Prefrontal networks in schizophrenia

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Insights from neuroimaging

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1. Introduction

The aim of this thesis is to investigate the role of the prefrontal cortex in the pathology of schizophrenia. The prefrontal cortex has an important regulating role in brain function and is connected to almost every part of the brain. These regulating brain functions include executive function, goal-directed behavior, memory processes, initiative, and social behavior. These higher order functions have been shown to be often disturbed in schizophrenia (Heinrichs 2001). Studies have shown that the prefrontal cortex is hypoactive in schizophrenia (Glahn et al. 2005; Hill et al. 2004). Taken together, dysfunction of the prefrontal cortex and its connections to other brain regions may underlie the higher order deficits observed in schizophrenia. Different studies in this thesis have investigated the link between specific prefrontal functions and underlying prefrontal networks in schizophrenia. In addition, this thesis focuses on the treatment options of negative symptoms, which may also originate from prefrontal dysfunction. First, I will start with a general introduction on prefrontal function.

The prefrontal cortex

The prefrontal cortex (PFC) comprises the most anterior part of the brain. The anatomy of the PFC can be defined in different ways, but we will consider all the brain areas anterior to the motor cortex as prefrontal cortex (Fuster 2009). It has shown an extensive relative growth during the evolutionary development of mammals. In comparison to other mammals, humans have the largest prefrontal cortex relative to their body size (Fuster 2009). The prefrontal cortex has a role in complex social and cognitive processes and goal-directed behavior (Goldberg 2009). It evaluates and plans actions as well as integrates and coordinates new information. In this sense, the prefrontal cortex could be seen as the “conductor of the orchestra” (Goldberg 2009).

To perform its role, the PFC intimately interacts with all parts of the brain (Glahn et al. 2005; Minzenberg et al. 2009). A rough distinction in the prefrontal cortex and its connections can be made between the ventromedial prefrontal cortex and the dorsolateral prefrontal cortex, although both are heavily

interconnected (Fuster 2009; Goldberg 2009). The ventromedial PFC (VMPFC) is most strongly connected to medial thalamus, hypothalamus, amygdala, and limbic and medial temporal cortex and is thought to have functions in emotional, instinctive, and affect-modulated behavior (Fuster 2009). The dorsolateral prefrontal cortex (DLPFC) is more strongly connected to the lateral thalamus, the dorsal caudate nucleus, and the neocortex (Fuster 2009) and has an important role in executive cognitive functions (Fuster 2009). For an overview, see Figure 1 and Figure 2. Both the lateral and medial PFC are connected to the anterior cingulate cortex (ACC) (Allman et al. 2001). The ACC has functions in self-control, focused problem solving, error recognition, and adaptive response to changing conditions (Allman et al. 2001). The next section will focus on interaction between the PFC and different brain systems.

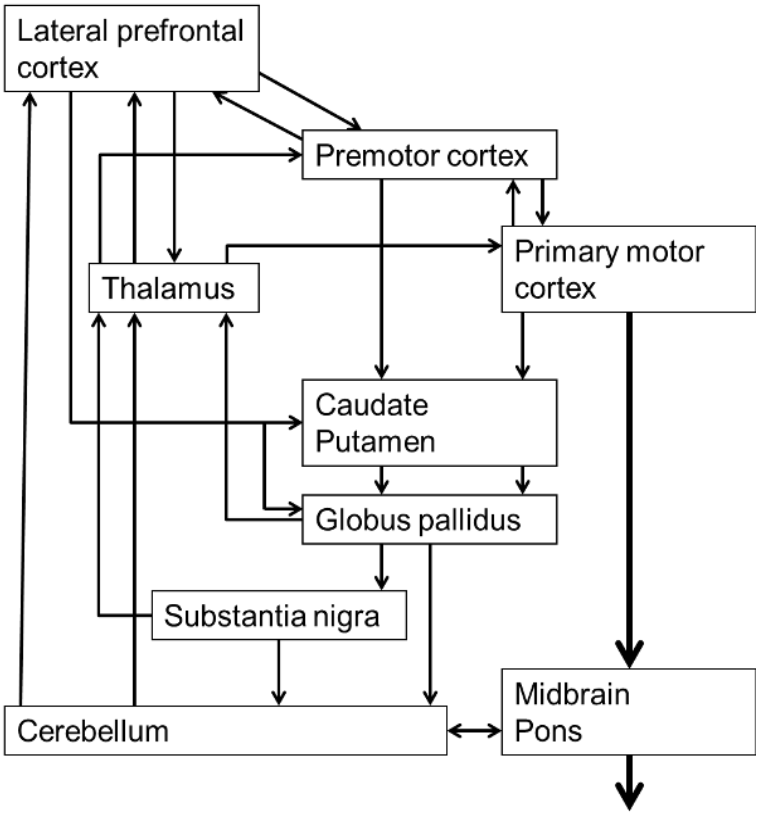

Figure 1 Main connections of the lateral prefrontal cortex to other brain regions (Fuster 2009)

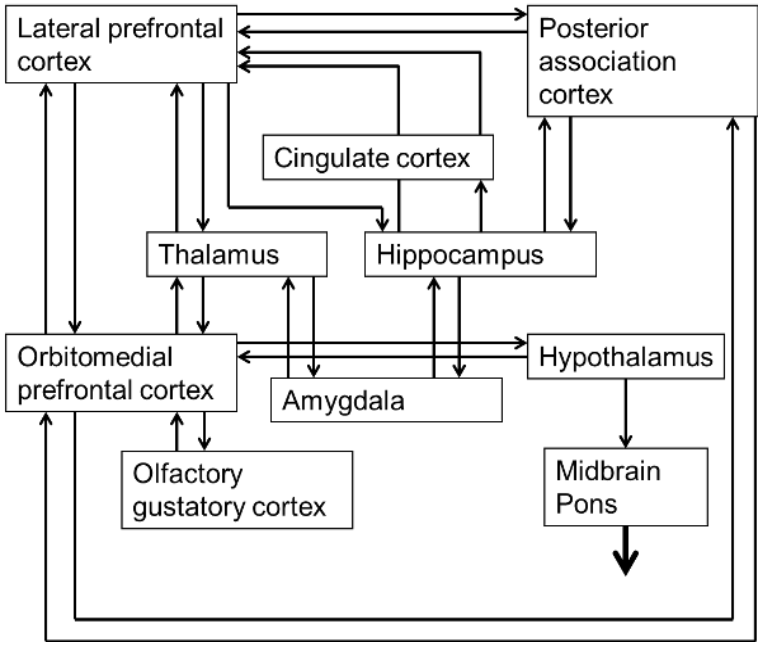

Figure 2 Main connections of the medial prefrontal cortex to other brain regions (Fuster 2009)

Default mode network

In 1974, Ingvar and Franzen reported a study of the brain during rest and during task performance using Xenon 133 inhalation (Ingvar and Franzen 1974). They observed that the frontal brain had higher activity during the resting state than during some cognitive challenges. They concluded that this "hyperfrontal" pattern of brain activation corresponded "to undirected, spontaneous, conscious mentation, the 'brain work,' which we carry out when left alone undisturbed". This research let to the first clue of increased activity during rest localized in specific brain regions that prominently include the prefrontal cortex.

In 2001 Gusnard and Raichle wrote an influential paper about brain activity during rest (Gusnard and Raichle 2001). Until that moment, functional Magnetic Resonance Imaging (fMRI) research mainly focused on task-related increases in activation of brain areas (Buckner et al. 2008). Over a variety of these tasks, a consistent network of areas was deactivated during task performance compared to rest conditions. PET research on resting state - defined as lying down and doing nothing in particular - had shown a set of brain areas with high oxygen consumption and blood flow having much overlap with the brain areas showing

increased activation during rest. Gusnard and Raichle referred to this pattern of brain activity during rest as the “default mode of brain function” (Gusnard and Raichle 2001; Raichle et al. 2001). The network of areas showing this high activation during rest was from then on referred to as the “default mode network” (Buckner et al. 2008; Raichle et al. 2001), see Figure 3.

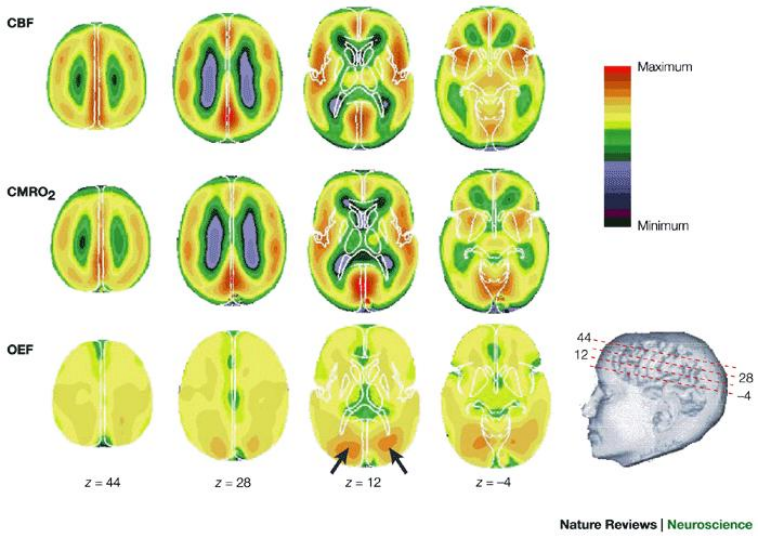

Figure 3 Outline of default mode network as discovered by PET research (Gusnard and Raichle 2001)

This “default mode” activity during rest was hypothesized to be involved in information processing related to the self (Gusnard and Raichle 2001). Only when external stimuli require attention, activity within the network is attenuated (Wicker 2003). Areas in this network include the ventral and dorsal medial prefrontal cortex (vMPFC and dMPFC), anterior cingulate cortex (ACC), the posterior cingulate cortex (PCC)/retrosplenial cortex (RspC) and adjacent precuneus, inferior parietal lobule (IPL), medial temporal cortex (MTG), and hippocampal formation (Buckner et al. 2008; Raichle and Gusnard 2005). The default mode network (DMN) appears to encompass subnetworks consisting of an anterior part containing the ACC/MPC, a posterior part containing the PCC, precuneus and IPL, and a ventral part containing the temporal areas and ventral prefrontal regions (Buckner et al. 2008; Northoff et al. 2006). These subnetworks

were postulated to be involved in specific and distinguishable functions, which will be covered in more detail throughout the thesis (Buckner et al. 2008).

Resting state connectivity

Imaging studies during resting state may thus provide important information on brain function. Already in 1995, Biswal et al. started to study spontaneous fluctuations during rest in the Blood Oxygen Level Dependent (BOLD) signal measured by fMRI (Biswal et al. 1995). Since then, many studies have observed that networks of remote brain areas show synchronized slow fluctuations in the BOLD signal (Beckmann et al. 2005; Raichle and Gusnard 2005), that are relatively stable over time and conditions (Auer 2008). One of the networks that shows these synchronized fluctuations is the default mode network (Buckner et al. 2008; Fox and Raichle 2007), but more networks have been discovered since then, including networks involved in sensory and motor processing, memory, and executive functioning (Beckmann et al. 2005; Damoiseaux et al. 2006; Van de Ven et al. 2004). It appears that functionally linked brain areas show synchronized temporal fluctuations, while functionally distinct areas are anticorrelated (Buckner et al. 2008; Fox and Raichle 2007).

Evidence exists that these BOLD fluctuations reflect spontaneous neural activity (Smith et al. 2009; Van den Heuvel and Hulshoff Pol 2010). Resting state fluctuations may even predict an individual's task performance or behavior (Fox and Raichle 2007). For example, stronger fluctuations in the somatosensory cortex predict weaker finger presses in a subsequent task (Fox and Raichle 2007). Relations between cognitive function and resting state networks have also been shown (Smith et al. 2009). The default mode network has been related to self-reflection, daydreaming, autobiographic memory, future planning, attention, and motivated behavior (Buckner et al. 2008; Raichle and Gusnard 2005; Raichle et al. 2001; Spreng and Grady 2009). Some studies have even shown a more direct link between DMN activity and e.g. motivated behavior (Raichle and Gusnard 2005), or self-processing (Northoff and Bermpohl 2004; Qin and Northoff 2011; Whitfield-Gabrieli et al. 2011).

The medial prefrontal cortex shows the most consistent decrease in brain activation during task performance (Ingvar and Franzen 1974; Qin and Northoff 2011; Wicker 2003) and may be a key region of the DMN (Northoff and Bermpohl 2004; Northoff et al. 2006). The medial frontal cortex appears to have an important role in coordinating goal directed behavior based on self-evaluative processing, in the light of its connections with areas like hypothalamus, amygdala, and brainstem (Gusnard and Raichle 2001; Northoff and Bermpohl 2004; Raichle et al. 2001).

Many cognitive processes of the lateral PFC, such as linguistic processing, require selection of self-relevant stimuli, and in this sense the lateral PFC could be considered as the link between self-referential and higher order processing (Northoff and Bermpohl 2004; Northoff et al. 2006; Qin and Northoff 2011). Self-processing may be important for many brain functions, and may have an important role in schizophrenia, as will be shown throughout this thesis. But first, the next section will focus on ways to study resting state interactions between different brain networks.

Activity and connectivity

Studying interactions between brain regions in networks in fMRI research is called connectivity analysis. Connectivity analysis may further the understanding of neuronal systems in addition to traditional activation-based fMRI research (Fox and Raichle 2007; Van den Heuvel and Hulshoff Pol 2010). Whereas task-based activation can provide information about the anatomical function of specific brain areas, functional connectivity may provide information about the function of interaction between brain areas within a network (Van den Heuvel and Hulshoff Pol 2010).

Studying resting state fluctuations may even have some advantages over task-based fMRI. Subjects don't have to perform a task, so differences in performance between groups do not have to be controlled for and also relatively ill patients groups with limited capacities can be investigated (Fransson 2006; Smith et al. 2009). Cognitive capacities can then be predicted by studying resting state scans (Van den Heuvel and Hulshoff Pol 2010).

There are different methods to study connectivity (Van den Heuvel and Hulshoff Pol 2010). The simplest and most prevalent way is to extract time series from certain brain areas of interest, and correlate these to the rest of the brain as a measure of connectivity (Fox and Raichle 2007). The second most popular technique is independent component analysis (ICA) (Beckmann et al. 2005; Calhoun et al. 2001). This method decomposes the BOLD signal without a priori knowledge into components that are maximally independent. The temporal pattern within a component is then coherent. Some components reflect non-neural signals such as heart beats, but others reflect neuronal signals (Damoiseaux et al. 2006; Fox and Raichle 2007). An advantage of ICA is that no a priori assumptions are needed about the outline of the connectivity patterns in brain networks (Van de Ven et al. 2004; Van den Heuvel and Hulshoff Pol 2010) and it can investigate complex paradigms (Calhoun et al. 2001). ICA produces outlines of brain networks that are highly consistent across subjects (Damoiseaux et al. 2006).

Though ICA is a promising technique, there are some challenges. First, the number of components has to be chosen by the researcher, although methods have been suggested to objectively constrain the number of components (Calhoun et al. 2001). It may also be difficult to disentangle components that reflect neuronal networks from components that represent other effects (Fox and Raichle 2007; Van den Heuvel and Hulshoff Pol 2010). Finally, interpretation of a reduced magnitude of the spatial outline of a component, i.e. the extensiveness of the network, may be difficult compared to interpretation of more classic techniques (Calhoun et al. 2001; Fox and Raichle 2007; Van den Heuvel and Hulshoff Pol 2010). A large part of this thesis will be dedicated to altered connectivity in prefrontal brain networks in a complex mental illness: schizophrenia.

Disturbed prefrontal function in schizophrenia

As stated earlier, the prefrontal cortex has a role in a complex set of behaviors (Goldberg 2009; Goldman-Rakic 1994; Rissling et al. 2010; Wible et al. 2009) and because patients with schizophrenia show impairments in these cognitive

functions (Aleman et al. 1999; Heinrichs 2001), prefrontal dysfunction may be an important origin for their cognitive dysfunctions and other manifested symptoms (Goldberg 2009; Goldman-Rakic 1994). Hughlings-Jackson stated that negative symptoms involve loss of function through damage to some areas of the brain, whereas positive symptoms reflect disinhibition of function through damage to some specific, higher cortical area that inhibits that function (Jackson 1887). The prefrontal cortex may be an interesting candidate in this model, so that compromised prefrontal functioning leads to lack of initiative and other negative symptoms, and loss of control over other brain areas may lead to positive symptoms such as hallucinations and delusions (Frith et al. 2009; Goldberg 2009).

Decreased prefrontal activation has indeed been observed in patients with schizophrenia, albeit not consistently (Hill et al. 2004). However, when summarizing multiple studies the majority suggests a decrease in frontal brain activity in patients with schizophrenia (Davidson and Heinrichs 2003; Hill et al. 2004; Weinberger and Berman 1996), especially in the MPFC of the DMN during rest (Kuhn and Gallinat 2011). This decreased frontal activation is referred to as hypofrontality (Ingvar and Franzen 1974).

Although the majority of studies suggest hypofrontality in patients with schizophrenia, some studies suggest hyperfrontality in specific conditions. One of the explanations for observed hypofrontality and hyperfrontality may be the effect of cognitive load. Whereas healthy subjects may be able to increase activity in prefrontal regions with increasing cognitive efforts, patients may fail to do so after a certain point when the tasks becomes too complex (Jansma et al. 2004; Liddle and Pantelis 2003; Mendrek et al. 2004; Mendrek et al. 2007). Before this point, equal task performance may be observed in patients and healthy controls, but schizophrenia patients may show increased activity to compensate for impaired function in task-relevant brain areas (Fusar-Poli et al. 2007). After this point, decreased performance and decreased activation of prefrontal and other brain areas may be observed in patients (Di Pietro and Seamans 2008; Glahn et al. 2005).

Thus, schizophrenia patients indeed exhibit decreased prefrontal function. However, because the PFC has a close interaction with many other brain areas

and feedback loops exist, the PFC should not be seen as a stand-alone operating brain system (Goldberg 2009). This will be discussed next.

Prefrontal networks affected in schizophrenia

According to the "cognitive dysmetria" model of schizophrenia, a disturbed cortical-subcortical-cerebellar feedback may be the major cause of schizophrenia (Fusar-Poli et al. 2007). Besides prefrontal regions, a circuit including cerebellar, thalamic, temporal, and striatal regions would have an important role. Disturbed feedback mechanisms in this circuit may be caused by disturbed interactions between brain regions, and this would fit the "dysconnectivity model" of Frith (Frith et al. 2009).

Numerous studies have shown alterations in low-frequency fluctuations of the brain in schizophrenia, including in the DMN (Auer 2008; Buckner et al. 2008; Greicius 2008). Most studies showed a relation between symptoms of schizophrenia and dysconnectivity of mainly the frontal and temporal areas (Van den Heuvel and Hulshoff Pol 2010). Notably, whereas most studies reported lower connectivity between resting state networks, some studies reported higher connectivity compared to healthy controls (Greicius 2008). It has been suggested that schizophrenia patients show decreased connectivity of long-range connections, whereas they show increased local connectivity (Lynall et al. 2010; Van den Heuvel and Hulshoff Pol 2010). Schizophrenia may then indeed be seen as a dysconnectivity syndrome, where normally frontally dominated hierarchical networks are degraded and efficient signal transmission is hampered (Bassett et al. 2008). Disturbances of these frontal networks appear to be related to attention and memory deficits and negative symptoms (Bassett et al. 2011).

In the light of the functions of the DMN, some symptoms of schizophrenia may specifically relate to DMN dysfunction, such as misattribution of thoughts to the external world (Buckner et al. 2008; Northoff and Bermpohl 2004) or impaired self-reflection (Kuhn and Gallinat 2011; Van der Meer et al. 2010). Moreover, the DMN appears to be in dynamic interplay with a network involved in external attention (Fransson 2006). An imbalance in this interplay may lead to overactive brain networks, and a blurring of perception of the external world and inner

states (Buckner et al. 2008). The prefrontal cortex may have a core role in disturbed interactions of brain networks (Goldberg 2009). Also other networks that are orchestrated by the prefrontal cortex appear also to be disturbed in schizophrenia (Fuster 2009), and these may also results in cognitive deficits and negative symptoms (Sanfilipo et al. 2002). The next sections will describe several symptoms and potential underlying disturbances of brain networks.

Neural background of executive deficits

Cognition is a very broad term that can be divided in a neurocognitive, or executive, and a social cognitive domain (Foussias and Remington 2010). Cognitive deficits in schizophrenia are often diagnosed but difficult to treat and have a large impact on daily activities and occupation. Specification of the neuroanatomical and neurophysiological background of those symptoms may help to develop new treatment strategies (Heinrichs and Zakzanis 1998; Palmer et al. 2009; Rissling et al. 2010).

The lateral prefrontal cortex and the brain areas it is connected to may be involved in disturbances of executive functioning in schizophrenia (Fusar-Poli et al. 2007; Minzenberg et al. 2009), working memory (Goldman-Rakic 1994), cognitive control (Minzenberg et al. 2009) and disorganization (Goghari et al. 2010). Medial prefrontal networks may be more involved in negative symptoms and emotion processing (Chemerinski et al. 2002; Goghari et al. 2010). The anterior cingulate cortex (ACC) is highly integrated with the DLPFC and has shown similar abnormalities, which may relate to a failure to monitor internal and external states (Fusar-Poli et al. 2007; Glahn et al. 2005; Minzenberg et al. 2009).

Language may be important for executive functions in humans, which is all the more plausible given that it can be used to evaluate and plan action (Goldberg 2009). Language problems may even have a prominent role in disturbed executive functions, attention, and working memory (DeLisi 2001; Goldberg 2009). Interestingly, different aspects of language disturbances have been observed in schizophrenia, including hallucinations, verbal learning problems, and memory deficits (Crow 2008; Stephane et al. 2001; Wible et al. 2009).

