medial frontal cortex. The default mode network is currently a focus of considerable research interest in schizophrenia, with studies

finding evidence of both changes in task-related de-activation and abnormal connectivity at rest (for a review see Broyd *et al*[49]). Among other things, it has been suggested that failure of de-activation in the network might account for the cognitive impairment associated with the schizophrenia.[36,47] Our findings suggest that this is not the case.

Also interesting in this respect was the overlap between the structural and functional abnormalities that was evident in our study: in the VBM comparison between the controls and the cognitively preserved group, volume reductions were clustered in a medial frontal cortex region where failure of de-activation was also seen. We have previously examined this overlap in more detail,[50] and two other studies have had comparable findings. Camchong *et al*[51] found functional connectivity abnormality in the anterior node of the default mode network, plus white matter changes in subjacent regions on diffusion tensor imaging, and Salgado-Pineda *et al*[48] found failure of both de-activation and volume reductions in regions extending along the length of the cingulate gyrus.

Conclusions and limitations

This study provides evidence that structural brain abnormality in schizophrenia is a function of having the disorder, not the cognitive impairment that goes with it. In contrast, a substantial part of the functional imaging abnormality associated with schizophrenia appears to reflect cognitive impairment. Limitations of the study include the relatively small sizes of the groups with and without cognitive impairment. Also, since the cognitively preserved group was defined in terms of memory and executive function above fifth percentile cut-offs, it was not completely free of cognitive impairment; some fell into the poor normal memory range on the RBMT and the low average/borderline categories in the BADS. As discussed above, the inferences that can be drawn from positive findings in an fMRI comparison between cognitively preserved and cognitively impaired individuals are inevitably limited by the differences in performance between them on the task used. In general terms, more detailed knowledge about the trajectories of structural and functional brain change in schizophrenia might be needed before firm conclusions can be drawn about their relationship with cognitive impairment in the disorder.

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First received 10 Jun 2010, final revision 21 Feb 2011, accepted 21 Mar 2011

Funding

Supported by the Instituto de Salud Carlos III, Centro de Investigación en Red de Salud Mental, CIBERSAM and Marie Curie European Reintegration Grant (MERG-CT-2004-511069) given to E.P.-C. Four grants from the Spanish Ministry of Health – Instituto de Salud Carlos III: PI05/2693 provided to E.P.-C.; CP07/00048, PI05/1874 given to R.S.; FI05/00322 given to J.G.; CM07/00016 given to B.S-S.; CA06/0129 given to J.O.-G.

References

1 Kremen WS, Seidman LJ, Faraone SV, Toomey R, Tsuang MT. The paradox of normal neuropsychological function in schizophrenia. *J Abnorm Psychol* 2000; **109**: 743–52.

2 Heinrichs RW, Zakzanis KK. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. *Neuropsychology* 1998; **12**: 426–45.

3 Harrison PJ. The neuropathology of schizophrenia. A critical review of the data and their interpretation. *Brain* 1999; **122**: 593–624.

4 Reichenberg A, Harvey PD. Neuropsychological impairments in schizophrenia: integration of performance-based and brain imaging findings. *Psychol Bull* 2007; **133**: 833–58.

5 Palmer BW, Dawes SE, Heaton RK. What do we know about neuropsychological aspects of schizophrenia? *Neuropsychol Rev* 2009; **19**: 365–84.

6 Lewis SW. Computerised tomography in schizophrenia 15 years on. *Br J Psychiatry* 1990; **157** (suppl 9): 16–24.

7 Antonova E, Sharma T, Morris R, Kumari V. The relationship between brain structure and neurocognition in schizophrenia: a selective review. *Schizophr Res* 2004; **70**: 117–45.

8 Ellison-Wright I, Glahn DC, Laird AR, Thelen SM, Bullmore E. The anatomy of first-episode and chronic schizophrenia: an anatomical likelihood estimation meta-analysis. *Am J Psychiatry* 2008; **165**: 1015–23.

9 Bora E, Fornito A, Radua J, Walterfang M, Seal M, Wood SJ, et al. Neuroanatomical abnormalities in schizophrenia: a multimodal voxelwise meta-analysis and meta-regression analysis. *Schizophr Res* 2011; **127**: 46–57.

10 Heaton RK, Baade LE, Johnson KL. Neuropsychological test results associated with psychiatric disorders in adults. *Psychol Bull* 1978; **85**: 141–62.

11 Saykin AJ, Shtasel DL, Gur RE, Stafiniak P, Kester DB, Mozley LH, et al. Neuropsychological deficits in neuroleptic naive patients with first-episode schizophrenia. *Arch Gen Psychiatry* 1994; **51**: 124–31.

12 Weinberger DR, Berman KF, Zec RF. Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia. I. Regional cerebral blood flow evidence. *Arch Gen Psychiatry* 1986; **43**: 114–24.

13 Frith CD, Friston KJ, Herold S, Silbersweig D, Fletcher P, Cahill C, et al. Regional brain activity in chronic schizophrenic patients during the performance of a verbal fluency task. *Br J Psychiatry* 1995; **167**: 343–9.