Language processing occurs in a network of brain areas encompassing temporal and parietal regions, inferior and middle frontal gyrus, and anterior cingulate cortex (Allen et al. 2007; Allen et al. 2008; Li et al. 2009; Stephane et al. 2001; Wible et al. 2009). Problems in executive control and language may be caused by impaired control of prefrontal regions (ACC, premotor) (Li et al. 2009; Stephane et al. 2001) over posterior regions of the brain (Allen et al. 2008; Goldberg 2009; Wible et al. 2009). Resulting overactivation of these regions may then lead to positive symptoms, e.g. auditory verbal hallucinations by overly active language processing regions (Allen et al. 2008; Wible et al. 2009).

As previously indicated, resting state studies are not biased by differences in performance between groups and can provide interesting insights into brain function in addition to task-based fMRI. Language networks are studied in this thesis both during performance of a language task (in Chapter 3) and during resting state (in Chapter 2).

Language is a cognitive process at the border between executive functions and social cognition (Hashimoto et al. 2010; Li et al. 2009; Stephane et al. 2001; Wible et al. 2009). While the development of language obviously has increased cooperation between individuals, it may also have helped to gain higher levels of executive functioning through the acquired ability to formulate goals and also to the emergence of mental representations of the self (Goldberg 2009). Disturbances in overlapping brain regions may cause impairments in both self-processing and language processing (Li et al. 2009; Stephane et al. 2001). Language regions even show considerable overlap with regions of the DMN (Li et al. 2009; Wible et al. 2009) suggesting that they also share functions. The next section will focus on another important function of the PFC that may be compromised in schizophrenia: the neural basis of social problems in schizophrenia.

Neural background of social cognition and emotion

It has been proposed that poor social functioning of schizophrenia patients may be caused by poor social cognition (Nelson et al. 2009). Social cognition can be described as cognitive and emotional functions required to understand and

predict people's mental states and behavior (Mancuso et al. 2011; Nelson et al. 2009). Deficits in social cognition may play a role in the development of symptoms of schizophrenia, including delusions, incoherent speech, and third-person hallucinations (Frith 1995; Sass and Parnas 2003). These deficits may be caused by a failure to correctly represent self and other awareness (Frith 1995; Sass and Parnas 2003), which may lead to problems to interpret daily social activities, and a reduced ability to connect to other persons (Nelson et al. 2009). Self-processing disturbances manifest themselves as both hyperreflexivity (excessive self-focused attention) and as diminished self-processing (Parnas and Handest 2003; Sass and Parnas 2003).

Hyperreflexivity may lead to forming inappropriate associations between two stimuli (Parnas and Handest 2003; Sass and Parnas 2003). Creating associations between different emotional stimuli is called associative emotional learning. Patients with schizophrenia have shown impairments in associative emotional learning and concurrent abnormalities in brain activation (Murray et al. 2010). The prefrontal cortex has an important role in the formation of emotional associations (Achim and Lepage 2005), especially connections of the PFC to emotional parts of the brain such as amygdala and hippocampus (Das et al. 2007). Chapter 4 discusses the relation between associative emotional learning and altered connections between the prefrontal and amygdala-hippocampal complex.

Self-processing, but also other social cognitive functions, have been extensively related to prefrontal DMN regions (Buckner et al. 2008; Schilbach et al. 2008; Van der Meer et al. 2010). Patients with schizophrenia have shown consistent decreases in activation of DMN regions, which may accompany diminished self-related processing and social cognition (Kuhn and Gallinat 2011). Deficits in self-reflective processing may be a cause of poor insight into the symptoms of schizophrenia (David 1990; Northoff et al. 2006; Van der Meer et al. 2010). Insight can be defined as a decreased awareness of having a disorder, recognizing symptoms of the disorder, and good compliance to treatment (David 1990; Mintz et al. 2003). Impaired function of the self-reflection areas of the DMN, especially prefrontal dysfunction, may hamper proper recognitions of symptoms and awareness of being ill (David 1990; Van der Meer et al. 2010).

Chapter 5 reports on a study investigating the link between poor insight and default mode resting state connectivity.

Neural background of negative symptoms

Problems in self-processing may also relate to negative symptoms (Sass and Parnas 2003), which can be described as an absence of some behaviors, such as lack of motivation, lack of emotions, and lack of social interaction. Patients with schizophrenia appear to have a more analytic and conscious processing strategy of information, while processing strategies in healthy subjects may go automatically. This alternative strategy may develop as a result of a loss of awareness of the self and how to interact with the environment (Sass and Parnas 2003). Resulting hyperawareness of cognitive processing may result in a loss of emotional awareness and motivation because actions or thought are experienced as “non-self” (Sass and Parnas 2003).

Alexithymia is a trait characterized by a reduced ability to experience, imagine, identify, express, and describe emotions (Aleman 2005). These dysfunctions show resemblance to aspects of negative symptoms of schizophrenia (Van 't Wout et al. 2007; Yu et al. 2011). Patients with schizophrenia have indeed more difficulty with identifying, expressing, and describing feelings as measured with an alexithymia questionnaire (Cedro et al. 2001; Yu et al. 2011), which showed a correlation with negative symptoms (Van 't Wout et al. 2007). Negative symptoms may thus be partly reflected by the trait alexithymia (Van 't Wout et al. 2007).

The same brain areas that may underlie emotional deficits in schizophrenia, namely the amygdala, corpus callosum, and the prefrontal cortex, appear to be disturbed in alexithymia (Van 't Wout et al. 2007; Yu et al. 2011). Disturbed imagination of emotions as an aspect of alexithymia has been related to diminished activation of the prefrontal cortex (Mantani et al. 2005). Disturbed brain function in relation to emotional awareness and emotional experience has also been observed in other DMN brain regions (Berthoz et al. 2002; Kano et al. 2003; Karlsson et al. 2008; Lane et al. 1998; Moriguchi et al. 2006).

To summarize, alterations in brain functioning underlying emotional processing in alexithymia may share some resemblance in negative symptoms in schizophrenia and associated alterations in brain functioning in schizophrenia. Understanding more about the neural background of a trait related to negative symptoms may gain more insight in the etiology of negative symptoms and emotional deficits in schizophrenia without confounding effects such as other symptoms or medication. Chapter 6 reports on altered DMN function in healthy subjects with alexithymia, and may provide some insight in the neural basis of negative symptoms in schizophrenia.

The construct of negative symptoms

Negative symptoms, which can be considered as the primary symptoms of schizophrenia (Andreasen and Flaum 1991; Foussias and Remington 2010), are now often seen as a group of symptoms within one entity (Foussias and Remington 2010). But already in 1982, an interview was developed categorizing negative symptoms into five sub-dimensions, namely affective flattening, alogia, avolition, anhedonia, and attentional impairment (Andreasen 1982). In the same period, different efforts were made to define negative symptom groups (Goghari et al. 2010; Kirkpatrick et al. 2001).

An approach to study the relatedness of negative symptoms is through factor analysis (Blanchard and Cohen 2006; Peralta and Cuesta 1995). Different studies have shown that negative symptoms may have multiple sub-dimensions, with two sub-domains - expressive deficits and social amotivation - as the most consistent finding (Blanchard and Cohen 2006; Foussias and Remington 2010; Peralta and Cuesta 1995). Expressive deficits include flat affect and alogia, while social amotivation includes anhedonia, amotivation and asociality (Messinger et al. 2011). These two sub-domains (deficits in the expression of emotion and amotivation for social interactions) have now also been proposed for the DSM-V (Messinger et al. 2011).

Most studies on the construct of negative symptoms are not from recent years. Moreover, they investigated relatively small samples (< 200) (Blanchard and Cohen 2006; Foussias and Remington 2010; Peralta and Cuesta 1995). Chapter 7

attempts to capture the structure of negative symptoms by more robust methods. Negative symptom structure is determined in a large cohort of patients, and then confirmed in an independent and also large sample.

Neurotransmission in the prefrontal cortex

Effective treatment of negative symptoms and cognitive deficits may be the strongest determinant of good functional outcome (Horan et al. 2010). Unfortunately, treatment of negative symptoms with antipsychotics is often unsatisfactory. Before we will discuss the effects of antipsychotics on brain function in schizophrenia, a general introduction to neurotransmitters is necessary.

Neurotransmitters and neuromodulators are small molecules that make communication within the brain possible. Because of the orchestrating role of the PFC, different neurotransmitters play an important role in communication between the prefrontal cortex and other brain areas.

Many neurons, and interneurons, use glutamate (Glu) or Gamma Amino Buteric Acid (GABA) as neurotransmitters. Interneurons are diffusely distributed throughout the cortex, and have a general regulating role. While glutamate is excitatory, GABA is inhibitory (Fuster 2009). Glutamatergic tracks run from the cortex to subcortical structures, and from the hippocampus to the striatum and cingulate cortex of the frontal lobes (Belsham 2001; Laruelle et al. 2003). Glutamate is involved in learning and memory, locomotion, and perception (Belsham 2001). GABA-ergic neurons are abundant in the whole brain, and play a general role in inhibition and rhythmicity, often within feedback loops in brain circuits (Fuster 2009; Goldberg 2009).

Dopamine (DA) and noradrenaline (NE) are both neuromodulators that have a role in the prefrontal cortex and consequently they strongly influence executive functions (Goldberg 2009). The dopamine system runs from two regions in the brain stem to mainly prefrontal, striatal, and limbic regions. The striatal system has functions in cognitive integration, habituation, sensorimotor coordination, and initiation of movement, and the cortical and limbic networks

have functions in regulation of motivation, attention, and reward (Abi-Dargham and Laruelle 2005; Goldberg 2009).

Noradrenaline pathways from the brain stem innervate several nuclei in the hypothalamus and upper brain stem, but also the whole cortex and cerebellum (Fuster 2009; Goldberg 2009). Intermediate levels of both DA and NE are related to good cognitive performance, while high or low levels of DA or NE, e.g. caused by stress, may impair cognitive capacities of the prefrontal cortex, hippocampus, and amygdala (Di Pietro and Seamans 2008; Fuster 2009).

Serotonin (5-HT) is also synthesized in the brain stem, and shows strong projections to the limbic system and posterior brain regions, but also prefrontal brain regions (Busatto and Kerwin 1997; Fuster 2009; Goldberg 2009). 5-HT may have an important role in inhibitory control of the PFC on the rest of the brain, and in mental flexibility (Goldberg 2009). It has reciprocal interactions with other neurotransmitters (Lieberman 2004), e.g. with DA in the context of working memory (Fuster 2009; Meltzer et al. 2003) and with GABA in neuronal inhibition (Meltzer et al. 2003).

Acetylcholine (ACh), again from the brainstem, is involved in cognitive function and ACh neurons project diffusely throughout the brain. This neurotransmitter appears to have a modulating effect on DA in striatal regions. Moreover, ACh increases spontaneous neuronal activity in the DLPFC, while the PFC itself regulates ACh release in posterior parietal regions (Fuster 2009; Goldberg 2009).

With this basic knowledge about neurotransmitters, we can now move on to effects of antipsychotics on neurotransmitter systems.

Treatment of negative symptoms and other prefrontal dysfunctions

Historically, the first symptomatic treatment of schizophrenia was done with so-called typical antipsychotics that are potent blockers of the dopamine D_2 receptor. The efficacy of these dopamine blockers was based on the dopamine hypothesis of schizophrenia (Jarskog et al. 2007). The dopamine hypothesis states that positive symptoms may be caused by a superabundance of dopamine in the

striatal regions, while negative symptoms are caused by depletion of dopamine in the prefrontal cortex (Di Pietro and Seamans 2008; Fuster 2009; Lieberman 2004). This assumption is based on the observed effects of DA blocking antipsychotics. However, dopamine is possibly not the primary cause for pathology in schizophrenia (Grace 2000).

In fact, the pathophysiology of schizophrenia may involve disrupted synaptic connectivity that affects both inhibitory and excitatory brain circuits (Jarskog et al. 2007). It has been suggested that cortical glutamate may in fact be the primary factor in the pathology of schizophrenia. Decreased tonic activity of the cortical glutamate system may result in hypofrontality, as part of a larger network of brain regions that shows abnormalities (Belsham 2001; Grace 2000; Laruelle et al. 2003). On the other hand, the inhibitory effect of GABA-ergic interneurons in the DLPFC is also disrupted in schizophrenia (Belsham 2001; Di Pietro and Seamans 2008; Jarskog et al. 2007) and 5-HT receptor abnormalities have also been observed (Fuster 2009). Feedback loops via the dopamine system may lead to imbalance in the dopamine system with prefrontal hypodopaminergia a striatal hyperdopaminergia as a result (Belsham 2001; Di Pietro and Seamans 2008; Fuster 2009; Grace 2000; Jarskog et al. 2007).

Whereas the striatal overactivity may lead to positive symptoms, hypofrontality was postulated as the substrate for negative symptoms and cognitive impairments (Abi-Dargham and Laruelle 2005; Bishara and Taylor 2008; Jarskog et al. 2007). Moreover, deficits in glutamate and GABA transmission may cause interrupted associations in the cerebral cortex and disrupted integration in all domains, such as thinking, speech, emotion, and behavior (Fuster 2009).

Because early antipsychotics quite specifically block the dopamine receptor, they have a good effect on positive symptoms, but little or even a deteriorating effect on negative symptoms and cognitive impairments (Bishara and Taylor 2008; Jarskog et al. 2007). Therefore, newer antipsychotics have been developed with a more diverse receptor profile that may have subtle effects on negative symptoms and cognition (Arnt and Skarsfeldt 1998; Bishara and Taylor 2008; Jarskog et al. 2007). Two important pharmacological properties of this class of drugs may be a high affinity for the serotonin 5-HT_{2A} receptor and a lower D_2 affinity, which may

result in higher (medial) prefrontal dopamine levels (Busatto and Kerwin 1997; Di Pietro and Seamans 2008; Jarskog et al. 2007; Lieberman 2004; Meltzer et al. 1999; Meltzer et al. 2003) and effective glutamate transmission (Abi-Dargham and Laruelle 2005; Di Pietro and Seamans 2008; Meltzer et al. 2003). Despite the hypothesized superiority of these newer antipsychotics, the observed clinical effects appear to be limited or is at least not replicable (Abi-Dargham and Laruelle 2005; Arnt and Skarsfeldt 1998; Bishara and Taylor 2008; Davis et al. 2005; Leucht et al. 2009).

Neuroimaging studies have been conducted to investigate the effect of antipsychotic treatment on brain activation, including studies that specifically focused on the prefrontal cortex (Da Silva Alves et al. 2008; Davis et al. 2005; Röder et al. 2010; Vita and De Peri 2007). However, these studies made no clear distinction between antipsychotics or brain areas, only focused on one imaging technique, or are not recently updated. In general they found that antipsychotics decrease prefrontal function. But in the light of the ongoing discussion about whether atypical antipsychotics indeed have a more favorable spectrum of behavioral effects relative to typical antipsychotics and recent imaging findings an update may add to the field. In chapter 8 an overview is given of neuroimaging findings on the effects of different types of antipsychotics on prefrontal function.

One new approach to treat schizophrenia symptoms is the use of partial DA agonists. These work by binding to the dopamine receptor, and there mimicking the effect of dopamine but with a lower intrinsic activity (Jarskog et al. 2007; Lieberman 2004). In this way both hyper- and hypodopaminergia can be corrected without risk of overcompensation. Aripiprazole is the first partial dopamine agonist used in treating schizophrenia, and its extensive receptor interactions may help reducing anxiety, mood disturbances, cognitive deficits, and negative symptoms (Bishara and Taylor 2008; Jarskog et al. 2007; Lieberman 2004). Indeed, some evidence exists that the partial DA agonist aripiprazole may have some effect (Kane et al. 2008; Lieberman 2004). A study comparing the effectiveness of aripiprazole to a strong dopamine blocker on different aspects of negative symptoms is described in Chapter 9.

Outline of the thesis

This thesis focuses on different prefrontal functions that may be disturbed in schizophrenia. First, the function of lateral prefrontal regions is covered. Chapter 2 and 3 discuss language impairments as a key executive function, both during task performance in Chapter 3, and during resting state in Chapter 2. Chapter 4 discusses a process with both emotional and language aspects, and it focuses on the relation between associative emotional learning and prefrontal connections. Emotion processing, such as self-reflection, is one of the functions of the default mode network. Chapter 5 investigates the link between poor insight in schizophrenia and DMN resting state connectivity, because impaired self-reflective capacities may underlie poor insight. Further, chapter 6 reports on disturbed DMN function in healthy subjects with alexithymia. Alexithymia is a trait in which persons have problems to process feelings, and self-reflection could play an important role in emotional awareness. Studying alexithymia may also provide more insight into the neural basis of negative symptoms, because of the resemblance to alexithymia. However, before the neural basis of certain dysfunctions can be studied, good concepts of symptom dimensions are necessary. Chapter 7 shows that negative symptoms may consist of two sub-domains, which may have relevance for research into the neural correlates and into treatment. Chapter 8 investigates whether antipsychotics with different receptor profiles may have a different effect on prefrontal activation by revising the published neuroimaging literature. Chapter 9 expands on the notion of negative symptoms with different sub-domains and frontal activation by antipsychotics by investigating effects of aripiprazole (a dopamine agonist) on different negative symptoms.

2. Abnormal connectivity between attentional, language and auditory networks in schizophrenia

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Abstract

Introduction: Brain circuits involved in language processing have been suggested to be compromised in patients with schizophrenia. This does not only include regions subserving language production and perception, but also auditory processing and attention. We investigated resting state network connectivity of auditory, language, and attention networks of patients with schizophrenia and hypothesized that patients would show reduced connectivity. **Methods:** Patients with schizophrenia (N = 45) and healthy controls (N = 30) underwent a resting state fMRI scan. Independent components analysis was used to identify networks of the auditory cortex, left inferior frontal language regions and the anterior cingulate region, associated with attention. The time courses of the components where correlated with each other, the correlations were transformed by a Fisher's Z transformation, and compared between groups. **Results:** In patients with schizophrenia, we observed decreased connectivity between the auditory and language networks. Conversely, patients showed increased connectivity between

the attention and language network compared to controls. There was no relationship with severity of symptoms such as auditory hallucinations.
Discussion: The decreased connectivity between auditory and language processing areas observed in schizophrenia patients is consistent with earlier research and may underlie language processing difficulties. Altered anterior cingulate connectivity in patients may be a correlate of habitual suppression of unintended speech, or of excessive attention to internally generated speech. This altered connectivity pattern appears to be present independent of symptom severity, and may be suggestive of a trait, rather than a state characteristic.

Introduction

Problems in language processing have been consistently reported in individuals with schizophrenia (Crow 2008; DeLisi 2001), and also in healthy siblings (Docherty and Gordinier 2010), albeit to a lesser degree. These deficits cover a wide range of domains including language comprehension, production and attention, and specific processes such as semantics, verbal fluency and grammar (DeLisi 2001; Price 2010). Language problems have been related to auditory hallucinations (Crow 2008), formal thought disorder, disorganization and memory impairments (Docherty and Gordinier 2010). Neuroimaging studies in schizophrenia patients have shown abnormalities in brain areas related to language processing, including the auditory cortices (Li et al. 2009; Li et al. 2010), language areas such as Broca's (Li et al. 2010), as well as the anterior cingulate (ACC), which is involved in attention (Sabb et al. 2010) and speech monitoring (Allen et al. 2007). Several lines of research, including postmortem and brain imaging studies suggest that schizophrenia is characterized by abnormalities in concerted action between spatially distributed networks (Hubl et al. 2004; Kubicki et al. 2002; Shenton et al. 2001). Schizophrenia has therefore been described as a dysconnectivity disorder (Peled 1999). Aberrant connectivity between specific brain networks such as auditory, e.g. in the anterior superior temporal gyrus (STG) and language regions (Broca's and Wernicke's regions) may also underlie functional abnormalities observed in the disorder, i.e. language impairments (Li et

al. 2009; Li et al. 2010; Sabb et al. 2010). This study aims to study the connectivity between spatially distributed networks relevant for language processing.

Auditory verbal hallucinations (AVH) are one of the key symptoms of schizophrenia, which have been hypothesized to be related to problems in language comprehension and generation (Crow 2008; Stephane et al. 2001; Wible et al. 2009). In this framework, Crow and Frith et al. hypothesized that dysfunctional connections between fronto-temporal language and auditory brain regions may lead to language processing impairments, such as the misattribution of one's own verbal thoughts as spoken words outside the head (Crow 2008; Frith et al. 2009). The fronto-temporal dysconnectivity idea is supported by electrophysiological studies showing reduced fronto-temporal connectivity during talking (Ford et al. 2010), and reduced synchrony during the prespeech phase (Ford et al. 2007) in people with schizophrenia, particularly in those with AVH. Diffusion tensor imaging (DTI) studies and functional magnetic resonance imaging (fMRI) studies also showed a decreased connectivity between lateral frontal and the temporal areas in people with schizophrenia (Hubl et al. 2004; Li et al. 2010; O`Daly et al. 2007), also related to verbal learning (Hashimoto et al. 2010; Karlsgodt et al. 2008), verbal fluency capacity (Jeong et al. 2009), and hallucinations (Lawrie et al. 2002). Finally, computer simulations, verified by patient studies, showed that fronto-temporal dysconnectivity may result in erroneous word detection and spontaneous word generation (Hoffman and McGlashan 1998; Hoffman 1999).

In addition to abnormal fronto-temporal connectivity, decreased connectivity of auditory and language areas with the ACC may contribute to misattribution of speech, which may lead to AVH (Allen et al. 2007). DTI studies (Kubicki et al. 2002; Park et al. 2004) and functional imaging studies (Fletcher et al. 1999) support this idea by showing decreased left-sided connectivity between temporal and ventral prefrontal areas/ACC. Decreased connectivity of the ACC with other brain areas may also underlie a broad range of other language deficits, such as impairments in perception, comprehension, retrieval, and production (Price 2010). In conclusion, the literature suggest that impairments in language

processing in schizophrenia may be related to aberrant connectivity between brain areas implicated in language processing and attention.