14 Fletcher PC, McKenna PJ, Frith CD, Grasby PM, Friston KJ, Dolan RJ. Brain activations in schizophrenia during a graded memory task studied with functional neuroimaging. *Arch Gen Psychiatry* 1998; **55**: 1001–8.

15 Hill K, Mann L, Laws KR, Stephenson CM, Nimmo-Smith I, McKenna PJ. Hypofrontality in schizophrenia: a meta-analysis of functional imaging studies. *Acta Psychiatr Scand* 2004; **110**: 243–56.

16 Van Snellenberg JX, Torres IJ, Thornton AE. Functional neuroimaging of working memory in schizophrenia: task performance as a moderating variable. *Neuropsychology* 2006; **20**: 497–510.

17 Glahn DC, Ragland JD, Abramoff A, Barrett J, Laird AR, Bearden CE, et al. Beyond hypofrontality: a quantitative meta-analysis of functional neuroimaging studies of working memory in schizophrenia. *Hum Brain Mapp* 2005; **25**: 60–9.

18 Minzenberg MJ, Laird AR, Thelen S, Carter CS, Glahn DC. Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. *Arch Gen Psychiatry* 2009; **66**: 811–22.

19 Tan HY, Callicott JH, Weinberger DR. Dysfunctional and compensatory prefrontal cortical systems, genes and the pathogenesis of schizophrenia. *Cereb Cortex* 2007; **17** (suppl 1): i171–81.

20 Weinberger DR, Egan MF, Bertolino A, Callicott JH, Mattay VS, Lipska BK, et al. Prefrontal neurons and the genetics of schizophrenia. *Biol Psychiatry* 2001; **50**: 825–44.

21 Callicott JH, Mattay VS, Verchinski BA, Marenco S, Egan MF, Weinberger DR. Complexity of prefrontal cortical dysfunction in schizophrenia: more than up or down. *Am J Psychiatry* 2003; **160**: 2209–15.

22 Tan HY, Sust S, Buckholtz JW, Mattay VS, Meyer-Lindenberg A, Egan MF, et al. Dysfunctional prefrontal regional specialization and compensation in schizophrenia. *Am J Psychiatry* 2006; **163**: 1969–77.

23 Karlsgodt KH, Sanz J, van Erp TG, Bearden CE, Nuechterlein KH, Cannon TD. Re-evaluating dorsolateral prefrontal cortex activation during working memory in schizophrenia. *Schizophr Res* 2009; **108**: 143–50.

24 de Vries PJ, Honer WG, Kemp PM, McKenna PJ. Dementia as a complication of schizophrenia. *J Neurol Neurosurg Psychiatr* 2001; **70**: 588–96.

25 Wexler BE, Zhu H, Bell MD, Nicholls SS, Fulbright RK, Gore JC, et al. Neuropsychological near normality and brain structure abnormality in schizophrenia. *Am J Psychiatry* 2009; **166**: 189–95.

26 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (4th edn) (DSM-IV)*. APA, 1994.

27 Del Ser T, Gonzalez-Montalvo JI, Martinez-Espinosa S, Delgado-Villapalos C, Bermejo F. Estimation of premorbid intelligence in Spanish people with the Word Accentuation Test and its application to the diagnosis of dementia. *Brain Cogn* 1997; **33**: 343–56.

28 Nelson HE, Willison JR. *The Revised National Adult Reading Test*. nferNelson, 1991.

29 Wilson B, Cockburn J, Baddeley A, Hiorns R. *The Rivermead Behavioural Memory Test*. Thames Valley Test Company, 1985.

30 Wilson BA, Burgess PW, Emslie H, Evans JJ. *Behavioural Assessment of the Dysexecutive Syndrome (BADS)*. Thames Valley Test Company, 1996.

31 Smith SM. Fast robust automated brain extraction. *Hum Brain Mapp* 2002; **17**: 143–55.

32 Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, et al. Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage* 2004; **23** (suppl 1): s208–19.

33 Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc Natl Acad Sci U S A* 2000; **97**: 11050–5.

34 Ashburner J, Friston KJ. Voxel-based morphometry – the methods. *Neuroimage* 2000; **11**: 805–21.

35 Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage* 2001; **14**: 21–36.

36 Pomarol-Clotet E, Salvador R, Sarro S, Gomar J, Vila F, Martínez A, et al. Failure to deactivate in the prefrontal cortex in schizophrenia: dysfunction of the default mode network? *Psychol Med* 2008; **38**: 1185–93.

37 Gevins A, Cutillo B. Spatiotemporal dynamics of component processes in human working memory. *Electroencephalogr Clin Neurophysiol* 1993; **87**: 128–43.

38 Green DM, Swets JA. *Signal Detection Theory And Psychophysics*. Krieger, 1966.

39 Wechsler D. *Wecshler Adult Intelligence Scale (3rd edn)*. The Psychological Corporation, 1997.

40 Guy WE. *ECDEU Assessment Manual for Psychopharmacology*. US Department of Health, Education, and Welfare, 1976.

41 Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987; **13**: 261–76.

42 Fornito A, Yucel M, Patti J, Wood SJ, Pantelis C. Mapping grey matter reductions in schizophrenia: an anatomical likelihood estimation analysis of voxel-based morphometry studies. *Schizophr Res* 2009; **108**: 104–13.

43 Harvey PD, Lombardi J, Kincaid MM, Parrella M, White L, Powchik P, et al. Cognitive functioning in chronically hospitalized schizophrenic patients: age-related changes and age disorientation as a predictor of impairment. *Schizophr Res* 1995; **17**: 15–24.

44 Wright IC, Rabe-Hesketh S, Woodruff PW, David AS, Murray RM, Bullmore ET. Meta-analysis of regional brain volumes in schizophrenia. *Am J Psychiatry* 2000; **157**: 16–25.

45 Weinberger DR, Marenco S. Schizophrenia as a neurodevelopmental disorder. In *Schizophrenia (2nd edn)* (eds SR Hirsch, DR Weinberger): 326–48. Blackwell, 2003.

46 Hulshoff Pol HE, Kahn RS. What happens after the first episode? A review of progressive brain changes in chronically ill patients with schizophrenia. *Schizophr Bull* 2008; **34**: 354–66.

47 Whitfield-Gabrieli S, Thermenos HW, Milanovic S, Milanovic S, Tsuang MT, Faraone SV, et al. Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. *Proc Natl Acad Sci U S A* 2009; **106**: 1279–84.

48 Salgado-Pineda P, Fakra E, Delaveau P, McKenna PJ, Pomarol-Clotet E, Blin O. Correlated structural and functional brain abnormalities in the default mode network in schizophrenia patients. *Schizophr Res* 2011; **125**: 101–9.

49 Broyd SJ, Demanuele C, Debener S, Helps SK, James CJ, Sonuga-Barke EJ. Default-mode brain dysfunction in mental disorders: a systematic review. *Neurosci Biobehav Rev* 2009; **33**: 279–96.

50 Pomarol-Clotet E, Canales-Rodriguez EJ, Salvador R, Sarró S, Gomar JJ, Vila F, et al. Medial prefrontal cortex pathology in schizophrenia as revealed by convergent findings from multimodal imaging. *Mol Psychiatry* 2010; **15**: 823–30.

51 Camchong J, Macdonald 3rd AW, Bell C, Mueller BA, Lim KO. Altered functional and anatomical connectivity in schizophrenia. *Schizophr Bull* 2009; **37**: 640–50.

Annex 2

Examination of the cognitive profiles of groups of schizophrenic patients designated as ‘preserved’ and ‘impaired’ on the basis of scoring on two batteries of memory and executive function (the RBMT and the BADS).

Study objective

The study described in this annex was undertaken to test whether the method of separation of groups of cognitively preserved and impaired schizophrenic patients used in the study described in the main part of this thesis resulted in an efficient separation on a range of other tests of cognitive execution, including tasks not assessing memory or executive functions. A secondary aim was to determine the pattern of separation. For example, it might be anticipated that the cognitively impaired group would show an especially severe impairment in some areas of function, such as in attention, executive function and declarative memory, whereas their performance on measures of language and visual/visuospatial function would be less severely affected. Additionally, given the findings described in section 16 concerning 'cognitively near-normal' patients with schizophrenia (Palmer *et al.*, 1997; Seaton *et al.*, 1999; Kremen *et al.*, 2000; Weickert *et al.*, 2000; Hill *et al.*, 2002; Horan and Goldstein, 2003; Keefe *et al.*, 2005; Wilk *et al.*, 2005), it might be predicted that the cognitively preserved group would still show some degree of compromise compared to controls in one or more of the domains of attention (Seaton *et al.*, 1999; Weickert *et al.*, 2000), executive function (Weickert *et al.*, 2000; Horan and Goldstein, 2003) or declarative memory (Hill *et al.*, 2002).

Method

Participants

The patient sample consisted of 25 cognitively preserved participants with schizophrenia and 29 cognitively impaired participants with schizophrenia, defined according to the same criteria as in the main study (see section 31 for a

more detailed description). As in the main study, the two patient samples were recruited from long stay wards (*n*=24) and acute and subacute units (*n*=22), although a minority were out-patients/day hospital attenders (*n*=8). All were taking antipsychotic medication (atypical *n*=29, typical *n*=5, both kinds *n*=20). The control group consisted of 22 healthy individuals recruited from the community.

Some of the patients in this study also participated in the imaging study (cognitively preserved patients 17/25, cognitively impaired patients 18/29). Most of the controls in this study (20/22) also took part in the imaging study.

Assessment of cognitive processes

The tests used are described in detail below, and they are summarized in Table I.

Executive functioning

This was evaluated using three working memory tests from the WMS-III (Wechsler, 2000): Letter-Number Sequencing, Digits Backward and Spatial Span Backward. We also used the Modified Six Elements Test, one of the subtests of BADS (Wilson *et al.*, 1996), since this is one of the few tests currently available which assesses multitasking and priority setting.