During resting state fMRI scans, the brain shows large fluctuations in the Blood Oxygen Level Dependent (BOLD) signal, which are relatively stable within brain networks consisting of functionally connected regions (Salvador et al. 2005). This coherence of BOLD fluctuations within networks is referred to as resting state functional connectivity, and may be a more natural measure of brain function than task-based fMRI (Raichle and Gusnard 2005) as it reflects intrinsic brain interactions (Van de Ven et al. 2004). Furthermore, it has been suggested that these interactions may reflect overall brain function (Fox and Raichle 2007) and predict task performance or behavior (Fox and Raichle 2007). Evaluating resting state functional connectivity may therefore be a valuable tool for the identification of dysfunctional networks in the brain associated with psychiatric disorders such as schizophrenia (Auer 2008; Fox and Raichle 2007). Independent component analysis (ICA) is the method of choice to study temporal fluctuations between brain networks in the resting state, i.e. in the absence of a specific cognitive task (Auer 2008; Calhoun et al. 2001). This data-driven method separates the BOLD signal into spatially independent networks (components) by maximizing the spatial independence between voxel time courses (Van de Ven et al. 2004; Van de Ven et al. 2005). Together with the time course, a spatial map is created per subject, which shows the contribution of every voxel in the brain to a certain network (component). Brain areas that show similar fluctuations, i.e., have a similar time course and thus belong to one network, can this way be identified (Jafri et al. 2008). Those networks show a close correspondence to networks identified by activation studies (Smith et al. 2009). Thus, ICA is a suitable tool to study the large scale connectivity between different networks.

ROI-based analysis is a widely applied technique to study functional connectivity in fMRI research. It works by taking average time courses of the raw BOLD signal based on predefined regions, and correlating these. Our aim here is to study large scale connectivity between different networks. We considered ICA more suitable for our research question than seed-based ROI connectivity as we were interested in intrinsic networks that can be identified in a model-free, data-

driven way. Most importantly, Rosazza et al. showed that the largest differences in results between ICA and ROI analysis were observed for long range connections, which are the focus of our study (Rosazza et al. 2011). Moreover, ICA tends to separate signal of no interest from signal of interest (brain activation) and may give a better representation of brain activation than the raw MRI signal and contain less noise (Fox and Raichle 2007; Van de Ven et al. 2004). Finally, it may be difficult with ROI analysis to clearly define a complete brain network, without missing certain brain areas or including areas that show different temporal patterns (Fox and Raichle 2007; Van de Ven et al. 2004). Therefore, ICA is the optimal choice to study alterations in concerted action between spatially distributed brain networks (Hubl et al. 2004; Kubicki et al. 2002; Shenton et al. 2001) as we described earlier.

Few studies have used ICA as yet to investigate brain networks in schizophrenia in auditory networks. Van de Ven et al. used ICA to investigate the cortical connectivity patterns during AVH, reporting a relationship between time courses in the auditory cortex (superior temporal gyrus; STG) and the onset of AVH's (Van de Ven et al. 2005). Jafri et al. used ICA to investigate the connectivity between spatially independent brain networks of schizophrenic patients compared to healthy controls but they did not specifically investigate language and auditory networks (Jafri et al. 2008).

Given the relevance of these networks for the neurobiology of schizophrenia, we specifically focused on language and auditory processing networks in the present study. ICA is a very suitable analysis method given the data-drive nature of ICA. The first aim was to identify complete brain networks related to language processing in the data, by investigating whether predefined language-related brain regions could be identified as an ICA component. These regions included STG, Wernicke's and Broca's area, and the anterior cingulate cortex. The second aim was to study the difference in connectivity between networks comparing schizophrenia patients and healthy controls, by comparing the correlations of the time courses of different brain networks.

Methods

Subjects

This study was approved by the local medical ethical committee according to the Declaration of Helsinki. The study sample consisted of a mixed sample of in- and out-patients of local psychiatric clinics diagnosed with schizophrenia by their physician (SZ; N = 45) and a group of healthy controls (HC; N = 30). Patients were participants in an fMRI study on neural correlates of auditory hallucinations or a study on cognitive emotional processing; in both studies a resting state scan was part of the research protocol. In patients the diagnosis of schizophrenia based on the DSM IV was confirmed by a semi-structured interview (Schedules for Clinical Assessment in Neuropsychiatry; SCAN 2.1) - (Giel and Nienhuis 1996). Symptom severity was determined by the Positive and Negative Syndrome Scale (PANSS) - (Kay et al. 1987).

Exclusion criteria for the study consisted of MRI incompatible implants, possible pregnancy, claustrophobia, and non-native Dutch speakers. All subjects gave oral and written informed consent after the study procedure had been fully explained. All subject data was handled anonymously.

Healthy controls were recruited by advertisements in local newspapers, and matched for age, gender, handedness, and education level to the patient groups. See Table 1 for the demographical data. Difference in age between groups was tested with an independent samples t-test ($\alpha = 0.05$). Educational level was determined using a six point scale of Verhage which runs from primary school (1) to university level (6) and tested with a Mann–Whitney U test ($\alpha = 0.05$) (Verhage 1984). A Chi-square test ($\alpha = 0.05$) was used to test for differences in gender and handedness. Handedness was confirmed with the Edinburgh handedness inventory (Oldfield 1971). For patients, medication status was also determined.

Experimental procedure

All subjects underwent a resting state fMRI scan. They were instructed to close their eyes, relax, think of nothing particular, and to stay awake. A 3 T Philips Intera MRI scanner (Best, The Netherlands) equipped with an eight-channel SENSE head coil was used to acquire 200 whole brain echoplanar functional images (EPI's), TR

2.3 s and TE 28 ms. The volumes contained 39 or 43 interleaved slices (3.8×3.8×3 mm) with no gap and a 85° flip-angle (FOV = 220×117×220 mm). A high-resolution, transverse T1 anatomical was also acquired for anatomical reference (160 slices; voxel size 1×1×1 mm; FOV 256×220×256mm).

Table 1 Overview of the demographical data; mean values (standard deviations in parentheses) or ratios are indicated

	Patients	**Controls**	**p-value**
Age (years)	34.7 (11.4)	33.4 (10.5)	0.67
Education (level)	3.5 (1.1)	4.1 (1.1)	0.053
Males/females	28/17	15/15	0.42
Handedness (left/right)	5/40	6/24	0.47
PANSS P3 (AVH)	3.7 (1.9)	-	-
PANSS Positive	15.5 (5.0)	-	-
PANSS Negative	14.4 (4.4)	-	-
PANSS General	29.1 (8.3)	-	-

Participants also performed a language processing task in the same fMRI session as the resting state scan. Although the functional neuroimaging correlates of that task are beyond the scope of this paper, we present the behavioral data to provide an indication of language processing differences between groups, which may aid interpretation of our findings. The task (Aleman 2005) required subjects to evaluate bisyllabic Dutch words that were presented one at a time in the middle of the screen. In one condition a valence judgment was required, by indicating whether the presented word was positive or negative to the subject (semantic condition; e.g. stimulus: “summer”; answer e.g. “positive”). In the second condition, a metrical stress judgment was required, by indicating the syllable that carried the metrical stress (phonetic condition). The task consisted of 24 trials for the semantic condition and 24 trials for the phonetic condition that were presented mixed in pseudorandom order.

Data analysis

The raw images were converted to ANALYZE format and analyzed using Statistical Parametric Mapping (SPM5; FILWellcome Department of Imaging Neuroscience, London, UK) running in Matlab 7.1. Images were first corrected for slice-time differences and realigned to the first functional image. All motion parameters were checked for spurious motion and all subjects that moved more than 3 mm were excluded from further analysis. The mean image created during realignment was coregistered to the anatomy, together with the functional images, and the anatomy and functional images were normalized to the T1 template of SPM (voxel size 3×3×3 mm). Finally, images were smoothed with a 10mm FWHM isotropic Gaussian kernel.

Following preprocessing, images were processed in the Group ICA FMRI Toolbox (GIFT) (http://icatb.sourceforge.net/gift/gift_startup.php) - (Calhoun et al. 2001). First, the mean number of independent components (IC's) was estimated using Maximum Description Length (MDL) and Akaike's criteria (Li et al. 2006), to prevent splitting or merging of components (Smith et al. 2009). Estimation showed an estimate of 30 components. Intensity normalization, which implied scaling the time courses to a mean of 100, was applied to the images before running the ICA procedure. Then, images of all subjects were decomposed into a set of 30 spatially independent components by the Infomax algorithm. Stability of the components, i.e. investigating whether a component has the tendency to split or merge with another component (Rosazza et al. 2011), was validated by running the ICASSO toolbox implemented in GIFT using twenty iterations with both random iterations and bootstrapping (Himberg et al. 2004).

In order to exclude components with artifacts, components maps of the ICA were sorted based on the white matter and gray matter masks of SPM using the automated spatial sorting facility of GIFT. Validity of the components was further verified by visually comparing the components with previously identified networks (Beckmann et al. 2005; Damoiseaux et al. 2006; Smith et al. 2009).

Next, potential components of interests were identified by searching components that showed a substantial overlap with anatomical masks of predefined regions of key brain structures in language processing. The anatomical

masks used for sorting were created by WFU pickatlas (http://www.nitrc.org/projects/wfu_pickatlas). Masks provided by WFU pickatlas are based on brain regions defined by Talairach and Tournoux (Talairach and Tournoux 1998) that were implemented in this toolbox after conversion to MNI space (Lancaster et al. 1997; Lancaster et al. 2000). We tried to identify the auditory cortex network, language networks (Broca's and Wernicke's area), and the anterior cingulate of the attention network. The characteristics of the key regions are summarized in Table 2.

Table 2 Key areas of interest; Regions were derived from the WFU pickatlas; The second column indicated the name of the area as present in the atlas; The third column gives the size of the area in mm^3 and the fourth column a few examples of references on which we based the areas involved in language processing

Area of interest	Anatomical region in WFU pickatlas	Size of area (mm^3)	Reference from literature
Auditory network	Bilateral superior temporal gyrus	21.0	Hashimoto et al. 2010; Karlsgodt et al. 2008; Li et al. 2009; Li et al. 2010; Price 2010; Shergill et al. 2002; Simons et al. 2010
Attention network	Anterior cingulate gyrus	6.2	Allen et al. 2007; Fletcher et al. 1999; Price 2010; Sabb et al. 2010
Language network Broca's area	Brodmann area 44/45	2.1	Ford et al. 2010; Jeong et al. 2009; Li et al. 2010; Price 2010
	Inferior frontal gyrus	19.0	Stephane et al. 2001
Language network Wernicke's area	Brodmann area 22	3.4	Allen et al. 2007; Ford et al. 2010; Price 2010
	Heschl's gyrus	0.95	Stephane et al. 2001

Shortly, the auditory cortex was defined as STG and the anterior cingulate cortex as ACC. Because the language areas have different definitions, Wernicke's area was both defined as Brodmann area 22 and Heschl's gyrus, and Broca's area both as BA 44/45 and inferior frontal gyrus (IFG).

Time courses of selected components were visually inspected and converted to power spectra to check for the presence of artifacts (Cordes et al. 2000). Hereafter, correlations were calculated between the time courses of all selected networks (Jafri et al. 2008) and converted to z-scores by a Fischer's *Z* transformation, where $z = 1/2 \ln((1+r)/(1-r))$ where *r* represents the correlation. These data were loaded in Statistical Package for Social Sciences (SPSS 16). Between group comparisons were conducted using Mann–Whitney U tests ($\alpha = 0.05$).

In an additional analysis, the PANSS items P2 Conceptual disorganization, P3 Hallucinations (which mainly concerned AVH) were correlated - using a non-parametric Spearman correlation ($\alpha = 0.05$) - with the Z-scores, to investigate whether there was a link between symptom severity and connectivity between the auditory, language, and attention networks.

With regard to the language processing task, for both groups the mean reaction times and accuracy for the phonetic and semantic condition were calculated. For the semantic condition there are no correct answers as they depend on subjective ratings. Still, the agreement of a subject's response with the opinion of independent raters (from a previous study: (Aleman 2005) could be judged. Finally, the percentage of positively rated words was determined, as patients may have a more negative bias toward words. These measures were compared between groups using a Mann–Whitney U test ($\alpha = 0.05$) because the data were non-normally distributed. The measures were tested separately because both conditions measure a distinct concept.

Results

Patient characteristics and language processing task

Eventually, 30 healthy controls and 45 patients with schizophrenia (after exclusion of two due to excessive movement) participated in the study. A group comparison

showed no significant differences in age, education level, gender or handedness (see Table 1). Most patients had a diagnosis of schizophrenia paranoid type (N = 32), and a few patients had another diagnosis according to the interview: schizophrenia disorganized type (N = 1), schizophrenia undifferentiated type (N = 4) psychotic disorder NOS (N = 4), and some missing diagnosis (N = 4). Possibly, the correct diagnosis was not given by the algorithm of the SCAN sometimes, because essential data were missing. The average duration of illness was 119 months, but was variable (*SD* = 134, *min* = 1, *max* = 480 months). The patients reported to use the following medication; antipsychotics: aripiprazole (9×), chlorprotixene (1×), clozapine (15×), haloperidol (4×), olanzapine (9×), paliperidone (1×), penfluridole (1×), perphenazine (1×), pimozide (1×),

pipamperone (1×), quetiapine (7×), risperidone (10×), sulpiride (1×), and zuclopentixole (2×); antidepressants: amytriptyline (1×), bupropione (1×), citalopram (3×), clomipramine (1×), fluoxetine (2×), fluvoxamine (1×), mirtazapine (1×), paroxetine (2×), nortriptylin (1×), trazodone (1×), and venlafaxine (2×); benzodiazepines: diazepam (3×), flurazepam (1×), lorazepam (3×), oxazepam (7×), temazepam (5×); other: atenolol (1×), biperiden (6×), carbamazepine (1×), lithiumcarbonate (6×), pantaprazol (2×), promethazine (1×), and valproic acid (1×).

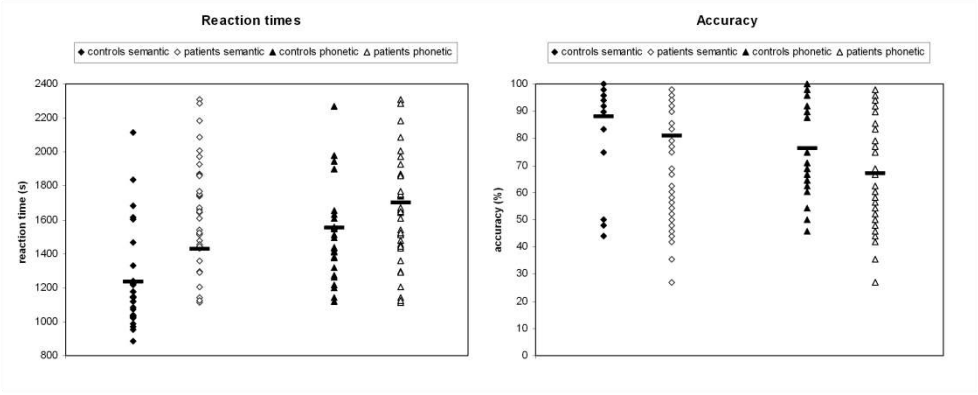

Figure 4 Reaction times (left graph) and performance (right graph) on the valence evaluation task, for both the semantic and phonetic condition; Patients have longer reaction times and a lower accuracy compared to healthy controls

Performance on the valence evaluation task is shown in Figure 4. Reaction time in the semantic condition was significantly longer for patients (*U* = 307.5, *z* =

−2.55, p = 0.011), and showed a trend for the phonetic condition (U = 353.0, z = −1.93, p = 0.054). Moreover, patients performed slightly worse on the phonetic condition (U = 347.5, z = −2.01, p = 0.045), and in the semantic condition tended to show a lower agreement with the valence ratings of a separate control sample (U = 361.5, z = −1.82, p = 0.069). There was no difference however, in valence rating as expressed by the percentage positively rated (50.2% for controls and 50.1% for patients). Thus, patients rated different words as positive compared to controls.

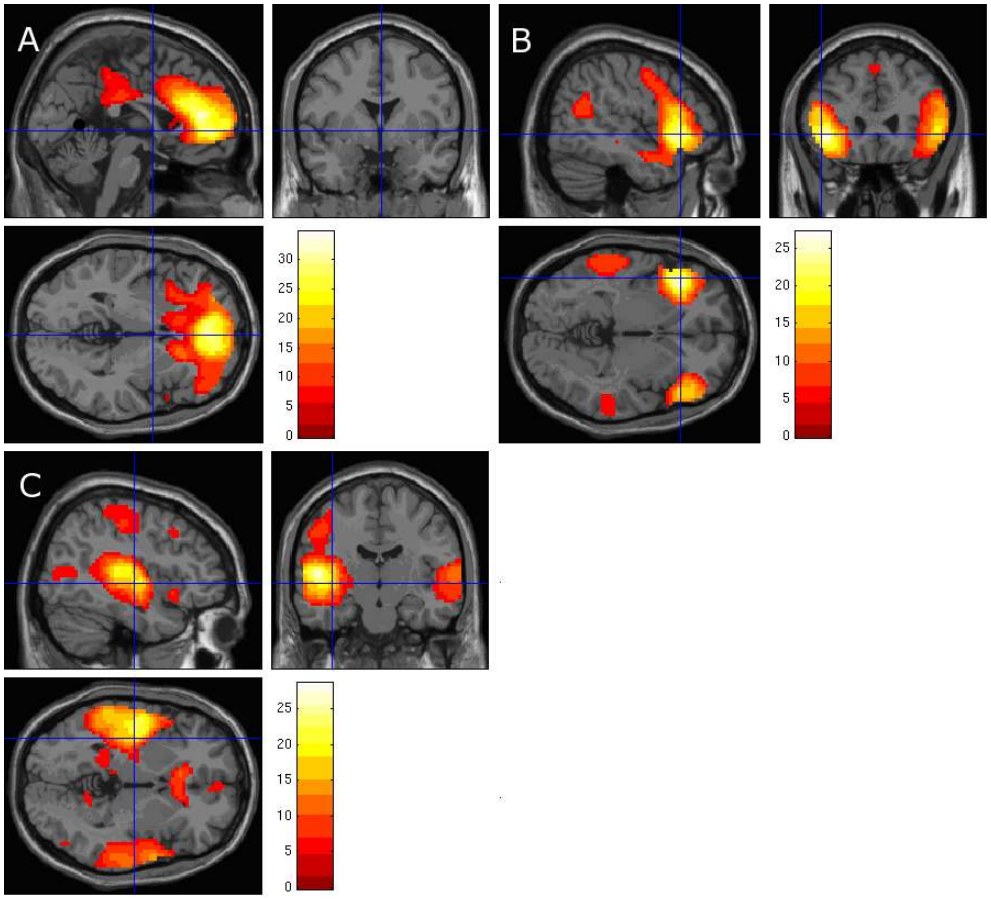

Figure 5 The brain networks found with ICA: A) anterior cingulate network with some posterior cingulate, inferior parietal lobule and prefrontal cortex; B) language component with mainly Broca's area and its homologue, and also Wernicke's area and its homologue; C) auditory network with superior temporal gyrus and lingual gyrus, anterior cingulate, and medial frontal cortex

Table 3 Brain areas encompassed by the language areas identified by ICA (FWE, $p < 0.05$, $k > 50$)

Network	Cluster size	Peak T	x,y,z (mm)	Area
ACC network	6436	34.64	-6 42 15	anterior cingulate gyrus
	346	9.27	0 -27 30	cingulate gyrus
	67	7.11	54 -42 54	inferior parietal lobule
STG network	3170	28.48	-51 -18 6	superior temporal gyrus
	1045	13.52	60 -24 6	superior temporal gyrus
	220	10.78	-9 24 0	anterior cingulate gyrus
	191	8.17	12 -54 -9	lingual gyrus
	72	7.57	3 51 -6	medial frontal gyrus
Broca's network	2135	27.18	-45 24 -6	inferior frontal gyrus (Broca's area)
	1131	18.71	48 27 0	inferior frontal gyrus (Broca's homologue)
	372	10.42	-6 57 27	posterior STG (Wernicke's area)
	51	6.3	63 -36 0	posterior STG (Wernicke's homologue)

ICA network results

Estimation of the number of independent components yielded a mean of 30 components. ICASSO showed good stability of the components with an inter-cluster similarity of > 0.8 and no crosstalk with other components. After running the ICA, three different components of interest were identified (Allen et al. 2008; Hoffman and McGlashan 1998), namely: an auditory component that mainly included STG (46% overlap with STG mask), the attention network with mainly ACC (36% overlap with ACC mask), and a language network with mainly Broca's area and also Wernicke's. This network showed overlap with both masks for Broca's area (20% overlap with the BA 44/45 mask and 57% overlap with the IFG mask). There was no substantial overlap with the masks for Wernicke. We will

refer to these networks as STG network, Broca's network, and ACC network respectively. Information regarding peak voxels can be found in Table 3.