Memory

Verbal and visual short-term memory were respectively assessed using Digits Forward and Spatial Span Forward, both from the WMS-III. Long-term memory was assessed by means of two other tests form the WMS-III: Logical Memory Immediate for verbal recall, and Faces Immediate for visual recognition.

Immediate recall of the Rey-Osterrieth Complex Figure Recall (Rey, 1997) was also used as a measure of visual recall.

Language

Two tests were included here. One was the Spanish Edition of the Boston Naming Test (García-Albea and Sánchez Bernardos, 1986). The other was the Spanish translation of the 39-item version of the Token Test (Spreen and Strauss, 1998), a measure of comprehension of grammar.

Visual/visuospatial function

For this, four subtests of the Visual Object and Space Perception Battery (VOSP) (Warrington and James, 1991) were used. This battery contains nine tests covering different aspects of visual object recognition and visuospatial skills. The four subtests were chosen on the basis that they covered a range of different aspects of functioning, and that the range of scores in normal subjects was relatively wide (i.e. there were no ceiling effects) (see Table I). In addition, copying of the Rey-Osterrieth Complex Figure was included.

Data analysis

Statistical analyses were carried out using the SPSS statistical software for Windows (version 15). Data were compared using appropriate tests (χ^2, Mann-Whitney's U-tests, t-tests and ANOVA). In some cases variables were transformed (e.g. through a log transformation) if data did not follow a normal distribution (Howell, 1997). ESs for differences between the controls and the schizophrenia groups and between both schizophrenia groups were calculated in the cognitive study using Cohen's *d* (Cohen, 1988).

Table I. Tests used for the different domains of cognition.

Test	Brief description
Executive functions	
Letter-Number Sequencing (WMS-III)	Verbal mental tracking: Requires ordering of an orally presented, increasingly long sequences of mixed letters and one digit-numbers. The subject has to give first the letters alphabetically and then the numbers in ascending order.
Digits Backward (WMS-III)	Verbal mental tracking: Requires reversing orally presented increasingly long series of numbers numbers.
Spatial Span Backward (WMS-III)	Visual mental tracking: The subject has to touch an increasingly longer series of cubes in the reverse order they are touched by the examiner.
Modified Six Elements Task (BADS)	Multitasking ability: The subject has to carry out parts, but not all, of six different activities according to a set of rules and with time constraints.
Memory	
Digits Forward (WMS-III)	Verbal short-term memory: Requires simple repetition of an increasingly long series of orally presented numbers.
Spatial Span Forward (WMS-III)	Non-verbal short-term memory: Requires touching a sequence of cubes in the same order as they are touched by the examiner.
Logical Memory Immediate (WMS-III)	Immediate verbal recall: The subject listens to two short stories and immediately afterwards has to reproduce as much of the information in it as possible
Faces Immediate (WMS-III)	Immediate visual recognition: Watching carefully at 24 different faces and immediately afterwards recognizing them among a series of 48 consecutively presented faces.
Rey Figure immediate recall	Immediate visual recall: Drawing all the information remembered three minutes after having copied it.
Language	
Boston Naming Test	Verbal expression: Naming of 60 drawings of objects.
Token Test	Verbal comprehension: Doing a series of orders of increasing complexity using diverse tokens that vary in geometric shape, colour and size.

Visuospatial functions	
Number Location (VOSP)	Spatial skills: Correctly identifying the number located in the equivalent place of the square than a point.
Cube Analysis (VOSP)	Spatial skills: Identifying the number of cubes drawn (identifying 3D out of 2D).
Object Decision (VOSP)	Object recognition: 20 different items in whose the aim is to identify the only silhouette out of four possibilities corresponding to an actual object.
Silhouettes (VOSP)	Object recognition: Naming the actual object corresponding to 20 silhouettes shown.
Rey Figure Copy	Visuospatial, visuoperceptive, and construction skills: Copying an abstract, complex drawing.

Results

Demographic and psychopathological characteristics of the sample

The three subject groups were matched for age, sex and premorbid IQ as estimated using the TAP (see Table II). The two groups of patients with schizophrenia showed similar illness duration and similar overall severity of illness as measured using the CGI. They also showed comparable levels of positive and negative symptoms, but the cognitively impaired patients showed significant higher scores on disorganization than the cognitively preserved patients. The cognitively impaired patients were also taking significantly higher doses of antipsychotic medication than the cognitively preserved patients.

As expected, the cognitively preserved patients showed higher scores than the cognitively impaired patients on the BADS (mean=10.07, SD=4.00, range 4-18 vs mean=15.84, SD=2.58, range 12-21) and the RBMT (mean=4.82, SD=1.74, range 1-10 vs mean=9.64, SD=1.29, range 8-12).

Table II. Mean values, standard deviations and statistical results of demographic, and psychopathological characteristics of the cognitive sample.

	Controls (*n*=22)	Participants with schizophrenia (*n*=54)		Group statistics
		Preserved (*n*=25)	Impaired (*n*=29)	
Age	42.94 (13.03)	39.60 (10.11)	41.16 (8.36)	F=0.600 *p*=0.552
Sex (M/F)	15/7	18/7	21/8	χ^2=0.125 *p*=0.939
TAP Estimated IQ[1]	103.45 (8.87)	103.10 (10.24)	99.16 (9.09)	F=1.668 *p*=0.196
Years of illness	-	19.24 (9.53)	22.96 (9.70)	t=-1.417 *p*=0.162
PANSS total score	-	69.64 (14.26)	77.03 (15.24)	t=-1.832 *p*=0.073
Positive Syndrome (PANSS)	-	14.80 (5.02)	16.45 (5.49)	t=-1.145 *p*=0.258
Negative Syndrome (PANSS)	-	15.52 (5.69)	18.07 (4.19)	t=-1.890 *p*=0.064
Disorganized Syndrome (PANSS)	-	8.00 (2.99)	10.69 (3.24)	t=-3.152 ***p*=0.003**
CGI score	-	4.17 (1.01)	4.69 (0.93)	M-W U=250.00 *p*=0.65
Antipsychotic dosage (CPZ equivalent mg)	-	524.28 (418.14)	690.62 (334.45)	t=-2.480 ***p*=0.012**[2]

[1] One preserved participant had missing data for this analysis.
[2] After $\log^{10}$ transformation.

Neuropsychological test scores

General intellectual function

The findings are shown in Table III. On WAIS-III Full-Scale IQ, the cognitively preserved patients were numerically, but not significantly lower than the controls. In contrast, the cognitively impaired patients showed a lower mean IQ than both the controls and the cognitively preserved patients, significantly in the former and at trend level in the latter. Differences were in the same direction for Verbal IQ, but did not reach significance in any comparison, whereas the

cognitively impaired patients' scores were significantly lower than the other two groups on Performance IQ.

Table III. Mean values, standard deviations and statistical results of the IQ measures of the cognitive subsamples.

	Controls (*n*=22)	Participants with schizophrenia (*n*=54)		Group statistics
		Preserved (*n*=25)	Impaired (*n*=29)	
Full-Scale IQ (WAIS-III)	101.23 (12.62)	95.28 (16.83)	87.45 (14.72)	F=5.482 ***p*=0.006**; I≤P (t=1.824; *p*=0.074) **I<C** (t=3.517; *p*=0.001)
Verbal IQ (WAIS-III)	104.91 (14.48)	101.80 (18.50)	95.66 (15.91)	F=2.128 *p*=0.126
Performance IQ (WAIS-III)	96.82 (16.53)	89.36 (14.97)	80.90(13.76)	F=7.148 ***p*=0.001**; **I<P** (t=2.164; *p*=0.035) **I<C** (t=3.752; *p*<0.001)

Executive functioning

As Table IV shows, the cognitively preserved schizophrenic patients showed no significant differences compared to the controls on any of the four executive tests used. On the other hand, the cognitively impaired patients performed significantly more poorly than both the cognitively preserved patients and the healthy participants on all four executive tasks. However, the difference between the cognitively impaired patients and the healthy controls in Digits Backward did not reach statistical significance.

Table IV. Mean values, standard deviations and statistical results in the executive tests of the cognitive sample.

	Controls (*n*=22)	Participants with schizophrenia (*n*=54)		Group statistics
		Preserved (*n*=25)	Impaired (*n*=29)	
Letter-Number Sequencing (WMS-III)	9.73 (3.21)	9.04 (3.40)	5.76 (2.81)	F=12.174 ***p*<0.001**; **I<P** (t=3.884; *p*<0.001) **I<C** (t=4.697; *p*<0.001)
Digits Backward (WMS-III)	5.55 (2.32)	5.72 (2.54)	4.52 (1.46)	F=2.550 *p*=0.085; **I<P** (t=2.089; *p*=0.044) I≤C (t=1.822; *p*=0.078)
Spatial Span Backward (WMS-III)	5.32 (1.13)	4.76 (1.23)	3.79 (1.35)	K-W χ^2=19.703; ***p*<0.001** **I<P** (M-W U=186.00; *p*=0.002) **I<C** (M-W U=107.50; *p*<0.001)
6 Elements Task (BADS)	3.41 (0.91)	3.20 (1.08)	1.93 (1.36)	K-W χ^2=18.768; ***p*<0.001** **I<P** (M-W U=174.00; *p*=0.001) **I<C** (M-W U=126.00; *p*<0.001)

Memory

Table V presents the results for the five memory tasks. The cognitively preserved patients with schizophrenia showed no significant difference when compared to controls on most tests, but they were significantly impaired on one task, Logical Memory. The cognitively impaired group did not differ from both the cognitively preserved group in the two short-term memory tasks (Digits Forward and Spatial Span Forward). However, their performance was significantly lower than the controls on Spatial Span Forward. The cognitively impaired group showed a significantly lower score than both the controls and the cognitively preserved patients on all three long-term memory tasks.

Table V. Mean values, standard deviations and statistical results in the memory tests of the cognitive sample.