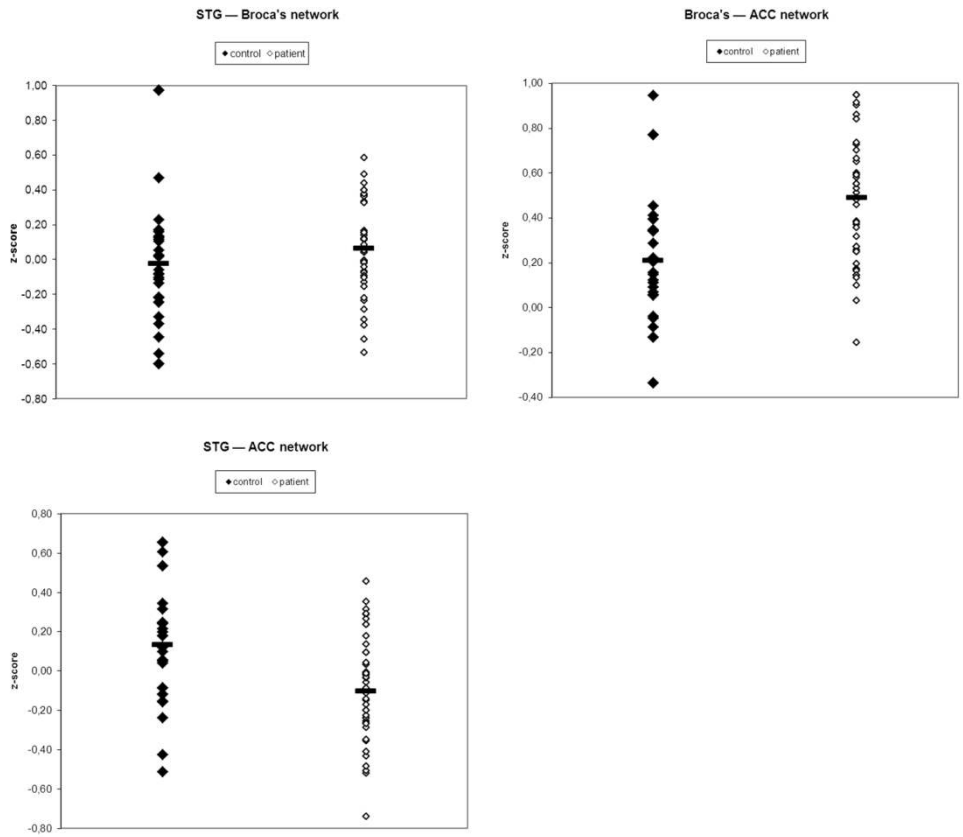

Figure 6 Graph showing the average z-scores for all connections for the different subject groups; There was a significant difference in average Z-scores of the STG - Broca's network connection and the Broca's - ACC network connection

A stringent threshold of FWE, $p < 0.05$, $k > 50$ was applied because of the robust nature of the component maps. The language network contained Broca's area, and to a lesser degree Broca's right-sided homologue as well as Wernicke's area and its right homologue. The auditory component was constituted of the bilateral STG, encompassing the primary and secondary auditory cortex, and additionally the lingual gyrus, anterior cingulate, and medial frontal gyrus. The ACC component contained additionally some cingulate cortex, and inferior parietal lobule. Interestingly, the components also weakly contained some brain

areas encompassed by another component, e.g. ACC in the language network, which may indicate a weak coherence between those networks. Visual inspection of time courses and power spectra showed no deviating pattern in one of the components. Most of the fluctuations were present in the 0.01–0.2 Hz frequency range consistent with default mode network fluctuations. Spatial maps of the components are presented in Figure 5.

Mann Whitney U tests comparing patients and controls revealed significant differences in the Z-scores associated with the connection between ACC and Broca's networks ($M_{controls}$ = 0.21, *SD* = 0.30, $M_{patients}$ = 0.49, *SD* = 0.32, *p* = 0.0005), which were higher in patients, and the Z-scores associated with the connection between STG and Broca's networks ($M_{controls}$ = 0.52, *SD* = 0.25, $M_{patients}$ = 0.37, *SD* = 0.26, *p* = 0.024), which were lower in patients (see Figure 6). There was no significant correlation between Z-scores and symptom severity as measured by PANSS items.

Discussion

In this study, we tested the hypothesis of reduced connectivity between the auditory and language networks in patients with schizophrenia. The ICA yielded three components of interest related to language processing, namely the auditory cortex (STG network), fronto-temporal language regions (Broca's network), and the attention network (ACC network). Decreased connectivity was observed in patients between the auditory and language networks. However, patients showed increased connectivity between the attention and language network compared to controls. Figure 7 depicts the observed connections in a model. Contrary to our expectations, we observed no relationship with severity of auditory hallucinations.

As expected, decreased connectivity between the language areas (primarily language production areas in the IFG, i.e. Broca and its homologue) and the auditory areas (mainly STG) was observed in patients with schizophrenia. This is in correspondence with the concept of reduced fronto-temporal connectivity (Frith et al. 2009; Hubl et al. 2004; Kubicki et al. 2002; Shergill et al. 2002; Vercammen et al. 2010). A number of other functional MRI studies also found evidence of

reduced connectivity between these regions during different language processes, including talking, verbal learning, verbal fluency, and word detection, supporting our finding (Ford et al. 2010; Hashimoto et al. 2010; Jeong et al. 2009; Karlsgodt et al. 2008). Functional changes may also be linked to reduced anatomical connectivity, as revealed by DTI studies measuring white matter integrity (Hubl et al. 2004; Li et al. 2010; O`Daly et al. 2007).

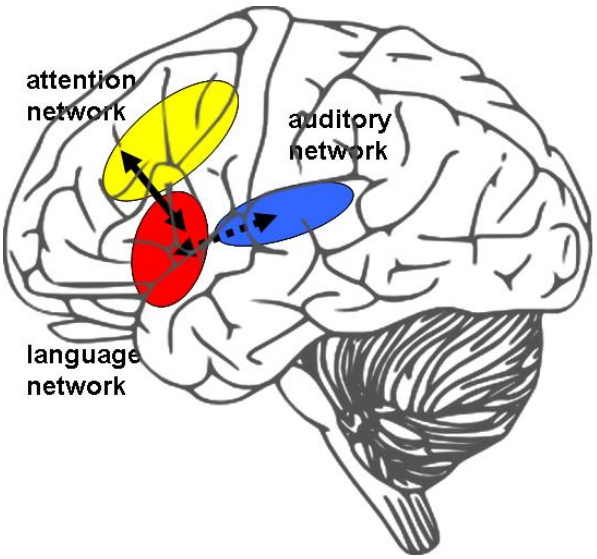

Figure 7 The connectivity model based on the ICA data; The bold arrow indicates increased connectivity for the schizophrenia patients compared to controls; The dashed arrow indicates decreased connectivity of patients compared to controls

As our results concern the resting state, this is a significant extension of previous findings. That is, it suggests disconnection of language related regions also during the default mode resting state. This finding may imply reduced control from the frontal language areas over the more receptive processing areas. Alternatively, as these regions are not exclusively involved in language processing, they may concern a broader domain of executive and auditory perception and memory functions (Li et al. 2002; Stirling et al. 2001).

More recent studies also focused on functional connectivity between brain networks in schizophrenia. Patients with schizophrenia showed a reduced global integration and functional organization of brain regions, specifically in for fronto-temporal areas (Van et al. 2010), or in relation to a verbal fluency task (Lynall et

al. 2010). These findings show some support for our hypothesis that decreased fronto-temporal connectivity may be associated with language processing difficulties. These functional abnormalities may originate from degeneration of long range white matter tracts, including the fronto-temporal connections (Lynall et al. 2010; Van et al. 2010). Eventually these effects may result in reduced global integration of information and disturbances in cognitive processes such as language.

Contrary to our hypothesis of overall reduced connectivity in schizophrenia, we observed increased functional connectivity between the attention and language network in patients compared to controls. Although schizophrenia has been conceptualized as a dysconnectivity disorder, other studies have also shown increased connectivity in patients with schizophrenia (Hoffman et al. 2011; Van et al. 2010). In our case, increased connectivity between speech production and attention areas may be related to exaggerated attention to self-generated (inner) speech (Vercammen and Aleman 2008), which may be related to hallucinatory predisposition often observed in schizophrenia (Evans et al. 2000). Other studies suggest that the ACC is involved in suppression of unintended (inner) speech (Price 2010). This process may be more habitually invoked by patients with schizophrenia, as the content of their inner speech is more frequently experienced as non-desired, leading to stronger connectivity.

We did observe a difference in performance on a language task. Patients showed a lower performance on a phonetic task, and made different semantic judgments as compared to controls. This may imply that there is indeed a link between language impairments and altered resting state connectivity, though caution is needed as larger groups would be necessary to directly compute associations between differences in connectivity and language performance, and more comprehensive testing would be in place. On the other hand, resting state fluctuations have been shown to predict individual's task performance or behavior (Fox and Raichle 2007). Future studies could use multiple tasks measuring several language domains separately to be able to make more specific inferences.

We observed no relationships between connectivity measures and current symptom severity. Consistent with prevalence figures (Nayani and David 1996),

most of the participants in the current study in fact had a lifetime history of hallucinations, and thus regardless of their current symptoms, may have had a general disposition toward hallucinations. As previously noted, the endogenous oscillations of brain networks measured with ICA may be more indicative of stable trait characteristics, rather than state dependent phenomena (Meyer-Lindenberg 2009). Therefore, the absence of a relationship with current symptom severity may be due to the fact that our measurement lacked sensitivity for the more fleeting state characteristics of hallucinations. Other studies also failed to find differences between patients with and without AVH, e.g. in terms of collary discharge (Ford and Mathalon 2005), language imagery (Simons et al. 2010), and verbal fluency (Diederen et al. 2010). Ideally, future studies would compare those without a history of hallucinations to those with a history and those with active hallucinations, in order to establish the relationships between changes in neural connectivity and symptom presence.

This is the first study that investigated regions relevant for language processing in schizophrenia using ICA in the resting state. Some previous studies have used correlation analysis (e.g. Vercammen et al. 2010). The data-driven nature of ICA has some advantages over ROI analysis, as identified brain networks may have higher biological validity than artificially defined ROI's (Van de Ven et al. 2004). Furthermore, ICA tends to separate signal of no interest (Cordes et al. 2000) into separate components (Fox and Raichle 2007), and the signal to noise ratio of ICA time courses is probably higher than time courses of the raw BOLD signal.

Some limitations of our study should be mentioned. First of all, it is difficult to determine the correct number of components, and to prevent the splitting or merging of components (Fox and Raichle 2007; Smith et al. 2009). We tried to reduce this risk by estimating the optimal number of components (Li et al. 2006) and running the ICASSO toolbox (Himberg et al. 2004), which showed good stability. Moreover, we also ran ICA with more or less components (20, 25, 35 and 40), and this did not change our findings (data not shown), which is in agreement with Rosazza et al. (Rosazza et al. 2011).

It should also be noted that ICA is an exploratory analysis method, and selection of components during resting state is based on criteria determined by the researcher. In addition, altered resting state connectivity analysis gives no direct evidence for disturbances in certain functions such as language. However, close inspection of the components showed that “the language network” clearly encompassed areas located in regions corresponding to Broca's and Wernicke's area (IFG and temporo-parietal junction, strongest presence on the left side) and the “STG network” (two areas, that converge with the primary and secondary auditory cortex). It has been shown that resting state networks may indeed show partial correspondence to task-related networks (Smith et al. 2009). Also, the power spectra showed that the components time courses mostly contained low-frequencies, while signal of no interest (e.g. heart beat) also contains higher frequencies (Cordes et al. 2000). In conclusion, resting state analysis is a relevant addition method to study intrinsic connectivity of the brain besides task-induced connectivity, which may be more artificial (Van de Ven et al. 2004).

Finally, almost all subjects took antipsychotic medication. Although a recent review showed that the effect of antipsychotics on the BOLD signal is possibly limited (Röder et al. 2010), we cannot rule out that medication affected our study results.

In conclusion, patients with schizophrenia showed reduced connectivity between the auditory and language networks. Such reduced connectivity could contribute to impairments in language expression and comprehension. An abnormally increased connectivity between the attention and the language network could be related to habitual suppression of unintended speech, or to excessive attention to internally generated speech.

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3. Reduced information flow to Broca's area in schizophrenia patients with auditory hallucinations

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Abstract

Introduction: Auditory-verbal hallucinations (AVH) are frequently associated with activation of left superior temporal gyrus (including Wernicke's area), left inferior frontal gyrus (including Broca's area), and the right hemisphere homologues of both areas. It has been hypothesized that disconnectivity of frontal and temporal areas on the one hand, and of interhemispheric transfer on the other, may underlie hallucinations in schizophrenia. We investigated reduced information flow in this circuit for the first time using dynamic causal modeling, which allows for directional inference. **Methods:** A group of healthy subjects and two groups of schizophrenia patients - with and without AVH - performed a task requiring inner speech processing during functional brain scanning. We employed dynamic causal modeling to create connectivity models between left hemispheric speech processing areas and their right hemispheric homologues. Bayesian model

averaging was used to estimate the connectivity strengths and evaluate group differences. **Results:** Patients with AVH showed significantly reduced connectivity from Wernicke's to Broca's area (97% certainty) and a trend toward a reduction in connectivity from homologues of Broca's and Wernicke's areas to Broca's area (93% and 94% certainty). The connectivity magnitude in patients without hallucinations was found to be intermediate. **Discussion:** Our results point towards a reduced input from temporal to frontal language areas in schizophrenia patients with AVH, suggesting that Broca's activity may be less constrained by perceptual information received from the temporal cortex. In addition, a lack of synchronization between Broca and its homologue may lead to the erroneous interpretation of emotional speech activity from the right hemisphere as coming from an external source.

Introduction

Disturbing auditory-verbal hallucinations (AVH`s) or "hearing voices" are a characteristic symptom of schizophrenia. Hallucinations have been defined as perceptual experiences in the absence of corresponding external stimuli (David 2004b). AVH are the most prevalent type of hallucinations in schizophrenia (Aleman and Larøi 2008), ranging from hearing spoken words and sentences to having full conversations between multiple voices, and experiencing command hallucinations. AVH frequently interfere with everyday functioning and reduce the quality of life (Gaite et al. 2002). Research into brain anatomy and function related to AVH`s has been accumulating in recent years. Although some key brain regions have been identified, the specific underlying dysfunctions within these regions or abnormalities of interaction between these regions remain to be elucidated (Allen et al. 2008).

Neuroimaging studies of auditory-verbal hallucinations have consistently revealed activation of the left superior temporal gyrus (STG; including the temporoparietal junction (TPJ), or Wernicke's area) during hallucinations (Allen et al. 2008). Numerous studies have also demonstrated activation of the left inferior frontal gyrus (IFG; including Broca's area) (Jardri et al. 2011; Kuhn and Gallinat 2010) and its homologue, as well as the right temporal cortex (including

Wernicke's homologue) (Sommer et al. 2008). Broca's region, situated in the IFG and Brodmann areas 44/45, is involved in explicit speech production (Dronkers et al. 2007) and has also been shown to be activated during speech imagery, or covert speech production (Aleman et al. 2005). Wernicke's area, which is situated in the posterior section of the STG at the junction with the occipital and parietal lobes, including the posterior part of Brodmann area 22 and parts of Brodmann areas 39/40, is involved in the comprehension of language (Damasio 1992). The right hemisphere homologues of Wernicke's and Broca's areas are involved in the emotional context of speech (Heilman et al. 1975; Wildgruber et al. 2006) and are strongly connected with their left counterparts (Karbe et al. 1998).

Rather than dysfunction in a singular brain region, aberrant connectivity within this fronto-temporal bihemispheric network may underlie AVH in schizophrenia (Brown and Thompson 2010; Lawrie et al. 2002; Ribolsi et al. 2009). However, the few studies that have so far investigated connectivity between the two areas in relation to auditory verbal hallucinations were limited by small sample sizes (Lawrie et al. 2002), lack of a non-hallucinating comparison group (Vercammen et al. 2010), or lack of a task targeting language processing (Hoffman et al. 2011; Vercammen et al. 2010), and merely investigated correlations rather than effective connectivity.

It has been hypothesized that a disconnection of the frontal and temporal areas may underlie hallucinations in schizophrenia (Lawrie et al. 2002). Here, we test this hypothesis for the first time using dynamic causal modeling (DCM), which allows for a comparison between groups of the strengths of intrinsic connectivity between neuronal populations, by incorporating the effects of measured hemodynamic responses. Because DCM incorporates hemodynamic responses for each region and each subject separately, the regional hemodynamic variations do not prevent the estimation of neuronal coupling parameters (Friston 2011), which could inhibit the causality inferences (Schippers et al. 2011; Smith et al. 2012). DCM is a specialized method for testing a specific hypothesis (Stephan et al. 2010), thus it is a convenient technique to validate the hypothesis of disrupted connections between Broca's area and Wernicke's area. Of specific interest is also the role of the right IFG (Broca's homologue), which was shown to be overactive

in the largest functional Magnetic Resonance Imaging (fMRI) study of hallucinations to date (Sommer et al. 2008). A lack of synchronization between both areas may lead to the erroneous interpretation of emotional speech activity from the right hemisphere as coming from an external source.

Methods

Subjects

Data from 47 schizophrenia patients and 31 healthy subjects were included, who participated in one of 2 studies at our Neuroimaging Center over the past 5 years, in which the metrical stress evaluation task was used (Vercammen et al. 2010). The diagnosis of schizophrenia was confirmed by the Schedules for Clinical Assessment in Neuropsychiatry (SCAN 2.1) interview (Giel and Nienhuis 1996). The severity of the symptoms was determined by the Positive and Negative Syndrome Scale (PANSS) interview (Kay et al. 1987). The patients were divided into 2 groups according to the hallucination item (P3) of the PANSS, the first consisting of those with AVH (AVH group, N = 30) – scoring above 3 (a score corresponding to “mild” psychopathology) (Kay et al. 1987), and the second comprised of those without AVH (NoAVH group, N = 17) – scoring up to 2. These patients were hallucination free for at least 6 months prior to inclusion in the study. After a complete description of the study had been given to the subjects, written informed consent was obtained.

Stimuli

During an fMRI scan, the patients performed a metrical stress evaluation task as described previously (Aleman et al. 2005). The experiment also included another condition, involving semantic (emotion) decision making and a baseline condition (fixation cross). Two-syllable Dutch words appeared on a screen for 2 seconds, followed by the fixation cross for 3 seconds. The stimuli were presented in blocks consisting of 12 word-fixation-cross combinations. There were 4 alternating blocks of each condition lasting for 60 seconds each interspersed with a resting period of 30 seconds. In the first condition, ‘inner speech’, which initiates phonological processing of imagined speech (Aleman et al. 2005), the subjects had to indicate

whether the metrical stress was located on the first or second syllable by pressing the appropriate response button. For half of the stimuli metrical stress fell on the first syllable and for the other half on the second syllable. The second condition involved making a semantic judgment, i.e., whether the word presented was positive or negative. Since here we were interested in "inner speech" and not in emotional processing, our analysis was restricted to this condition, compared to the baseline.

Functional magnetic resonance imaging data acquisition

The images were acquired using a 3T Philips Intera MRI scanner (Philips, Best, The Netherlands). The standard 8-channel SENSE head coil was used to acquire whole brain echo-planar functional images (EPIs). Thirty-nine axial slices were acquired with the following parameters: TR 2500 ms; TE 30 ms; flip angle 80°; SENSE factor 2; field of view 224 mm; matrix 64x64; slice thickness 3.5 mm with no slice gap, yielding voxels of 3.5x3.5x3.5 mm in size. In addition, T1-weighted anatomical images were acquired: 3D/FFE/CLEAR to co-register and normalize functional data (TR = 25 ms, TE = 4.6 ms, flip angle = 30°, FOV = 256 mm, matrix 256x256 mm, slice thickness 1.0 mm).

Preprocessing

The collected magnetic resonance data in the form of 4-dimensional (4-D) volumes were first converted to ANALYZE format using the MRIcro software, then processed using the statistical parametric mapping program SPM8 (www.fil.ion.ucl.ac.uk/spm). The interleaved EPI images were first corrected for slice timing acquisition as part of the pre-processing procedure and then realigned to the first functional image. The T1-weighted images were used as the template to co-register the mean EPI image. The co-registered data were subsequently normalized onto the MNI template and the resulting normalization parameters were applied to all the EPI images. The functional data were spatially smoothed using an 8 mm isotropic Gaussian Kernel before the statistical analysis. As a final step, motion correction was applied to remove the effect of spin history effects due to motion (Friston et al. 1996).

First-level data analysis

Statistical analysis at the first level was performed using a general linear model (GLM), and a random effects analysis was conducted on the group level. The regressors for the experimental conditions were convolved by a canonical hemodynamic response function in order to estimate, voxel by voxel, the parameters denoting the unique (linear) contribution of each condition to the measured BOLD signal in each subject. Low-frequency signal drift was corrected for by applying a high-pass temporal filter with a cut-off of 250 s.

In order to identify those areas involved in speech processing during the task, a contrast per subject was created of the 'inner speech' condition vs. fixation cross, which yielded reliable activation in the speech area. The contrast of the phonological vs. semantic condition did not show such activation and was therefore not considered suitable for the purpose of our analysis (i.e. to investigate the language network using dynamic causal modeling). The resulting beta-weighted images were used as input in the random effects analysis (RFX) for group inferences. The RFX maxima from the contrast served as the basis for time-course extraction for the DCM analysis (so called guiding coordinates). Because language processing is lateralized for right-handed people, but not consistently for left-handed people (Knecht et al. 2000), only right-handed subjects were considered for DCM analysis.

VOI Extraction

The time courses were extracted for each subject in the proximity of the guiding coordinates (within a radius of < 16mm) and belonging to a given region of interest. In details, the brain activation above a certain threshold (set by $p < 0.05$) of each subject were overlaid with a priori created anatomical masks, using wfu_pickatlas (Maldjian et al. 2003), covering Broca, Wernicke and their homologues. The highest activated voxel within 16 mm of the guiding coordinate and within that overlapping anatomical mask was chosen as the center for a sphere with radius = 5 mm. Then, the time courses from voxels within this sphere were extracted. Subsequently, the first eigenvariate of all the extracted time courses was calculated. In this way the representative time courses for Broca's

and Wernicke's areas and their homologues were extracted for each subject that had sufficient activation in all 4 regions and used further in the DCM analysis.