	Controls (*n*=22)	Participants with schizophrenia (*n*=54)		Group statistics
		Preserved (*n*=25)	Impaired (*n*=29)	
Digits Forward (WMS-III)	8.59 (2.38)	7.96 (2.30)	7.38 (1.76)	K-W χ^2=3.649; *p*=0.162
Spatial Span Forward (WMS-III)	5.55 (0.74)	5.16 (1.18)	4.72 (1.10)	F=3.970; ***p*=0.023** **I<C** (t=3.023; *p*=0.004)
Logical Memory Immediate Recall (WMS-III)	37.86 (9.45)	29.72 (15.14)	15.21 (6.96)	F=28.410 ***p*<0.001**; **P<C** (t=2.239; *p*=0.031) **I<P** (t=4.408; *p*<0.001) **I<C** (t=9.865; *p*<0.001)
Rey Figure Immediate Recall	18.75 (7.41)	16.98 (6.66)	9.40 (5.35)	F=15.782 ***p*<0.001**; **I<P** (t=4.639; *p*<0.001) **I<C** (t=5.237; *p*<0.001)
Faces Immediate Recognition (WMS-III)	35.50 (4.27)	35.24 (4.08)	31.90 (5.22)	F=5.107 ***p*=0.008**; **I<P** (t=2.592; *p*=0.012) **I<C** (t=2.635; *p*=0.011)

Language

As shown in Table VI, the cognitively preserved patients showed numerically, but not significantly lower scores than the controls on both the Token Test and the Boston Naming Test. In contrast, the cognitively impaired patients had significantly lower scores on both tasks when compared to the controls. They also had significantly lower scores than the cognitively preserved patients on the Token Test, and at trend level (p=0.08) on the Boston Naming Test.

Table VI. Mean values, standard deviations and statistical results in the language tests of the cognitive sample.

	Controls (n=22)	Participants with schizophrenia (n=54)		Group statistics
		Preserved (n=25)	Impaired (n=29)	
Token Test	160.45 (2.18)	159.08 (3.52)	150.76 (11.40)	F=40.871 ***p*<0.001**[1]; **I<P** (t=5.475; p=0.001) **I<C** (t=7.040; p<0.001)
Boston Naming Test	53.73 (3.10)	52.24 (5.08)	49.00 (7.58)	F=4.564 ***p*=0.014**; I≤P (t=1.814; p=0.075) **I<C** (t=3.040; p=0.004)

[1] After $y=e^{(x/5)}$ transformation.

Visual/visuospatial function

Table VII shows the results of the five tests assessing visual object and visuospatial skills. The cognitively preserved group did not show statistically significant differences from the control group in any of the tests. In contrast, the

cognitively impaired patients showed significantly lower performance compared with both the controls and the cognitively preserved group on all tests.

Table VII. Mean values, standard deviations and statistical results in the visual spatial, perceptive and constructive tests of the cognitive sample.

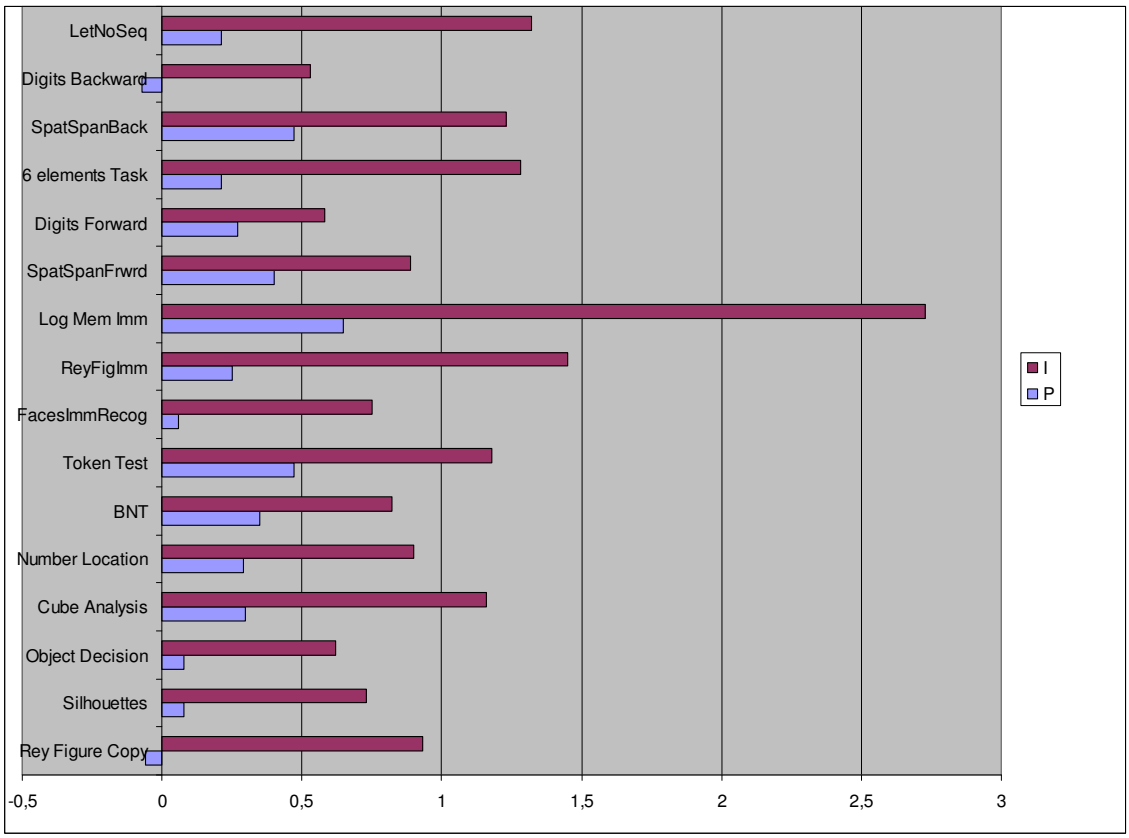
	Controls (*n*=22)	Participants with schizophrenia (*n*=54)		Group statistics
		Preserved (*n*=25)	Impaired (*n*=29)	
Number Location (VOSP)	9.32 (1.04)	9.00 (1.16)	7.59 (2.50)	K-W χ^2=12.254; ***p*=0.001** **I<P** (M-W's U=220.50; *p*=0.011) **I<C** (M-W's U=161.00; *p*=0.002)
Cube Analysis (VOSP)	9.36 (0.85)	9.00 (1.50)	7.17 (2.54)	K-W χ^2=15. 845; ***p*<0.001** **I<P** (M-W's U=189.50; *p*=0.002) **I<C** (M-W's U=139.00; *p*<0.001)
Object Decision (VOSP)	17.09 (2.37)	16.92 (1.94)	15.59 (2.43)	F=3.544 ***p*=0.034** **I<P** (t=2.215; *p*=0.031) **I<C** (t=2.207; *p*=0.032)
Silhouettes (VOSP)	20.59 (4.31)	20.28 (3.67)	17.24 (4.90)	F=4.826 ***p*=0.011**; **I<P** (t=2.546; *p*=0.014) **I<C** (t=2.546; *p*=0.014)
Rey Figure Copy	33.25 (1.93)	33.38 (2.45)	28.33 (7.22)	F=8.787 ***p*<0.001**[1]; **I<P** (t=3.596; *p*=0.001) **I<C** (t=3.345; *p*<0.002)