Effective connectivity

Our aim was to test the hypothesis that disconnections between the frontal and temporal areas, and between the left and right hemispheric counterparts of these areas underlie the occurrence of hallucinations, as well as aiming to probe the strength of inter-hemispheric influence. Therefore, we investigated the effective connectivity strengths between 4 regions of interest: the Broca's (B) region, the Wernicke's (W) region, and their homologues in the right hemisphere (BH and WH). Our study was performed using three groups of participants: a control group, a NoAVH group (schizophrenia patients without AVH), and an AVH group (schizophrenia patients with AVH). The effective connectivity was investigated using the DCM technique introduced by Friston (Friston et al. 2003). Briefly, in DCM an initial model is created describing 1) the relation between the BOLD response and the 4 regions of interest (ROI), 2) the connectivity between these regions, and 3) the modulation of this connectivity induced by the task. In DCM a predicted BOLD response is created for each ROI using the balloon model (Buxton et al. 1998; Stephan et al. 2007), which forms a link between the neuronal state and the predicted BOLD signal. This predicted response is compared to the measured BOLD response, and the parameters of the DCM and balloon models are then adjusted iteratively using Bayesian estimation to obtain the best fit. This results in a set of estimated parameters that describe the connectivity strengths between the relevant brain regions, the modulatory influence of the inputs, the strengths of the inputs, and the hemodynamic coefficients per region, together with the free energy for the model. For our analysis it is important to mention that the outcomes are not single parameters but a normal distribution of these parameters consisting usually of 10000 samples. In most cases in the literature the mean values calculated from these distributions are used.

We created 64 models for each subject involving the 4 abovementioned regions of interest: B, W, BH and WH. We assumed bilateral intra-hemispherical connections in all the models because these connections are usually very strong, and we varied all the inter-hemispherical connections. Four representative

models are depicted in Figure 8, illustrating the variation between homologue connectivities. For the parallel connections (those between homologues), we assumed that there is always a connection from left to right and studied the feedback from right to left (Figure 8; 4 different possibilities). Furthermore, we explored all possible diagonal connections (between B and WH or between W and BH, thus 16 possibilities). These combinations resulted in a total of 4×16 = 64 models.

The DCMs were then compared using Bayesian model selection (BMS) (Penny et al. 2004) for each group of subjects separately. As a result of BMS an exceedance probability is calculated for each model in a set of models. The exceedance probability is the probability of one model being more likely than any other model in the set (Penny et al. 2004; Stephan et al. 2009b). If the exceedance probability is distributed differently within the model set for different groups of subjects, this serves as an indication of distinctive functioning of brain networks between groups.

To make inferences on connectivity parameters such as the connectivity strength between 2 brain regions, an average model can be computed by means of Bayesian model averaging (BMA). BMA computes averaged parameters within a chosen family of models and as such, summarizes group-specific coupling parameters (Penny et al. 2010). BMA was used to calculate the posterior distributions of the connectivity parameters (consisting of 10000 samples), which were then used to obtain the posterior means and exceedance probabilities (that the parameter is larger than zero).

We also investigated whether the connectivity strengths between the brain regions differed, using a previously described method (Curcic-Blake et al. 2012) that combines BMA and a bootstrapping method. In short, the average model was calculated for each group of participants using BMA. The difference between groups was evaluated by comparing the connectivity strengths between brain regions. This comparison was performed by a bootstrapping procedure (10000 random sample differences) between each pair of the posterior distributions of connectivity parameters from each group. Here we randomly chose a sample (out of 10000) from group 1 and a sample from group 2, then calculated the

difference, a procedure that was repeated 10000 times to obtain the distribution of differences. The percentage of sample pairs with a difference larger than zero was examined. A positive difference in connectivity in more than 95% of the pairs of samples was considered statistically significant.

Table 4 Demographic data of subjects; The left column lists the demographic variables, the second to fourth columns from left show average values of the variables across the group and the standard deviation within brackets; Education level was rated according to a six point scale defined by Verhage (1984), which ranges from primary school (1) to university level (6); Non-parametric tests were used to test the group difference for PANSS (Mann-Whitney test), the reaction time and accuracy of the performance (Kruskal-Wallis test), and gender (Chi-square test)

	Mean (SD)			**Significance**	
	Healthy (N = 18)	**Schizophr. (no AVH) (N = 14)**	**Schizophr. (AVH) (N = 21)**	**3 groups**	**no AVH vs. AVH**
Age (years)	31 (10)	30 (5)	4 (13)	$F(2,44) = 0.51$ (0.45)	
Gender (# males)	11	13	11	$X^2(2,44) = 6.45$ (0.04)	
Education	4.4 (0.7)	3.7 (1.2)	4.1 (1.0)	$F(2,43) = 1.85$ (0.17)	
PANSS Pos.		12.5 (4.9)	15.6 (4.1)		$U = 73.5$ (0.08)
PANSS Neg.		13.4 (4.8)	14.7 (5.1)		$U = 95$ (0.39)
PANSS Gen.		25.3 (6.2)	28.0 (7.7)		$U = 95$ (0.39)
Reaction times (s)	1.6 (0.2)	1.6 (0.2)	1.6 (0.4)	$H(2) = 0.91$ (0.63)	
Accuracy	71.2 (16)	61.5 (12)	67.9 (25)	$H(2) = 2.01$ (0.37)	

As a final comparison, we created and averaged models for each subject individually using BMA. This step, in addition to the group-level BMA calculations described above, was aimed at investigating subject specificities in the language network. To further evaluate the effect of the hallucinations, we performed an ANOVA analysis of the connectivity strengths with respect to groups. This analysis

was repeated with respect to gender as a covariate to exclude the possible effect of gender.

Table 5 Results of conventional analysis, Random Effects (RFX), phonetic > fixation cross; The columns list (from left to right) the anatomical regions that belong to the cluster, the Brodmann area, the MNI coordinates of the highest activated voxel within the cluster, the Z-score at that point and the number of voxels within the cluster, $p < 0.001$, $k > 20$, $T > 3.2$

Control vs. Patient	**BA**	**x**	**y**	**z**	***Z***	***k***
Culmen 3 -46 -23 3.8 27		3	-46	-23	3.8	27
Patient vs. Control						
R Superior Frontal Gyrus/Medial Frontal Gyrus /Anterior Cingulate	10/32	15	44	-2	4.4	116
R Precentral Gyrus/Inferior Frontal Gyrus	44	54	2	13	3.5	21
L Middle Temporal gyrus	39	-45	-70	19	4.0	31
L Superior Temporal Gyrus/Inferior Parietal Lobule	40/42/13/2 2	-57	-34	22	3.8	28
Cingulate Gyrus/Precuneus/Paracentral Lobule	24	0	-1	40	4.4	56
Cingulate Gyrus	5/31/7	12	-25	37	3.6	77
Paracentral Lobule/Postcentral Gyrus	4/5	0	-43	64	3.7	24
Hallucinating vs. Non-hallucinating patients						
R Lingual Gyrus/Fusiform Gyrus/Cuneus	17/19/18	24	-64	-8	3.5	61
L Posterior Cingulate/ Lingual gyrus/Cuneus/Culmen	30/19	-18	-67	4	3.5	42
R Cuneus	18/19	6	-82	19	3.5	22

Results

Subjects

Among the initial number of subjects, 18 right-handed healthy subjects and 36 right-handed schizophrenia patients showed significant activation in all 4 brain regions of interest. In this group of patients, 22 had a score on a PANSS item P3 of more than 3 and were thus placed in the AVH group. The three groups did not differ in age $F(2,50) = 0.81$, $p = 0.45$ (Table 4). However, the groups differed in gender $\chi^2(2,50) = 6.43$, $p = 0.04$. Therefore, to exclude the possibility that gender differences produce a confounding effect, we performed the group DCM analysis on the full groups and we additionally controlled the results for the gender of the participants. The groups did not differ by performance, education level or PANSS symptom severity (Table 4).

Table 6 Results of conventional analysis – the choice of VOIs, Random Effects (RFX), phonetic > fixation cross ($p < 0.01$, FWE); The columns list the chosen centers of the VOI sphere close to the highest activated voxel within the region of interest, the Brodmann area, the MNI coordinates, and the Z-score at that point

	BA	x	y	z	*Z*	*k*
Wernicke's area	22/39/40	-45	-40	43	Inf	217
Broca's area	45/44	-54	11	22	7.2	71
Wernicke's homologue	44/45	57	14	10	6.2	50
Broca's homologue	22/39/40	39	-49	46	Inf	166

fMRI results and VOI guiding coordinates

The metrical stress task evoked brain activation in all the groups in Broca's and Wernicke's regions and their homologues, besides other brain areas such as the anterior cingulate gyrus (ACC) (FWE corrected, Figure 8). The random effects GLM for group comparison among healthy participants and the patient groups revealed

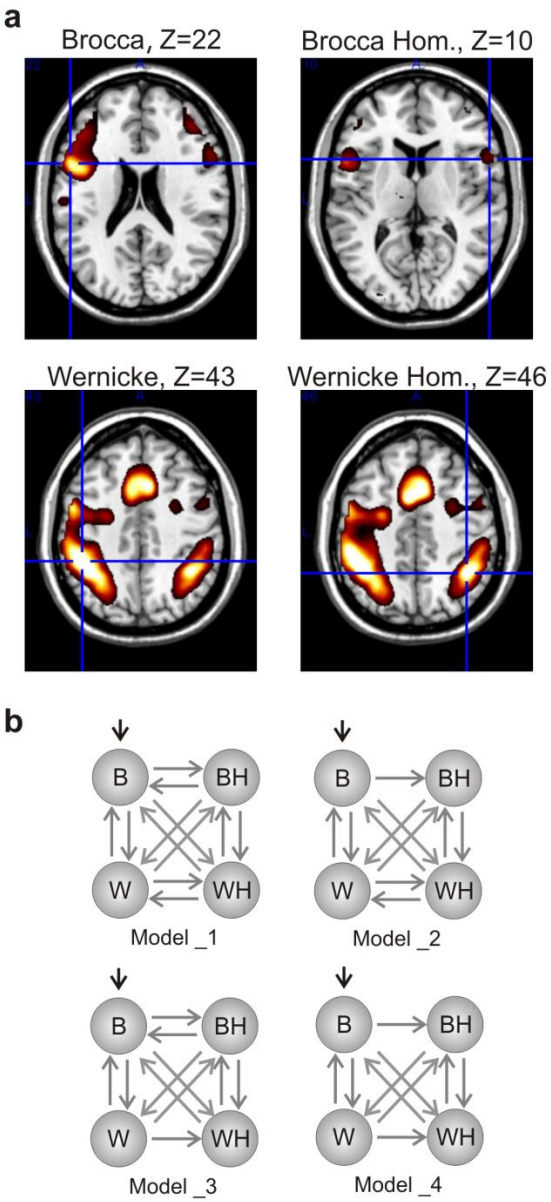

Figure 8 Results of conventional analysis; a) The contrast indicates phonological > fixation cross (random effects one-sample t-test) for all subjects, revealing activation of the bilateral IFG and STG ($p < 0.01$, FWE, $T > 3.1$) b) Illustrations of the four families of DCM that were created; Family_1 consisted of models having bidirectional connections between B and BH, and between W and WH, Family_2 had bidirectional connections between WH and W, and forward connections from B to BH but no feed-back from BH to B, Sixty-four DCM models were created by varying all the possible diagonal connections (e.g. from Wernicke's homologue to Broca)

a number of group differences (Table 5). However, these differences did not survive the correction for multiple comparisons. Guiding coordinates for subsequent VOI extraction were chosen from the group RFX GLM analysis of all participants for the phonological versus fixation cross contrasts (Table 6).

DCM BMS results

BMS clearly revealed that the best family was that with bilateral connections between regions on the left hemisphere and their corresponding homologues (Family_1; see Figure 8, Effective Connectivity subsection of Methods) for all 3 groups (Figure 9). The same result was obtained when the procedure was repeated only for male subjects. However, the BMS for all the models was not fully consistent in all the groups. The best model among all those tested for the healthy group was clearly the full model (belonging to Family_1 and having all the diagonal connections) with an exceedance probability of 96%. For the 2 patient groups the BMS was less clear. The full model had an exceedance probability of only 62% for the NoAVH group and 80% for the AVH group. This implies that the full model cannot be considered exclusive for the 2 patient groups, even though it is the most probable model among the set that was tested. We may conclude that there are some differences in the BMS between healthy controls and schizophrenia patients for the given set of models.

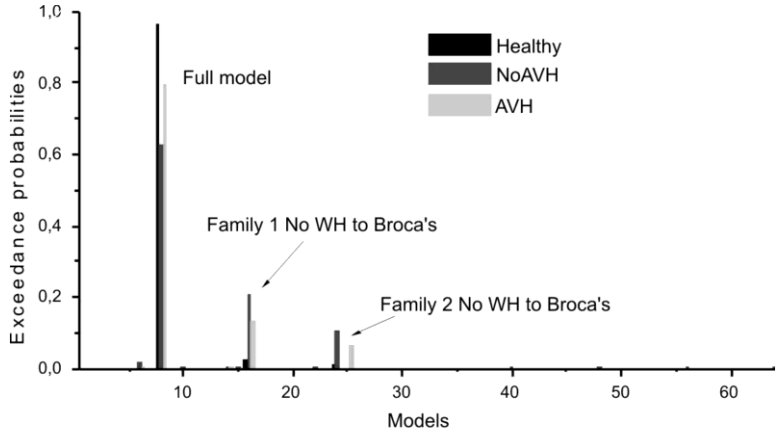

Figure 9 Results of BMS, showing the exceedance probabilities for healthy controls (black), schizophrenia patients with no auditory-verbal hallucinations (dark gray) and schizophrenia patients with auditory-verbal hallucinations (light gray)

Table 7 Differences between posterior parameters for the effective connectivity calculated by bootstrapping between the three groups of subjects; The upper columns show the percentage of sample differences for which one group had a higher connectivity than the other; A significant difference is considered to be above 95%; Differences with certainty from 90-95% are considered to have a trend toward significance; The middle columns show the difference of the means of the posterior parameters between groups; The lower columns show the mean posterior parameters for each group

	64 models	B to W	W to B	B to BH	BH to B	W to WH	WH to W	VH to WH	WH to BH	B to WH	W to BH	BH to W	WH to B
Prob. (%)	Healthy - AVH	57	97	36	93	58	55	70	72	67	67	66	94
	Healthy - NoAVH	25	82	47	75	61	63	56	57	74	55	58	79
	NoAVH - AVH	82	75	39	75	47	41	63	64	39	60	57	74
Diff. of mean (1/s)	Healthy - AVH	0.01	0.11	-0.02	0.09	0.01	0.01	0.03	0.03	0.02	0.02	0.02	0.09
	Healthy - NoAVH	-0.04	0.06	0.00	0.04	0.02	0.02	0.04	0.01	0.03	0.01	0.01	0.02
	NoAVH - AVH	0.05	0.05	-0.02	0.04	-0.01	-0.02	0.02	0.02	-0.01	0.02	0.01	0.04
Mean (1/s)	Healthy - AVH	0.44	0.08	0.28	0.07	0.21	0.21	0.17	0.17	0.33	0.18	0.18	0.07
	Healthy - NoAVH	0.47	0.01	0.03	0.03	0.20	0.18	0.17	0.18	0.30	0.17	0.17	0.02
	NoAVH - AVH	0.43	-0.03	0.30	-0.01	0.20	0.20	0.14	0.14	0.31	0.16	0.16	-0.02

For the comparison of parameters, the BMA connectivity strengths were randomly sampled from each group and then compared between groups. The distribution of parameter differences between the groups was calculated. A significant reduction (Table 7) in connectivity strengths was observed in the AVH patients (N = 22) compared to the healthy subjects (N = 18) for the connectivity from W to B (97% of differences were negative), from BH to B (93%), and from WH to B (94%), with reduced connectivity in the hallucinating patients. All the connectivity strengths in the healthy subjects were positive, whereas some of the connection strengths of the AVH group had negative mean values (such as from W to B; see Table 7). The connectivity strengths in the NoAVH patients (N = 14) for the same connections were intermediate compared to the other 2 groups, but were not significantly different (respective differences of 82%, 75%, and 79% from the healthy group and 75%, 75%, and 74% from the AVH group).

Table 8 Results of ANOVA analysis of group effect

	F	**Sig.**
W to B	3.3	0.045
BH to B	2.3	0.12
WH to B	2.9	0.067

Next, BMA was calculated for each subject separately, and these values were used for ANOVA analysis. We found an effect of the group on the average connectivities per subject for the connection strengths for W to B ($F(2,51) = 3.300$, $p = 0.045$) and a trend towards significance for the connection WH to B ($F(2,51) = 2.856$, $p = 0.067$). Post hoc Bonferroni tests revealed a difference between the connectivity strengths of healthy controls and the AVH group for the W to B connection ($p = 0.04$).

The results are summarized in Table 8. The same analysis was repeated including the gender of the participants as a covariate, yielding similar results (See Table 9).

Table 9 Results of the regression analysis with group and gender as independent variables and strength of connection as dependent variable

	Full model		Group		Gender	
	***F*(2,51)**	**Sig.**	***T***	**Sig.**	***T***	**Sig.**
W to B	3.4	0.04	2.5	0.015	-0.47	0.64
WH to B	3.1	0.056	2.3	0.023	-0.60	0.55
BH to B	2.4	0.10	2.1	0.042	-0.51	0.61

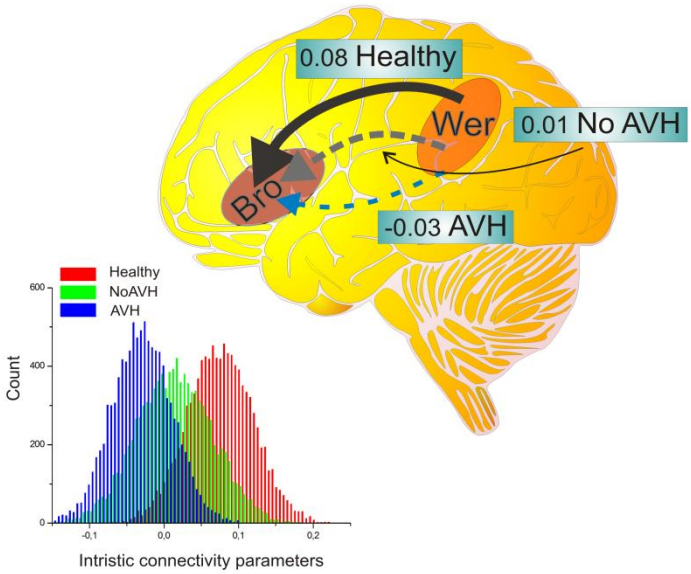

Figure 10 Upper panel: illustration of the main differences in language network for the three groups of subjects; The healthy controls have the strongest positive connectivity from Wernicke's area to Broca's area, the schizophrenia patients without hallucinations exhibit a weaker interaction, and this connection strength is negative or strongly diminished in schizophrenia patients with hallucinations, Negative connection strength suggests that activity in one region is proportional to the decrease of activity in another region; Lower panel: distributions of posterior probabilities for the connectivity parameters as calculated by BMA; It is evident that the distributions of connectivity strengths for healthy controls (red) and schizophrenia patients with hallucinations (blue) differ from Wernicke's area to Broca's area, The distribution of these parameters for non-hallucinating patients (green) is between that of healthy controls and AVH patients

Discussion

Our results point toward a reduced connectivity in the fronto-temporal language processing network in schizophrenia patients with auditory-verbal hallucinations. More specifically, during inner speech, Broca's area receives reduced input both from Wernicke 's area and from its contralateral homologue in patients with AVH. Our findings thus lend further support to the fronto-temporal dysconnectivity hypothesis of AVH, and go beyond that by suggesting directionality. The findings also show that the presence of AVH may be linked to an increased deficit that is present to a lesser degree in those with psychosis, but without current AVH. For an overview, see Figure 10 and Figure 11.

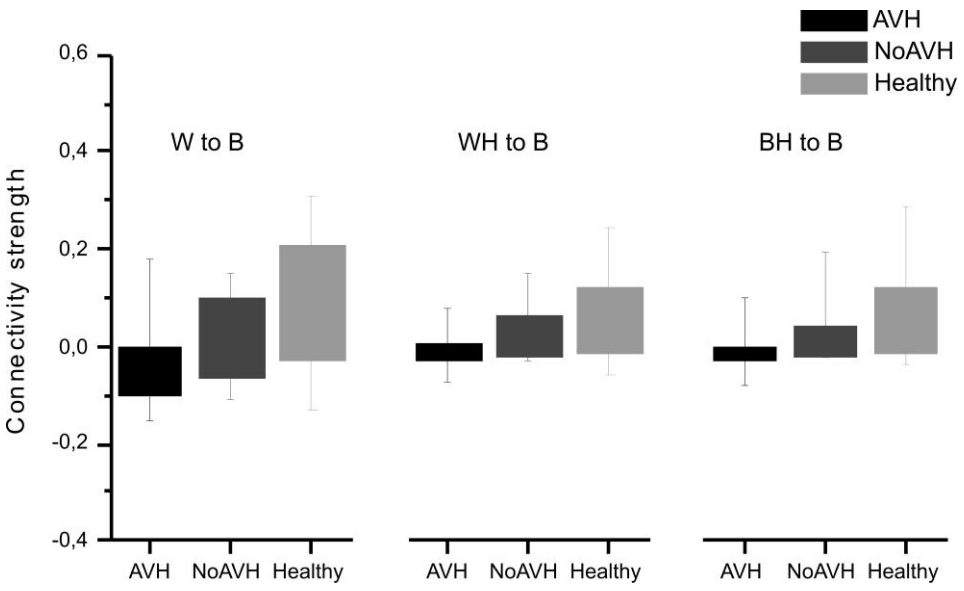

Figure 11 Results of BMA per subject; Each panel is a boxplot (25-75%) of connectivity strengths for particular connection (indicated on the panel); Maximal and minimal value are indicted by a stripe

Reduced information flow from other nodes in the speech processing network may, in everyday life, increase the spontaneous activity of Broca's area in attempts to "search for relevant information" or "fill in the information gaps" as it were. This may ultimately lead to overt action of Broca's and Wernicke's areas, which is consistent with the overactivation that has been observed in studies that measured changes in the BOLD signal during hallucinations (Jardri et al. 2011).

Thus, a lack of perceptual input may lead to increased top-down efforts from Broca's area (top = Broca's region – higher cognitive processes, down = sensory regions) that are less constrained by perceptual information, as has been hypothesized for hallucinations (Behrendt 1998; Grossberg 2000). According to these theories, top-down connections modulate or sensitize sensory regions through a balance between top-down excitation and inhibition, but they cannot activate the sensory regions under normal conditions. If these top-down signals become tonically hyperactive during a mental disorder, the top-down expectations can give rise to conscious experiences in the absence of bottom-up inputs. In our study of language processing we did not explicitly investigate 'state' characteristics of brain activity during hallucinations but instead invoked the language areas within a language network. It is possible that during the resting state, AVH patients have spontaneous fluctuations within the language network in association with AVH, which may be suppressed by controlled task-related activity during an experimental inner speech paradigm. Therefore, we did not expect overactivation of Broca's area in AVH patients during the task. This is in agreement with the results of a recent meta-analysis (Kuhn and Gallinat 2010) that compared the findings of so-called 'trait' studies, which investigate group differences, with studies investigating the brain activation of AVH patients in different 'states' (during the hallucination period vs. the non-hallucination period). Consistent overactivation of Broca's region was found during hallucinations, a feature that was not observed in 'trait' studies.

Furthermore, patients without hallucinations were in between patients with hallucinations, who had the lowest connectivity coefficients, and the healthy controls. It should be noted, however, that the "non-hallucinating" group contained people that did not have current hallucinations at the time of scanning, but who may have had AVH in the past. Therefore, it is a reasonable assumption that rather than representing dichotomous categories, our patient groups are actually on a continuum, where the AVH group may display a stronger or more acute deficit compared to the non-AVH group.

Our finding of impaired effective connectivity from Wernicke's region to Broca's region also yields information that may complement another hypothesis

that aims at explaining the occurrence of hallucinations in schizophrenia, namely the corollary discharge hypothesis. This hypothesis states that insufficient top-down feedback and control from higher cognitive areas (such as Broca's region) towards the primary and secondary auditory areas (such as Wernicke's region) in patients with hallucinations contributes to the improper source attribution of voices. Recent experimental studies point towards a delay in this feedback rather than to genuinely diminished connectivity (Hoffman et al. 2011; Whitford et al. 2011). The DCM method is based on the dynamics of the system and as such is not suitable to investigate delays in activation directly. However, our finding that a change in activation of Broca's region is less associated with the activation of Wernicke's region in patients with verbal hallucinations helps to explain the delay in corollary discharge found in patients with auditory hallucinations. Thus, besides a diminished connectivity from frontal to temporal areas, a putative underlying mechanism of reduced corollary discharge, our findings do suggest that a reduced reverse signal (from Wernicke's to Broca's area) may also play a role. A reduced information flow from the speech perception area in the left TPJ implies a loss of feed-back to Broca's area. It has been shown that reduced perceptual input triggers top-down influences in perception, i.e. active search for percepts guided by stored knowledge (Baskent 2012; Hannemann et al. 2007). With regard to speech processing, an fMRI study showed that only Broca's area (BA 44) activated to unintelligible speech presented at low signal-to-noise ratios, whereas an extended fronto-temporal network (including Broca's and Wernicke's areas) was active during intelligible speech at high signal-to-noise ratios (Hannemann et al. 2007). This supports an active role of Broca in trying to make sense of possible speech stimuli in the environment. Therefore, reduced information flow to Broca's are could prime increased top-down efforts from Broca's area that are less constrained by perceptual information, as has been hypothesized for hallucinations (Aleman and Larøi 2008; Behrendt 2003; Grossberg 2000). This hypothesis dovetails with the early suggestion of an overly "active listening attitude" in patients with AVH, when anticipating meaningful speech (Hoffman 2010). On the other hand, recent evidence from time-resolved sparse fMRI shows that the "top-down" influences of prior knowledge and semantic expectations in

speech processing is not necessary from frontal areas to temporal areas but can also be based on feed-forward processing in which results of lower-level perceptual processing are passed to inferior frontal regions. This would be consistent with the route observed in our study and needs further investigation.

A second finding of our study concerned the reduced connectivity between Broca's area and its homologue which should be interpreted with caution as it was only marginally significant. This may be associated with the emotional content of hallucinations, as the right IFG has been implied in emotional aspects of speech (Allen et al. 2008; Wildgruber et al. 2006). Indeed, our task employed words with emotional connotations. It has been suggested that a lack of synchronization between both areas may lead to the erroneous interpretation of emotional speech activity from the right hemisphere as coming from an external source (Jaynes 1979; Olin 1999). Interestingly, for both areas that show reduced information flow to the left IFG (left TPJ and right IFG), reduced gray matter volumes have been reported in relationship to hallucinations (Barta et al. 1990; Gaser et al. 2004). Allen et al. (2008; overview) suggested that Broca's homologue may show reduced connectivity with Broca's area, thereby hampering adequate speech monitoring (Allen et al. 2008).

We are aware of only 1 previous study that investigated effective connectivity in relationship to hallucinations in schizophrenia (Mechelli et al. 2007), using a verbal self-monitoring task involving distorted speech. The authors found reduced connectivity from the left STG to the anterior cingulate (an area consistently involved in self-monitoring). Although the task used was clearly different, using external speech, and engaged a different brain circuit, the results are consistent with our findings regarding a reduced information flow from posterior temporal to frontal regions in patients with hallucinations. Our study has the advantage that the subjects had to engage their own inner speech to perform the task, which may be a more appropriate proxy to the processes involved in AVH.

Other studies of functional connectivity and hallucinations have mainly focused on the resting state, and did not investigate directionality. Nevertheless, most findings implicate language-related areas. For example, Vercammen et al.

reported reduced connectivity of the left TPJ with the ACC and amygdala in association with AVH severity in schizophrenia using resting state fMRI (Vercammen et al. 2010). No patients without hallucinations were included. When patients were compared to healthy control subjects, reduced connectivity between the left TPJ and right IFG was observed, 2 nodes that were also implicated in our current analyses. Another recent study (Hoffman et al. 2011) of functional connectivity in the resting state reported elevated connectivity between Wernicke's region, its homologue, and the left IFG in schizophrenia patients with hallucinations as compared to patients without hallucinations, but not in comparison to healthy control subjects. These variable results may be explained by the absence of a specific task, where it remains unclear which cognitive processes are reflected in the interaction between language network nodes. Furthermore, these studies did not clarify whether the connectivity changes reflected "down-stream" effects from Broca or "up-stream" effects from Wernicke to Broca. A clear advantage of the current study is the task-based theoretical framework of a priori regions and directional influences in addition to taking into account the nature of the hemodynamic response, which might account for different findings.

Our results are consistent with anatomical connectivity studies investigating both the inter-hemispheric pathways between language areas (Hubl et al. 2004; Mulert et al. 2012) involving the anterior corpus callosum, and the pathways connecting the frontal areas and the superior temporal areas such as the arcuate fasciculus (Hubl et al. 2004), which is part of the superior longitudinal fasciculus (Shergill et al. 2007). These studies found an association of auditory hallucinations with abnormalities in fractional anisotropy in these pathways.

Our findings also point towards more generalized changes in language circuitry, i.e. differences that may be attributable to schizophrenia rather than the presence and/or severity of hallucinations. That is, the full model had much lower exceedance probability in both groups of schizophrenia patients as compared to controls. As we mentioned earlier, this is indicative of differences between the healthy controls and schizophrenia patients in the brain network that was tested. This leads us to suggest that there are differences in the language processing

pathways of healthy controls and schizophrenia patients. In particular, the model with the next best fit lacked a connection from Wernicke's homologue to Broca's area, indicating that the connection from Wernicke's homologue to Broca's area might be diminished in both groups of schizophrenia patients.

Some limitations of our study should be noted. We used DCM, which is a modeling technique based on a preexisting hypothesis. The main limitation of this technique is that the number of regions has to be predefined by the hypothesis, thus it is not used to explore all possible nodes of the putative network. Furthermore, the causality in a modeling technique such as DCM has to be understood in terms of the model used. In our particular case of bilinear interaction, activation in one brain area is thought to cause a change in activation in another brain area. This is one plausible biological model, and represents a first step in disentangling the complicated brain functioning. Because it is applied equally in all three groups, the model provides a suitable framework to make comparisons between groups. Furthermore, the application of DCM is favorable for so called fMRI "sub-sampling" (involving a slow sampling rate, such as TR of 2.5 s, and slow hemodynamic response to a neuronal activation, which fMRI measures) because it incorporates an explicit forward model of neuronal hidden states (neuronal dynamics) and is not confounded by sub-sampling or low-pass filtering of the hemodynamics (Valdes-Sosa et al. 2011). As we mentioned in the introduction, DCM incorporates hemodynamic responses for each region and each subject separately, such that regional hemodynamic variations do not prevent the estimation of neuronal coupling parameters (Friston 2011). This is especially useful when comparing different groups, as in our study, where some subjects can display a different hemodynamic response due to factors such as medication intake. Another limitation is that our conclusions are limited to processing differences associated with having recently experienced hallucinations (in the week prior to scanning). Patients in the non-hallucinating group did not experience hallucinations in the six months prior to scanning. However, they may have experienced hallucinations earlier in their illness, and thus may still have trait characteristics associated with hallucinations. Future research should further

disentangle state and trait characteristics by including patients who have never experienced hallucinations, even though such patients may be difficult to find.

In summary, our results point towards a reduced connectivity between frontal and temporal language areas in schizophrenia patients with auditory-verbal hallucinations. A reduced information flow from the speech perception area in the left TPJ may lead to a loss of feed-back and increased top-down efforts that are less constrained by perceptual information from Broca's area, as has been hypothesized for hallucinations. Finally, the reduced information flow from Broca's right hemispheric homologue, which engages during emotional and non-literal speech processing, may isolate emotional language activity in the right hemisphere. It may thus eventually acquire an "independent" nature, due to a failure of integration into normal language processing, reflecting the emotional non-self-content of hallucinations.

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4. Functional connectivity during associative emotional learning in patients with schizophrenia

In prep.

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Abstract

Background: Emotional deficits are one of the core features of schizophrenia. Problems in associative emotional learning and the related ability to verbalize emotions have both been implicated in schizophrenia. We investigated whether schizophrenia patients demonstrated impaired function of limbic and prefrontal areas during associative emotional learning. **Methods:** Eighteen schizophrenia patients and eighteen controls filled out an alexithymia questionnaire and performed an associative emotional learning task during fMRI scanning. Participants had to remember positive, negative, and neutral picture-word pairs and had to indicate whether they felt the pair was associated. We conducted standard GLM analysis and independent component analysis (ICA) on the fMRI-data. Both the GLM results and an identified task-related ICA component were compared between groups with a random effects analysis. **Results:** GLM analysis showed significant activation of visual areas, temporal areas,

amygdala/hippocampus, and prefrontal cortex (PFC) during associative emotional learning, but no difference in activation between schizophrenia patients and controls. ICA analysis identified a network of similar brain areas, with additionally the cingulate cortex (ACC), mainly responding to negative stimuli. Schizophrenia patients showed a trend for decreased connectivity of PFC and ACC regions to the rest of this network. Compared to controls, patients reported more difficulties in identifying, analyzing, and verbalizing their emotions, but equal levels of subjective emotional arousal. **Conclusions:** The trend for decreased ACC/PFC functional connectivity in patients might be associated with their reported cognitive-emotional processing difficulties. The absence of differences in areas related to emotional arousal (amygdala and hippocampus) might indicate intact subjective-emotional experience.

Introduction

Emotional deficits are one of the core features of schizophrenia (Bleuler 1911). Patients show abnormalities in emotion perception, emotion regulation, and emotion expression (Phillips et al. 2003b). However, the experience of emotions seems to be intact or even heightened (Kring and Neale 1996). These disturbances in emotion processing along with other social cognitive abilities affect functional outcomes such as independent living skills and social functioning (Pinkham et al. 2003). Structural and functional brain abnormalities have been demonstrated in areas related to these emotional processes in patients with schizophrenia (Phillips et al. 2003b). To increase our understanding about emotional disturbances in schizophrenia, it is critical to study their underlying neural mechanisms.

The formation of inappropriate associations is regarded to be a possible factor underlying certain symptoms of schizophrenia, specifically positive symptoms (Bleuler 1911). Associative emotional learning refers to creating a link between emotional stimuli and other stimuli, for instance, one's emotional state and a word to describe it. When someone in a later occasion gets in the same emotional state, the associated word will be recalled. Impairments in associative emotional learning might be associated with difficulties in describing one's feelings with words (emotional verbalizing) (Aleman 2005). Individuals with

difficulties in emotional verbalizing may perform worse on emotional processing tasks (Lane et al. 1996) and use less healthy emotion regulation strategies (Swart et al. 2009) which might result in increased stress and a lower level of well-being. Deficits both in emotional verbalizing (Van 't Wout et al. 2007) and associative emotional learning (Exner et al. 2004) have been demonstrated in schizophrenia, though some studies showed normal associative leaning (Murray et al. 2010).

Activation of prefrontal cortex (PFC) and amygdala has been associated with learning of emotional stimuli (LaBar and Cabeza 2006). Furthermore, the formation and retrieval of associations between items may rely upon the prefrontal cortex (PFC) and medial temporal lobe (specifically the hippocampus) (Achim and Lepage 2005). During emotional processing, altered brain activation in hippocampus, amygdala, and PFC has been demonstrated in schizophrenia patients (Phillips et al. 2003b). Moreover, connections between amygdala and ACC may be impaired in these patients during fear processing, suggesting that these pathways may contribute to a schism between emotion and thought in schizophrenia (Das et al. 2007).

Abnormal functional integration of brain regions has been suggested to be an important pathophysiological mechanism of schizophrenia, also referred to as the dysconnection hypothesis (Stephan et al. 2009a). Most prominently, the prefrontal cortex has been implicated in dysconnectivity in schizophrenia (Friston 1998). Because associative emotional learning involves multiple underlying processes, recruitment of different task-specific brain regions is essential. We hypothesized that schizophrenia patients would demonstrate different activation and functional connectivity between aforementioned brain regions during associative emotional learning.

Differences in functional connectivity can be analyzed using independent component analysis (ICA) (Calhoun et al. 2004). This is a data-driven approach in which spatially independent networks (components) with similar time courses can be detected based on their shared temporal characteristics (Calhoun et al. 2001). Connectivity analysis with ICA may further the understanding of neural systems beyond the standard analysis on task-related brain activation (Fox and Raichle

2007; Van den Heuvel and Hulshoff Pol 2010), as complete brain networks can be studied with ICA (Van den Heuvel and Hulshoff Pol 2010). Previous studies using ICA have already demonstrated abnormal connectivity in schizophrenia patients (Calhoun et al. 2009).

The aim of this study was to investigate differences in activity and connectivity underlying associative emotional learning in schizophrenia patients compared to controls. We were specifically interested in the neural background of the encoding phase of associative emotional learning, as other studies focused on the retrieval phase (Murray et al. 2010). We expected to identify the amygdala, hippocampus, and PFC as task-involved brain areas. We hypothesized that both activity and connectivity would be decreased in patients with schizophrenia (Fakra et al. 2008; Phillips et al. 2003b).

Methods

Participants

All participants were native Dutch speakers. Exclusion criteria included substance abuse within the past three months, neurologic history or contraindications to MR. All participants provided written informed consent. The study was approved by the medical ethical committee of the University Medical Center Groningen.

Twenty patients (four females) meeting DSM-IV criteria (American Psychiatric Association 2000) for schizophrenia were recruited from the University Center for Psychiatry at the University Medical Center Groningen. Both inpatients and outpatients were included. Diagnosis was confirmed by a trained rater, using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN-2.1) - (Giel and Nienhuis 1996). In the week prior to the fMRI experiment clinical symptoms were assessed with the Dutch version of the Positive and Negative Syndrome Scale (PANSS) - (Kay et al. 1987). Eighteen patients used antipsychotic medication and two patients were unmedicated. All patients were clinically stable at the time of assessment.

Table 10 Demographical, questionnaire and behavioral data for controls and patients; Mean scores (M), standard deviations (SD) and p-values are presented

	Controls (N = 18)		**Patients (N = 18)**		
	M	***SD***	***M***	***SD***	***p***
Gender (male/female)	12/6		15/3		0.25
age	28.4	8.1	29.4	5.8	0.67
Education (low/middle/high)	6/4/8		7/3/8		0.90
BVAQ subscales					
BVAQ cognitive component	52.9	14.3	66.1	15.2	.011
BVAQ emotional component	45.8	7.9	42.5	8.7	0.24
Verbalizing	20.7	7.3	25.0	5.3	
Analyzing	16.5	4.7	20.0	6.0	
Identifying	15.8	5.0	21.1	7.1	
Fantasizing	24.9	8.6	21.5	6.3	
Emotionalizing	20.9	5.9	21.0	4.2	
PANSS					
PANSS Positive	n/a		13.0	5.0	n/a
PANSS Negative	n/a		13.7	4.6	n/a
PANSS General	n/a		25.6	5.3	n/a
PANAS					
PANAS Positive	33.4	4.6	27.2	6.8	0.003
PANAS Negative	13.2	2.3	18.6	6.6	0.003
Picture-word pairs recognition task % correct					
Overall	81		68		0.003
Negative pairs	81	10	69	16	
Positive pairs	82	11	67	13	
Neutral pairs	80	13	68	14	

Twenty controls (six females), matched for age, education level, handedness and gender, participated in this study. Additionally, controls were excluded if they had any history of psychiatric disorders or a first-degree family member with a psychotic disorder. Data from two patients (one male, one female)

and two controls (two males) were excluded due to inhomogeneity of the fMRI-data or technical problems with data acquisition. Detailed demographical and clinical data are presented in Table 10. De patients used the following antipsychotics (N): aripiprazole (3), clozapine (2), olanzapine (2), paliperidone (1), penfluridole (1), perphenazine (1), quetiapine (1), quetiapine & haloperidol (1), risperidone (3), and zyclopentixol (1).

Bermond-Vorst Alexithymia Questionnaire (BVAQ)

The BVAQ (Vorst and Bermond 2001) is a 40-item self-report scale, which is subdivided into five subscales (eight items per scale), comprising the alexithymia features as defined by Nemiah and Sifneos (Nemiah and Sifneos 1970), namely Verbalizing, Analyzing, Identifying, Emotionalizing and Fantasizing. Previous studies have repeatedly shown that the BVAQ has good psychometric characteristics and the five factor structure is supported by factor analyses (Vorst and Bermond 2001). Bermond and colleagues have made a second order distinction in which they group the Identifying, Verbalizing, and Analyzing scales into a Cognitive component and the Emotionalizing and Fantasizing scales into an Emotional component (Bermond et al. 2007). Higher scores on these subscales indicate more pronounced alexithymic characteristics. The items in the Cognitive component of the BVAQ are highly correlated (r = 0.80) with the Toronto Alexithymia Scale (Vorst and Bermond 2001; Zech et al. 1999). Answers are rated on a 5-point scale (1=certainly does not apply to me, up to 5= certainly applies to me). Examples of questions in the BVAQ are: 1) “When I am upset, I know whether I am scared, sad or angry” (Identifying); 2) “I hardly reflect on my emotions” (Analyzing); 3) “I find it difficult to verbally express my feelings” Verbalizing); 4) “I hardly daydream or fantasize” (Fantasizing); 5) “When something completely unexpected occurs, I remain calm and unmoved: (Emotionalizing).

Positive Affect and Negative Affect Schedule (PANAS)

Positive and negative affect were measured with the Positive and Negative Affect Schedule (PANAS) - (Watson et al. 1988) in Dutch. The PANAS measures the current affective state. Positive affect reflects the extent to which a person feels

enthusiastic, active, and alert (examples: “interested” and “excited”). Negative affect is a general dimension of distress (examples: “nervous” and “upset”). This scale consists of ten Positive affect items and ten Negative affect items (Watson et al. 1988). Answers are scored on a 5-point scale (1=certainly does not apply to me, up to 5= certainly applies to me). Higher scores indicate stronger affect (either positive or negative). The PANAS has been shown to be a reliable and valid measure of positive and negative affect. It has Cronbach’s alpha coefficients for Positive affect = 0.89 and Negative affect = 0.85 (Watson et al. 1988).

Associative Emotional Learning Task

This task concerned associative learning of pictures and words during fMRI using an event-related design. Negative, positive, and neutral pictures from the International Affective Picture System (IAPS) were presented together with words (Hermans and De Houwer 1994). In each trial a picture and a word were presented on a screen. The valence of the word and picture was congruent. An example would be a picture of a car crash and the Dutch word for ‘worries’.

The subjects were instructed to judge whether they felt that the picture and word were associated and to remember the combination. The goal of this instruction was to assure that participants were attending both the picture and the word as well as their relationship. No directions were given on how to associate the picture and the word. In this way we aimed to stimulate the subjects to engage cognitive-emotional processing while learning new material. Participants indicated whether the picture-word pair was associated by pressing a button on a response box during stimulus presentation or during the following fixation cross.

The task comprised 180 picture-word pairs (60 for each category). Each pair was displayed for 3 s, followed by fixation cross with a jittered duration (pseudorandomly selected between 2 and 20 seconds from: $f(x) = 18\,exp(-x) + 2$, where $x = [0, 18]$). The total duration of the fixation periods was identical to the total duration of the stimuli (540 s) to ensure a proper implicit baseline. The duration of the task was about 20 minutes.

Immediately after scanning, participants performed a recognition test. The same pictures as displayed in the scanner were presented randomly, but below the picture, three words were given (in random order): (1) the word that was paired with the picture (the correct answer); (2) a word semantically related to the paired word in the scanner; (3) an unrelated word. The subject had to choose the correct answer by pressing 1, 2 or 3 (on a keyboard).