[1] After $y=e^{(x/10)}$ transformation.

Comparison using effect sizes

Figure I summarises the ESs for the differences between the controls and a) the cognitively preserved patients and b) the cognitively impaired patients. It can be seen that in each case the difference is greater in the cognitively impaired patients. For the cognitively preserved patients 12/16 of the ESs were in the small range (0.1 to 0.3), and the rest were in the medium range (0.4 to 0.7). In contrast, the cognitively impaired group showed ESs which were in the medium range (5/16) or large range (≥0.8) (11/16).

Figure I. Effect size for the cognitive impairment in each function of both schizophrenia groups when compared to the healthy controls.



I: Cognitively Impaired Participants with Schizophrenia; P: Cognitively Preserved Participants with Schizophrenia; LetNoSeq: Letter-Number Sequencing; SpatSpanBack: Spatial Span Backward; SpatSpanFrwrd: Spatial Span Forward; Log Mem Imm: Logical Memory Immediate; ReyFigImm: Rey-Osterrieth Complex Figure Recall; FacesImmRecog: Faces Immediate Recognition; BNT: Boston Naming Test.

Conclusions

This study examined the validity of separating patients with schizophrenia into cognitively preserved and cognitively impaired groups, based on their performance on batteries of tests assessing only memory and executive function respectively. The results show that this strategy resulted in a separation on most of a range of other cognitive tests covering executive function and memory, as expected, but also language and visual/visuospatial function. The cognitively preserved patients tended to score below the healthy controls but mostly not at statistically significant level. On the other hand, the cognitively impaired patients scored significantly lower than the cognitively impaired patients on almost all areas of cognitive function examined. An analysis of the ESs for impairment in the two patient groups (compared to the controls) confirmed uniformly larger ESs for impairment in the cognitively impaired patients.

There were two exceptions to the pattern found. One of these concerned short-term memory. Verbal short-term memory, as measured by Digits Forward, was the only test on which the cognitively impaired group did not show a significant impairment compared to any of the two other groups. Here, both patient groups performed numerically but not significantly more poorly than the controls, and the cognitively impaired patients also performed numerically but not significantly worse than the cognitively preserved patients. The pattern was similar for non-verbal short-term memory (Spatial Span Forward), although here there was a single significant difference, in this case between the controls and the cognitively impaired patients. The findings here are consistent with the conclusions reached by McKenna *et al*. (2002) in a review of the literature on

memory impairment in schizophrenia. They found that the majority of around 12 studies suggested that verbal short-term memory was not impaired, and argued that this form of memory is spared or relatively spared in the disorder. It was less clear that this held true for non-verbal short term memory, however, since 6/10 studies found impairment on spatial span tasks. In summary, the findings in this study are consistent with the view that short-term memory, and particularly verbal short-term memory, is among the less impaired cognitive functions in schizophrenia, and tends to show relatively minor impairment even in patients with otherwise severe cognitive deficits.