Image acquisition

Scanning was performed using a 3 T Intera Philips scanner equipped with a SENSE head coil, Best, the Netherlands. For functional magnetic imaging of the Associative Emotional Learning Task, an EPI sequence with the following parameters was used: 39 slices, repetition time (TR) = 2000 ms; echo time (TE) = 28 ms; flip angle (α) = 70^{o}, in-plane resolution = 64x64 pixels, field of view (FOV) = 224 mm, isotropic voxels of 3.5 mm, 560 functional volumes in total.

For anatomical reference, a T1-weighted image (160 slices; isotropic voxels of 1 mm; TR 25 = ms; TE 4.6 ms; α = 30^{o}; FOV = 256 mm) covering the whole brain was acquired.

Data analysis of questionnaires

For the BVAQ, we calculated the score on the Cognitive component (sum of the Verbalizing, Identifying, and Analyzing subscales) and the Emotional component (sum of the Emotionalizing and Fantasizing subscales). To compare patients and controls on the BVAQ, the two components were entered as dependent variables and Group as independent variable into two analyses of variance (ANOVA). For the PANAS, the Positive and Negative components were entered as dependent variables and Group as independent variable into two ANOVAs.

Data analysis of behavioral data

Performance on the recognition task was compared between groups with a GLM repeated measures analysis with Valence (negative, positive, and neutral) as within-subject variable and Group as between-subject factor.

Data analysis of fMRI data

Data were analyzed with Statistical Parametric Mapping (SPM8; FIL Wellcome Department of Imaging Neuroscience, London, UK). Images were first slice-time corrected. After realignment, the functional images were coregistered to the T1-weighted image. This image was normalized to the standard T1-MNI (Montreal Neurological Image) brain (voxelsize 3x3x3 mm) and the same transformation was applied to the functional images. The latter were then smoothed with a Gaussian kernel of 10 mm FWHM.

We performed a standard GLM analysis. At a first level, three regressors were modeled for negative, positive, and neutral trials with a boxcar function convolved with a hemodynamic response function. A trial was modeled for the duration of stimulus presentation (3 s). For each participant, two contrasts were defined: positive valence versus neutral valence and negative versus neutral. Group effects were tested in a random effects analysis with the factors Subject, Group and Valence. Task effects and main effects of Group and Valence were determined in an analysis modeling the interaction between Group and Valence. The interaction between Valence and Group was tested in a model including the main effect of Subject and interaction between Group and Valence, but only contrasting the Group by Valence interaction. All test were performed at ($p < 0.001$, $k > 20$, *FWE* cluster correction at $p < 0.05$).

In the ICA, the functional data were decomposed into a set of independent components (neuronal networks and other signal sources) by the Group ICA FMRI Toolbox (GIFT) using the Infomax algorithm (http://icatb.sourceforge.net/gift/gift_startup.php) - (Calhoun et al. 2004; Calhoun et al. 2001). The mean number of independent components (IC`s) was estimated using Maximum Description Length (MDL) and Akaike's criteria (Li et al. 2006), to prevent splitting or merging of components (Smith et al. 2009). Images were intensity normalized before ICA estimation, which implied scaling the time courses to a mean of 100. The intensity normalized images were decomposed into a set of spatially independent components (for every subject) by the Infomax algorithm. A component consists of a time course showing the temporal

fluctuations of that component, and a spatial map that shows the contribution of every voxel to that component. Stability of the components, i.e. whether a component has the tendency to split or merge with another component, was validated by running the ICASSO toolbox implemented in GIFT using twenty iterations with both random iterations and bootstrapping (Himberg et al. 2004).

To select task-related component(s), the correlation of the time courses with all components and task regressors for positive, negative, and neutral stimuli was determined. The correlation between the task regressors and time courses was performed separately for the three valence conditions (positive, negative, neutral), because different brain networks (components) could be related to different valences. Components were selected if they had a moderate correlation (r ~ 0.3) with the task regressor and contained brain areas of interest (PFC, ACC, limbic regions).

GIFT separates the imaging data into components based on independence in space (Calhoun et al. 2004; Calhoun et al. 2001). Because this separation is executed on group level, subtle differences in ICA spatial maps of different individuals may disappear in group ICA, e.g. differences between patients and healthy controls (Calhoun et al. 2001). To partly overcome this effect, the time courses of all individual subjects were voxel-wise regressed against functional image time series of that subject. Maps with a beta-value indicating the fit of the time course with each voxel time series were compared between groups (p < 0.001, k > 20, FWE cluster correction of p < 0.05).

Results

Demographical data

Table 10 presents demographical data, questionnaire scores and task performance for patients and controls, and PANSS scores for patients. Patients and controls did not differ on level of education (χ^2 = 0.220, df = 1, p = 0 .90), age (F(1,34) = 0.18, p = 0 .67) or gender (χ^2 = 1.33, df = 1, p = 0.25).

BVAQ

Patients had a higher score on the Cognitive component (i.e. worse in verbalizing, identifying, and analyzing their feelings) than controls ($F(1,34) = 7.2$, $p = 0.01$) but groups did not differ on the Emotional component (i.e. same emotional arousal and degree of fantasizing) ($F(1,34) = 1.5$, $p = 0.24$; See Table 10).

PANAS

Patients had lower Positive affect scores ($F(1,34) = 10.39$, $p = 0.003$) and higher scores on Negative affect ($F(1,34) = 10.61$, $p = 0.003$) than controls.

Behavioral data

Patients recognized less picture-word pairs after scanning than controls ($F(1,32) = 10.0$, $p = 0.003$). There was no main effect of valence ($F(2,31) = 0.18$; $p = 0.84$) nor an interaction effect between valence and group ($F(2,31) = 1.0$; $p = 0.38$).

Table 11 Brain areas significantly activated in the associative emotional learning task in both groups during both positive and negative emotional stimuli versus neutral stimuli ($p < 0.001$, $k > 20$, FWE cluster corrected $p < 0.05$)

Cluster size	T	Z	x	y	z	Brain area
17931	14.07	Inf	52	-66	4	R middle temporal gyrus (BA 37)
1739	7.09	6.12	-10	56	34	L superior frontal gyrus
2097	6.68	5.84	-56	-2	-16	L middle temporal gyrus
309	5.92	5.30	54	-4	-18	R middle temporal gyrus
649	5.42	4.92	22	-4	-14	R parahippocampal gyrus/amygdala
357	5.28	4.82	44	16	24	R inferior frontal gyrus
165	4.99	4.59	54	30	12	R inferior frontal gyrus

Brain activation with GLM analysis

The task activated prefrontal and limbic areas across both groups: L & R middle temporal gyrus (MiTG), L superior frontal gyrus (SFG), R inferior frontal gyrus (IFG) and R amygdala/hippocampus. The left IFG, hippocampus, and amygdala were also active, but these clusters did not survive cluster-correction (Table 11 and Figure 12).

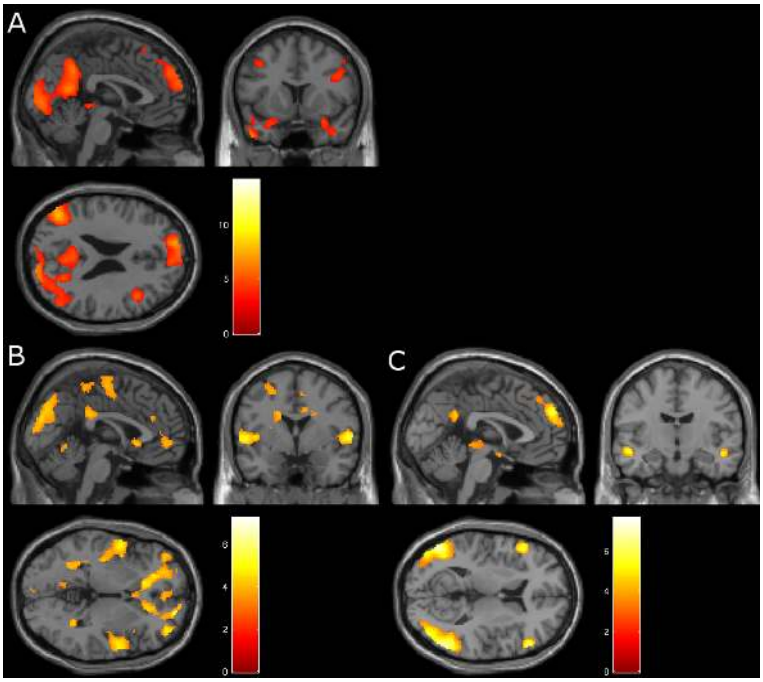

Figure 12 A) Main effect of the task for both groups and both valence conditions (positive & negative - neutral); B) Post-hoc test on valence for positive > negative; C) Post-hoc test on valence for negative > positive; All tests at $p < 0.001$, $k > 20$, cluster correction at $p < 0.05$

There was no main effect of group, i.e. the groups did not differ in brain activation in response to the task. There was a main effect of valence, but no interaction between valence and group. Post-hoc tests were used to investigate the effect of valence (pos > neg and neg > pos), see Table 12 and Figure 12. The positive emotional stimuli evoked more brain activation in L & R inferior parietal lobule (IPL), rostral cingulate gyrus, and R SFG. Negative stimuli resulted in more activation in the L & R MiTG, R IFG, and another, more extensive part of the R medial/superior PFC.

Connectivity with independent component analysis

The regressor for negative stimuli showed a correlation of $r = 0.30$ with a component containing the hypothesized emotional brain areas (ACC, PFC and limbic regions) amongst others ("negative emotion component"). The second component ($r = 0.23$) only contained visual areas. Both the positive and neutral task regressor showed the highest correlation with this same visual component (r

= 0.21 and *r* = 0.15 resp.). For these task regressors, the components with the second-highest correlation only contained other visual areas. For both the positive and neutral task regressor, the correlation with the time course of the "negative emotion component" was *r* < 0.1.

Table 12 Brain areas showing a stronger response to positive compared to negative stimuli and vice versa (*p* < 0.001, *k* > 20, FWE cluster corrected *p* < 0.05)

Cluster size	T	Z	x	y	z	Brain area
Positive > negative						
13645	7.25	6.22	52	-50	50	R inferior parietal lobule (BA 40)
3693	5.64	5.09	-32	-64	38	L inferior parietal lobule (BA 39)
408	4.69	4.35	8	-34	36	cingulate gyrus (BA 31)
254	4.63	4.30	28	18	56	R superior frontal gyrus
Negative > positive						
2813	7.64	6.47	54	-64	0	R middle temporal gyrus
2015	7.29	6.25	-50	-66	14	L middle temporal gyrus
1545	6.95	6.02	-52	-6	-14	L middle temporal gyrus (BA 20)
838	6.31	5.58	56	30	8	R inferior frontal gyrus
1163	6.22	5.51	6	54	30	R superior frontal gyrus (BA 9)
577	5.93	5.31	50	-8	-16	R middle temporal gyrus (BA 21)
2813	7.64	6.47	54	-64	0	R middle temporal gyrus

The "negative emotion component" was selected for further analysis. Its time course was voxel-wise regressed against the functional data of every subject. The maps with the resulting beta-weights were used in the random-effects analysis. The contrast of the main effect of the component contained occipital areas (BA 18), L & R MiTG, L & R IFG, thalamus, posterior cingulate cortex (PCC), precuneus, L & R amygdala, L & R hippocampus, and precentral and postcentral gyrus (See Table 13 and Figure 13; FWE, *p* < 0.05, *k* > 20; a more stringent threshold was used because of the high t-values in this contrast).

With regard to group differences, a two sample t-test comparing the negative emotion component between patients and controls demonstrated that patients showed lower connectivity in the ACC and medial frontal regions to other areas of the component (Table 14 and Figure 13), but these effects did not survive

cluster-correction. Patients did not show higher connectivity in regions of this component.

Table 13 Brain areas in the network identified after voxel-wise regression of the ICA time courses of every subject with their own functional image series (FWE, $p < 0.05$, $k > 20$)

Cluster size	T	Z	x	y	z	Brain area
12701	22.41	Inf	-36	-87	6	occipital areas (BA 18) R temporal pole/parahippocampal gyrus/amygdala R precentral (BA 6)/postcentral gyrus (BA 3) posterior cingulate/precuneus
113	8.78	6.30	-45	6	27	R inferior frontal gyrus
102	8.06	5.99	45	12	27	L inferior frontal gyrus
40	8.01	5.97	-3	-15	6	thalamus
87	7.93	5.93	-57	-3	18	L middle temporal gyrus
43	7.35	5.65	-42	-3	45	L precentral gyrus
68	7.35	5.65	-42	21	-27	L temporal pole/parahippocampal gyrus/amygdala
22	6.34	5.12	-42	-27	63	L postcentral gyrus (BA 3)

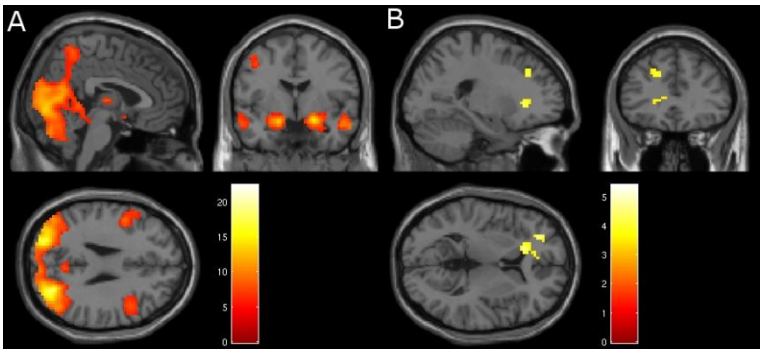

Figure 13 A) Voxels showing a significant contribution to the time course of the negative emotion component (FWE, $p < 0.05$); B) Brain areas showing lower connectivity in schizophrenia patients compared to healthy controls ($p < 0.001$, $k > 20$, uncorrected)

Table 14 Clusters that showed decreased connectivity in schizophrenia patients compared to healthy controls ($p < 0.001$, $k > 20$, uncorrected)

Cluster size	T	Z	x	y	z	Brain area
50	5.40	4.56	-15	27	3	L anterior cingulate cortex
24	4.66	4.07	-30	42	6	L middle frontal gyrus
27	4.19	3.73	12	18	51	R medial frontal gyrus
20	4.06	3.64	-21	30	36	L medial frontal gyrus

Discussion

The aim of this study was to investigate differences in activation and connectivity underlying associative emotional learning in schizophrenia patients compared to healthy comparison subjects. Patients with schizophrenia showed a trend for less connectivity of medial prefrontal areas to other brain regions within a network involved in negative emotional processing. Moreover, altered connectivity in the amygdala, and hippocampus was not observed. GLM did not yield any group differences. After scanning, patients remembered less words, but there was no effect of valence on the remembered words. Patients showed higher levels of alexithymia on the cognitive-emotional level, but not on the subjective-emotional level.

The absence of an effect of valence on the amount of remembered words may be partly caused by the low task difficulty. We aimed to have reasonable performance for all subjects, including relatively ill patients. The consequence may be that the task was to easy to detect behavioral changes on the level of emotion processing and significant changes in brain function in patients with schizophrenia. Future studies could use more challenging tasks to investigate the encoding stage of associative emotional learning.

GLM analysis showed activation in brain areas that have been related to associative and/or emotional learning (amygdala, hippocampus, IFG, and MeTG) (Murty et al. 2010). In addition, other activated areas in response to the task have been associated with emotional experience (MPFC), and autobiographical memory (PCC and precuneus) (Van der Meer et al. 2010).

In contrast to our hypothesis, patients and healthy controls did not differ in brain activation during the associative emotional learning task. Because the brain may not respond in a linear way to the task, task-related effects might not be captured by GLM analysis. Moreover, separate brain regions may respond normal to a task in patients, but there may be aberrant cooperation between different brain areas (Das et al. 2007; Friston 1998; Stephan et al. 2009a). Therefore, also an analysis sensitive for differences in network connectivity was executed, as discussed later in this section.

With regard to valence, the evaluation of positive compared to negative stimuli activated different brain regions in our study. In line with our findings, a previous study (Berthoz et al. 2002) has shown increased rostral medial prefrontal activation in response to positive stimuli and decreased dorsal ACC activation by negative stimuli in persons with impaired emotional processing (alexithymia) (Lane et al. 1996; Swart et al. 2009). Moreover, healthy controls have shown different patterns of prefrontal brain activation in response to negative stimuli during emotion inhibition (Vercammen et al. 2012) or affective processing (Diwadkar et al. 2012), while persons with schizophrenia or at risk for the disorder did not show these effects. We showed similar distinct effects of positive versus negative valence on brain activation, but failed to show altered activation in schizophrenia patients.

The ICA analysis identified a network of brain areas that responded specifically to the negative emotional stimuli of the task. We termed this component the negative emotion component. The component consisted of the same areas that were detected with the GLM analysis, and additionally contained ACC. Inspecting the task activation, it appeared that negative stimuli activated the task related areas more strongly, while positive stimuli showed a more widespread, but less intense activation of brain areas. Consistent with our results, other studies also reported the strongest modulating effects of negative stimuli on brain function (Diwadkar et al. 2012). Negative stimuli might provoke stronger coherent brain activation across a network that may be detected with ICA, while positive and neutral stimuli result in weaker, less coherent responses (not resulting in a specific brain network).

Schizophrenia patients demonstrated a trend for lower connectivity of prefrontal and cingulate areas to other areas within the negative emotion component compared to controls. Though not significant, we consider the results still worth of reporting, as they agree with our hypothesis and earlier findings (Anticevic et al. 2011; Das et al. 2007; Phillips et al. 2003b). Decreased connectivity of prefrontal regions has also been observed in schizophrenia patients during letter encoding (Meda et al. 2009) and in the default mode network (Camchong et al. 2011). Impaired connectivity of these areas within the emotional network could be related to the difficulties that patients had with recognition of the associations (Achim and Lepage 2005), although we showed no effect of valence on the remembered words as was hypothesized. Moreover, the ACC has shown altered activation during emotion processing in alexithymia (Berthoz et al. 2002; Lane et al. 1998). As patients reported more difficulties in cognitive-emotion processing (BVAQ) and a more negative affect state (PANAS), this might be related to the observed trend for reduced connectivity.

Schizophrenia patients showed no differences in activity and connectivity of hippocampus and amygdala, while fMRI studies on emotion processing in schizophrenia often show abnormalities in these limbic areas (Gur et al. 2007), though others failed to do so (Dowd and Barch 2010). Concerning connectivity, patients have shown higher connectivity in amygdala and parahippocampal gyrus during listening to emotional words (Escarti et al. 2010). The inconsistent findings may be due to differences in task requirements and in clinical presentation of patients (Aleman and Kahn 2005; Fahim et al. 2005). Intact amygdala activation has been observed in patients during an emotionally loaded working memory task (Anticevic et al. 2011; Becerril and Barch 2011) and during viewing of emotional pictures (Dowd and Barch 2010), but not in patients with severe anhedonia. As our patient group had no high levels of flat affect or anhedonia and showed similar self-reported emotional arousal as healthy controls, amygdalar and hippocampal function might be intact in our sample (Phillips et al. 2003a; Van der Meer et al. 2009).

A limitation of this study was that patients were taking antipsychotic medication, which may interact with brain activation and task performance. However, a review of Röder et al. (Röder et al. 2010) showed that the effects of antipsychotics on the BOLD response may be limited. Furthermore, there was no effect of valence on remembered words or an interaction with group, while there was effect of valence on brain function, which complicates interpretation of the results. Future studies should probably increase task difficulty and use neuroimaging both during the encoding and retrieval phase of learned associations.

Taken together, the trend for decreased ACC/PFC functional connectivity in patients might be associated cognitive-emotional processing difficulties or affect state. The absence of differences in areas related to emotional arousal (amygdala and hippocampus) might indicate intact subjective-emotional experience.

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5. Reduced connectivity in the self-processing network of schizophrenia patients with poor insight

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Abstract

Introduction: Lack of insight (unawareness of illness) is a common and clinically relevant feature of schizophrenia. Reduced levels of self-referential processing have been proposed as a mechanism underlying poor insight. The default mode network (DMN) has been implicated as a key node in the circuit for self-referential processing. We hypothesized that during resting state the DMN network would show decreased connectivity in schizophrenia patients with poor insight compared to patients with good insight. **Methods:** Patients with schizophrenia were recruited from mental health care centers in the north of the Netherlands and categorized in groups having good insight (N = 25) or poor insight (N = 19). All subjects underwent a resting state fMRI scan. A healthy control group (N = 30) was used as a reference. Functional connectivity of the anterior and posterior part of the DMN, identified using Independent Component Analysis, was compared between groups. **Results:** Patients with poor insight showed lower connectivity of

the ACC within the anterior DMN component and precuneus within the posterior DMN component compared to patients with good insight. Connectivity between the anterior and posterior part of the DMN was lower in patients than controls, and qualitatively different between the good and poor insight patient groups. **Discussion:** As predicted, subjects with poor insight in psychosis showed decreased connectivity in DMN regions implicated in self-referential processing, although this concerned only part of the network. This finding is compatible with theories implying a role of reduced self-referential processing as a mechanism contributing to poor insight.

Introduction

Patients with schizophrenia often have difficulties with social and emotional cognitive processing (Atkinson and Robinson 1961; Pinkham et al. 2008), including self-reflective processes (Amador and David 2004). Such impairments may have important consequences for successful functioning in a social community (Pinkham et al. 2003; Pinkham et al. 2008). Self-referential processing deficits, which may already be present before the onset of the disorder, have been proposed to underlie these social and emotional deficits as well as first rank schizophrenic symptoms (e.g. Frith 1995; Frith and Corcoran 1996; Nelson et al. 2009; Parnas and Handest 2003; Raballo et al. 2011; Sass and Parnas 2003). Such self-related processing deficits may include the formation and maintenance of an accurate representation of one's traits, abilities and attitudes, or self-reflection (Northoff et al. 2006; Van der Meer et al. 2010). This self-reflective processing is essential in the evaluation of one's personal behavior as well as in interpersonal communication (Atkinson and Robinson 1961). More specifically, it has been proposed that self-reflective processing may underlie poor illness insight in patients with schizophrenia (Flashman and Roth 2004; Lysaker et al. 2005; Van der Meer et al. 2010).