Another exception to the pattern of significant differences between cognitively preserved and cognitively impaired schizophrenic patients, but small and non-significant differences between cognitively preserved patients and controls was on one of the long-term memory tests used, Logical Memory. Here the cognitively preserved patients also showed significantly worse performance than the healthy controls, with a medium ES of 0.65. However, the cognitively impaired group had an ES for impairment of 2.73 on the test, the largest in this group. The findings here are broadly in agreement with the widely accepted view that long-term memory is one of the most severely impaired cognitive domains in schizophrenia (Aleman *et al.*, 1999; Mckenna *et al.*, 2002). They are also in agreement with findings from a meta-analysis that recall is more affected than recognition, and that verbal recall is more impaired than non-verbal recall (Aleman *et al.*, 1999).

References

Aleman A, Hijman R, de Haan EH, Kahn RS. Memory impairment in schizophrenia: a meta-analysis. *Am J Psychiatry* 1999; 156(9): 1358-66.

Cohen J. Statistical power analysis for the behavioural sciences. New York: Academic Press; 1988.

García-Albea JE, Sánchez Bernardos ML. La evaluación de la afasia y de los trastornos relacionados. 2nd ed. Madrid: Editorial Médica Panamericana; 1986.

Hill SK, Ragland JD, Gur RC, Gur RE. Neuropsychological profiles delineate distinct profiles of schizophrenia, an interaction between memory and executive function, and uneven distribution of clinical subtypes. *J Clin Exp Neuropsychol* 2002; 24(6): 765-80.

Horan WP, Goldstein G. A retrospective study of premorbid ability and aging differences in cognitive clusters of schizophrenia. *Psychiatry Res* 2003; 118(3): 209-21.

Howell DC. Statistical Methods for Psychology. 4th ed. Belmont, CA: Duxbury Press; 1997.

Keefe RS, Eesley CE, Poe MP. Defining a cognitive function decrement in schizophrenia. *Biol Psychiatry* 2005; 57(6): 688-91.

Kremen WS, Seidman LJ, Faraone SV, Toomey R, Tsuang MT. The paradox of normal neuropsychological function in schizophrenia. *J Abnorm Psychol* 2000; 109(4): 743-52.

Mckenna PJ, Ornstein T, Baddeley AD. Schizophrenia. In *Handbook of Memory Disorders* (ed. A. D. Baddeley, B. A. Wilson and M. Kopelman). Chichester, UK; 2002.

Palmer BW, Heaton RK, Paulsen JS, Kuck J, Braff D, Harris MJ, Zisook S, Jeste DV. Is it possible to be schizophrenic yet neuropsychologically normal? *Neuropsychology* 1997; 11(3): 437-46.

Rey A. Test de copia y de reproducción de memoria de figuras geométricas complejas. Rey. Madrid: TEA; 1997.

Seaton BE, Allen DN, Goldstein G, Kelley ME, van Kammen DP. Relations between cognitive and symptom profile heterogeneity in schizophrenia. *J Nerv Ment Dis* 1999; 187(7): 414-9.

Spreen O, Strauss E. A Compendium of Neuropsychological Tests. 2nd ed. New York: Oxford University Press; 1998.

Warrington EK, James M. Visual Object and Space Perception Battery. Bury St Edmunds, UK: Thames Valley Test Co; 1991.

Wechsler D. Escala de memoria de Wechsler. WMS-III. Madrid: TEA; 2000.

Weickert TW, Goldberg TE, Gold JM, Bigelow LB, Egan MF, Weinberger DR. Cognitive impairments in patients with schizophrenia displaying preserved and compromised intellect. *Arch Gen Psychiatry* 2000; 57(9): 907-13.

Wilk CM, Gold JM, McMahon RP, Humber K, Iannone VN, Buchanan RW. No, it is not possible to be schizophrenic yet neuropsychologically normal. *Neuropsychology* 2005; 19(6): 778-86.

Wilson BA, Alderman N, Burgess PW, Emslie H, Evans JJ. Behavioural Assessment of the Dysexecutive Syndrome (BADS). Reading, UK: Thames Valley Test Co; 1996.

Annex 3

Copy of the document of the Research committee of Benito Menni C.A.S.M. Psychiatric Hospital approving to develop the project.

GERMANES HOSPITALÀRIES
del Sagrat Cor de Jesús
BENITO MENNI
Complex Assistencial en Salut Mental

El Dr. **Josep Treserra Torres**, Director Mécico de Benito Menni Complejo Asistencial en Salud Mental, como Presidente de la Comisión de Investigación del Centro

CERTIFICA:

Que el Comité de Investigación de Benito Menni Complejo Asistencial en Salud Mental, en la sesión celebrada en el día de hoy, ha analizado el proyecto de investigación titulado:

« Bases neuroanatòmiques dels dèficits cognitius en l'esquizofrènia »

Cuyo investigador principal es Jordi Ortiz Gil, concluyendo que dicho estudio cumple los requisitos metodológicos necesarios y que es viable en todos sus términos, por lo que lo ha considerado adecuado y ha decidido su aprobación.

Lo que firmo en Sant Boi de Llobregat, Barcelona, a 13 de noviembre de 2008.