Impaired insight has been considered to be a core feature of schizophrenia (David 2004a). Poor insight in schizophrenia has been associated with poorer global functioning (Dickerson et al. 1997; Pyne et al. 2001; Stefanopoulou et al. 2009), greater severity of psychopathology (Mintz et al. 2003), increased relapses

and hospitalizations, poorer long term prognosis (Schwartz 1998) and reduced treatment compliance (Kemp and David 1996; Yen et al. 2005). Interestingly, lack of insight in schizophrenia appears to be self-specific, as most patients recognize symptoms in other patients, but fail to do so in themselves (Ries et al. 2007; Startup 1997). This implies that lack of insight may be caused by disturbed abilities of self-referential processing (Van der Meer et al. 2010). Thus, studying the neural link between insight and self-referential processing may reveal important clues with regard to the underlying deficit in patients lacking insight. If patients with schizophrenia have attenuated capacities to reflect on their situation and on other self-relevant information, this could be a barrier for obtaining insight that one suffers from a severe psychiatric disorder.

In terms of brain regions that underlie self-referential processing, research points towards a set of medial brain areas comprising the posterior cingulate cortex (PCC), anterior cingulate cortex (ACC), and the dorsomedial and ventromedial prefrontal cortex (d & vMPFC) (Johnson et al. 2002; Kelley et al. 2002), together referred to as the cortical midline structures (CMS) (Northoff and Bermpohl 2004; Northoff et al. 2006; Van der Meer et al. 2010). In patients with traumatic brain injury in the CMS (Schmitz et al. 2006), patients with mild cognitive impairment (Ries et al. 2007) and schizophrenia patients (Brüne et al. 2008; Carter et al. 2001; Cooke et al. 2008; Holt et al. 2011), an association between impaired insight and decreased activation of medial frontal and other CMS regions has been demonstrated.

The CMS show a large overlap with the so-called default mode network (DMN). This is a network of brain areas that are active during rest (Buckner et al. 2008; Raichle et al. 2001) and involved in processing related to the self (Gusnard and Raichle 2001; Raichle et al. 2001). The brain areas in the network show synchronized slow fluctuations (< 0.1 Hz) in the BOLD signal (Beckmann et al. 2005; Raichle and Gusnard 2005). Areas in this network include the ventral and dorsal medial prefrontal cortex (vMPFC and dMPFC), anterior cingulate (ACC), the posterior cingulate (PCC)/retrosplenial cortex (RspC) and adjacent precuneus, inferior parietal lobule (IPL), medial temporal cortex (MTG), and hippocampal

formation (Buckner et al. 2008; Raichle and Gusnard 2005). The default mode network appears to encompass subnetworks with distinct functions (Buckner et al. 2008), consisting of an anterior part) ACC/MPFC), a posterior (PCC, precuneus and IPL), and possibly a ventral part with temporal ventral prefrontal regions (Buckner et al. 2008; Northoff et al. 2006). Studies in schizophrenia patients have found disturbances in DMN structures, with mainly lower medial PFC compared to healthy controls (Bassett et al. 2008; Cole et al. 2011; Liu et al. 2008; Zhang et al. 2011), but also altered connectivity within posterior DMN areas, disturbed prefrontal-parietal communication (Holt et al. 2011; Jang et al. 2011; Lui et al. 2010; Lynall et al. 2010; Mannell et al. 2010; Skudlarski et al. 2010; Wolf et al. 2011; Woodward et al. 2011; Zhang et al. 2011), or reduced connectivity between other DMN regions (Jang et al. 2011; Lui et al. 2010; Lynall et al. 2010; Mannell et al. 2010; Ongur et al. 2010; Rotarska-Jagiela et al. 2010; Woodward et al. 2011). Of note, some studies showed increased frontal connectivity (Salomon et al. 2011; Salvador et al. 2010; Shen et al. 2010).

Structural MRI studies have related poor insight in schizophrenia patients to decreased volume of prefrontal and other DMN regions (Parellada et al. 2011; Shad et al. 2004), which may be related to poor self-monitoring (Cooke et al. 2008; Morgan et al. 2010; Orfei et al. 2012; Shad et al. 2006). Patients or people at risk for psychosis indeed show altered brain activation during self-reflection and theory of mind (Brüne et al. 2008; Carter et al. 2001; Holt et al. 2011; Modinos et al. 2011). Moreover, review studies have shown that schizophrenia patients have a decreased prefrontal and posterior DMN activation in resting state studies (Hill et al. 2004; Kuhn and Gallinat 2011). Finally, decreased white matter integrity between DMN areas was also related to poor insight (Antonius et al. 2011). No studies have as yet investigated resting state connectivity in relationship to poor insight in psychosis.

Connectivity analysis may further the understanding of neural systems beyond the task-activation fMRI designs (Fox and Raichle 2007; Van den Heuvel and Hulshoff Pol 2010). Resting state BOLD fluctuations may reflect spontaneous neural activity as most resting state patterns overlap with known brain networks (Smith et al. 2009; Van den Heuvel and Hulshoff Pol 2010), and they may even

predict individual's task performance or behavior (Fox and Raichle 2007). Moreover, their functional connectivity follows the anatomical outline of white matter bundles (Van den Heuvel and Hulshoff Pol 2010). Whereas task-based activation can provide information about the function of separate brain areas, functional connectivity may thus provide information about interaction of brain areas (Van den Heuvel and Hulshoff Pol 2010). Resting state research of the DMN is especially interesting with regard to the issue of insight, because we expect a relation between the key function of the DMN, namely self-referential processing, and insight.

Studying resting state fluctuations may have some advantages over task-based fMRI. Experimental control of differences in task performance between groups is not necessary and relatively ill patients groups with limited capacities can be investigated (Fransson 2006; Smith et al. 2009). Only intrinsic differences of the brain, and not differences in cognitive abilities, will explain differences in connectivity. Moreover, resting state functional connectivity may be a more natural, ecologically relevant, measure of brain activation than task-based fMRI (Raichle et al. 2001) as it reflects intrinsic brain interactions (Van de Ven et al. 2004).

Independent component analysis (ICA) can separate the fMRI signal into spatially independent networks that show shared temporal fluctuations (Calhoun et al. 2001; Van de Ven et al. 2004). Independent components (i.e. networks) contain brain areas that show similar fluctuations and are assumed to be functionally linked. The size and strength of the identified networks (components) may differ between individuals and groups sharing a specific trait (Calhoun et al. 2001; Van de Ven et al. 2004), as may cooperation between different networks (Jafri et al. 2008). In this study, we will focus on the DMN because this has been related to self-related processing (Gusnard and Raichle 2001). We expect to identify an anterior and posterior DMN subnetwork as described earlier, as these have been identified previously using ICA (Garrity et al. 2007; Jafri et al. 2008).

We hypothesize that schizophrenia patients with poor insight may show impaired connectivity of the DMN during rest, which may reflect attenuated self-

related processing associated with decreased awareness of symptoms (Northoff and Bermpohl 2004). We therefore compared connectivity of brain areas within anterior and posterior DMN components to the other parts of that component between patients with good and with poor insight. A healthy control group was used as a reference. Moreover, we conducted a group comparison of connectivity strength between the anterior and posterior DMN components, as we hypothesize that impaired connectivity between the anterior and posterior DMN may also contribute to impaired insight.

Methods

Ethics statement

The study was approved by the local medical ethical committee (Medische Ethische Toetsingscommissie van het Universitair Medisch Centrum Groningen) according to the declaration of Helsinki. All subjects gave oral and written informed consent after the study procedure had been fully explained. All subjects were capable of signing the informed consent as they were able to live independent, no permanent inpatients, had no care givers taking over responsibilities from them, and all allowed to sign informed consent themselves. All subject data was handled anonymously.

Study population

The study sample included 44 patients with schizophrenia. Patients were recruited from mental health care centers in the north of the Netherlands, three or four patients came from western parts of the Netherlands. Patients were participants in an fMRI study on neural correlates of auditory hallucinations or a study on cognitive emotional processing; in both studies a resting state scan was part of the research protocol. Diagnosis of schizophrenia according to DSM-IV criteria was confirmed with the SCAN 2.1 diagnostic interview (Giel and Nienhuis 1996). A healthy control group matched to the patients on age, gender, handedness, and education level was included. This group was included to deduce whether patients showed similar DMN properties as healthy subjects. Healthy controls were excluded in case of psychiatric history, which was confirmed with

the screenings questions of the SCAN 2.1 interview. For subject characteristics, see Table 15. Patients were asked to give an overview of the medication they were taking at the moment.

Table 15 Overview of demographical data of the good insight and poor insight groups and the control group; The PANSS General subscale is shown without item G12; The fifth column shows the Z (Mann-Whitney) or Chi-square (Kruskal-Wallis and Chi-square test for independence) values of the statistical comparisons and the sixth the p-values

	Good insight (N = 25)	**Poor insight (N = 19)**	**Controls (N = 30)**	**Statistical test score (Z or χ^2)**	**p-value**
Mean age (SD)	33.4 (11.2)	35.9 (11.9)	33.4 (10.5)	0.69	0.71
Mean education (SD)	3.52 (1.3)	3.53 (1.2)	4.1 (1.1)	1.1	0.59
Gender (M/F)	9/16	7/12	15/15	0.0	0.51
Handedness (L/R)	3/22	2/17	6/24	0.0	1.0
PANSS G12 (SD)	1.3 (0.5)	3.7 (0.8)		5.9	< 0.005
PANSS Positive (SD)	14.3 (4.8)	17.1 (4.8)		1.96	0.050
PANSS Negative (SD)	14.3 (4.3)	14.4 (4.8)		0.21	0.83
PANSS General -12 (SD)	25.8 (8.3)	28.1 (7.4)		1.34	0.18
Illness duration years (SD)	10.5 (9.6)	8.9 (8.2)		0.46	0.67
No antipsychotic (%)	0	21.1		6.1	0.11
Typical (%)	8.0	10.5			
Atypical (%)	68.0	47.4			
Typical + atypical (%)	2.0	10.5			

The patients reported to use the following medication; antipsychotics: aripiprazole (9x), chlorprotixene (1x), clozapine (15x), haloperidol (4x), olanzapine (9x), paliperidone (1x), penfluridole (1x), perphenazine (1x), pimozide (1x), pipamperone (1x), quetiapine (7x), risperidone (10x), sulpiride (1x), and zuclopentixole (2x); antidepressants: amytriptyline (1x), bupropione (1x), citalopram (3x), clomipramine (1x), fluoxetine (2x), fluvoxamine (1x), mirtazapine (1x), paroxetine (2x), nortriptylin (1x), trazodone (1x), and venlafaxine (2x); benzodiazepines: diazepam (3x), flurazepam (1x), lorazepam (3x), oxazepam (7x), temazepam (5x); other: atenolol (1x), biperiden (6x), carbamazepine (1x), lithiumcarbonate (6x), pantaprazol (2x), promethazine (1x), valproic acid (1x).

Measures

The most important measure of the study was connectivity of brain areas within the anterior and posterior DMN component to the rest of that component. Differences in connectivity within a component were compared between groups by doing a voxel-wise group comparison of the spatial maps of individual subjects. Connectivity between components was also determined by correlating the time courses of the anterior and posterior DMN component. These were converted to Z-scores and compared between groups.

Design

The primary goal was to compare connectivity measures between patients with good and poor insight. A matched healthy control group was used as a reference. If possible, differences were statistically compared, but as described below, in some cases only qualitative comparison was possible.

Behavioral data

All schizophrenia patients were interviewed with the Positive and Negative Syndrome Scale (PANSS) - (Kay et al. 1987). The PANSS interview measures three domains of symptoms, namely Positive and Negative symptoms and General pathology. Each item can be rated from 1 (not present) – 7 (extreme). The interviews were performed by experienced and trained raters. Based on the rating of the interview item that measures illness insight (G12), patients were

categorized into two groups with good insight (score 1 – 2, which are in the normal range) or poor insight (> 2). Even though this is only one single item, strong correlations with more thorough measures of insight such as the Scale to Assess Insight (SAI; r = 0.88), Scale to Assess Insight – Expanded (SAI-E; r = 0.90) , or the Insight and Treatment Attitudes Questionnaire (ITAQ; r = 0.90) have been demonstrated (Drake and Lewis 2003; Sanz et al. 2011), confirming that the PANSS G12 item reliably rating insight.

Education level was rated according to a six point scale defined by Verhage (Verhage 1984), which ranges from primary school (1) to university level (6). Handedness was confirmed by the Edinburgh handedness inventory (Oldfield 1971). Age and education level were compared between controls and the two patients groups with a Kruskal-Wallis H test (α = 0.05). Between patient group differences in PANSS subscales were tested with a Mann-Whitney U test. For the PANSS General pathology subscale the Insight item G12 was subtracted from the total score, because this item was a selection criterion for both groups. A Chi-square test for independence (α = 0.05) was used to test for differences in gender and handedness. All statistical tests were performed with Statistical Package for Social Sciences (SPSS) 16. Exclusion criteria for the study consisted of MRI incompatible implants, possible pregnancy, claustrophobia, and non-native Dutch speakers.

MRI procedure

All subjects underwent a resting state fMRI scan. They were instructed to close their eyes, relax, and to stay awake. Subjects were reminded of this just before the scan started. A 3 T Philips Intera MRI scanner (Best, The Netherlands) equipped with a 8-channel SENSE head coil was used to acquire 200 whole brain echo-planar functional images (EPI`s), TR 2.3 s, and TE 28 ms. The volumes contained 39 (old sequence) or 43 (after scanner upgrade) interleaved slices (3.8x3.8x3 mm) with a 0 mm slice gap and a 85° flip-angle (FOV = 220x117x220 mm). The duration of the scan was 460 seconds. A high-resolution, transverse T1

anatomical was also acquired for overlay of statistic images (160 slices; voxel size 1x1x1 mm; FOV 256x220x256 mm).

Analysis

The raw images were converted to ANALYZE format and analyzed using Statistical Parametric Mapping (SPM8; FIL Wellcome Department of Imaging Neuroscience, London, UK) running on Matlab 7.1. Images were first corrected for slice-time differences and realigned to the first functional image. The mean image created during realignment was co-registered to the anatomy, together with the functional images, and the anatomy and functional images were normalized (voxel size 3x3x3 mm) to the T1 template of SPM. Finally, images were smoothed with a 10 mm FWHM isotropic Gaussian kernel. Additional filtering was not necessary, because artifacts will generally represented by separate components in ICA (Calhoun et al. 2001; Van de Ven et al. 2004).

After the preprocessing, images were processed in Group ICA FMRI Toolbox (GIFT; http://icatb.sourceforge.net/gift/gift_startup.php) (Calhoun et al. 2001). For referential purposes, a separate ICA was conducted on the group of healthy control subjects. Healthy subjects were not included in the ICA of patients but treated separately, because subtle differences in spatial maps of patients, only distinguished based on insight score, may disappear due to inclusion of a group with different network properties, such as healthy controls (Calhoun et al. 2001).

The mean number of independent components (IC`s) was estimated using Maximum Description Length (MDL) and Akaike's criteria (Li et al. 2006), to prevent splitting or merging of components (Smith et al. 2009). Images were intensity normalized before ICA estimation, which implied scaling the time courses to a mean of 100. The intensity normalized images (patients and controls separately) were decomposed into a set of spatially independent components (for every subject) by the Infomax algorithm. A component consists of a time course showing the temporal fluctuations of that component, and a spatial map that shows the contribution of every voxel to that component. Stability of the components, i.e. whether a component has the tendency to split or merge with another component, was validated by running the ICASSO toolbox implemented

in GIFT using twenty iterations with both random iterations and bootstrapping (Himberg et al. 2004).

Selection of the components of interest for both healthy controls and patients, namely the anterior DMN (including the ACC/MPFC) and posterior DMN (PCC/precuneus/IPL), was done by selecting components showing a large spatial overlap with a priori defined anatomical masks. Thus, the component could also involve other brain areas, but involvement of the areas defined by the masks was crucial. These anatomical masks of the ACC/MPFC (to select the anterior DMN component) and of the PCC/precuneus (for posterior DMN component selection) were created with WFU–pickatlas (http://www.nitrc.org/projects/wfu_pickatlas). Masks provided by WFU pickatlas are based on brain regions defined by Talairach and Tournoux (Talairach and Tournoux 1998) that were implemented in this toolbox after conversion to MNI space (Lancaster et al. 1997; Lancaster et al. 2000).

Spatial maps of selected anterior and posterior DMN components were visually compared between patients and controls to establish whether similar networks were present in both groups. Statistical comparison of image maps of two different ICA`s is unjustified, because the outline of image maps may differ between groups due to the separate ICA unmixing procedure of the image time courses in both groups.

After that, for the patients the reconstructed individual spatial maps of the anterior and posterior DMN component were entered in a two sample t-test random-effects analysis comparing the good versus poor insight group. This analysis shows brain areas that are differently connected to the rest of the anterior or posterior DMN component. A statistical threshold was applied of $p < 0.001$, as has been done previously (Tie et al. 2008). The analysis was restricted to areas that significantly contributed to the ICA component, as previously described by (Garrity et al. 2007). This was done because ICA components maps have values close to zero in areas where the time course of that component is not represented. Voxel intensities in these areas are mainly determined by noise properties and may in group comparison lead to false-positive clusters. Since we

formulated a specific hypothesis comprising specific brain areas and used a mask to restrict the search volume, and because a comparison between two groups of patients was performed, cluster correction was not applied to avoid type II errors (Tie et al. 2008).

In an additional analysis, a voxel-wise linear regression was performed with the time courses of each voxel in the component maps of the DMN against the PANSS G12 Insight scores. Furthermore, a correlation was calculated between the anterior and posterior DMN component time courses of all subjects. The correlations were converted to Z-scores by a Fischer`s Z transformation with $Z = ½*\ln((1+r)/(1-r))$,where r represents the correlation. These data were loaded in SPSS. The correlations between the time courses of the anterior and posterior DMN of all patients were compared to those of controls and the correlations of patients with poor insight to those of patients with good insight using Mann-Whitney U tests ($\alpha = 0.05$).

Two additional analyses were performed. First, because there was a significant difference in the PANSS Positive subscale between groups, this subscale was added as a covariate to the group comparison. Second, as DMN regions have been shown to deactivate during task-performance, we also investigated whether the regions that we identified in the ICA group comparison overlapped with regions that showed task-related deactivation. For this, we analyzed the language task involving valence evaluation (positive, negative) of visually presented words that was performed by subjects during scanning. Deactivation of the DMN during task performance was shown by contrasting the fixation cross of the task with task blocks. The clusters showing a difference in DMN connectivity between the good and poor group were then overlayed on the task-related deactivation (Figure 16).

Results

Twenty five patients were classified as having good insight and nineteen patients were classified as having poor insight. The demographical characteristics of these two groups were compared, also with respect to the controls (Table 15). The PANSS Positive subscale was significantly different between groups, but there was

a significant correlation between PANSS G12 and the Positive symptom subscale (r = 0.36; p = 0.015), implying that patients with more positive symptoms had poorer insight. Therefore, the Positive symptom subscale was added as a covariate in the group comparisons, but this did not change the results. There was no significant difference in age, gender, handedness, education level and most PANSS scores, though the PANSS Positive subscale was significant.

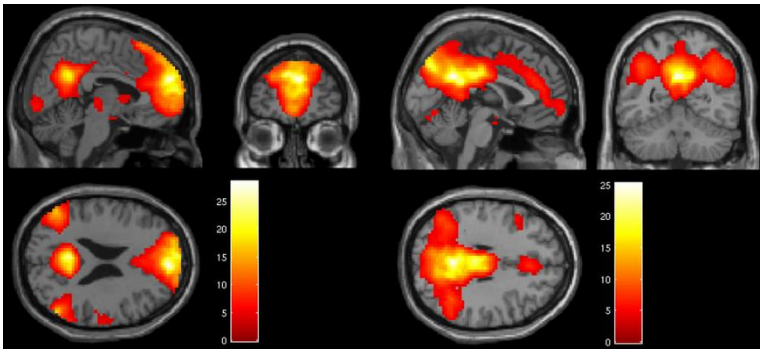

Figure 14 Components map of the DMN of healthy controls showing the anterior DMN on the left and the posterior part on the right (p < 0.001, k > 10)

This resulted in an estimate of 32 components for the patients and 30 for the healthy controls. The anterior default mode component encompassing the ACC/MPFC showed a spatial overlap correlation with the anatomical mask created by WFU Pickatlas of 21% for healthy controls (left side Figure 14) and of 56% for patients (left side Figure 15).

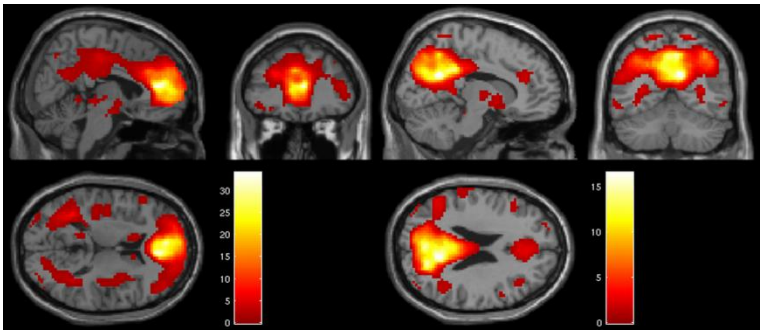

Figure 15 Components map of the DMN of schizophrenia patients showing the anterior DMN on the left and the posterior part on the right (p < 0.001, k > 10)

Overlap of other components was < 10%, indicating that the components of interest (anterior and posterior DMN) could be identified with high specificity. Visual inspection showed that the component map of the healthy controls had a more extended and stronger network contribution than the patients. The posterior component showed an overlap of 31% for healthy controls (right side Figure 14) and of 57% for patients (right side Figure 15).

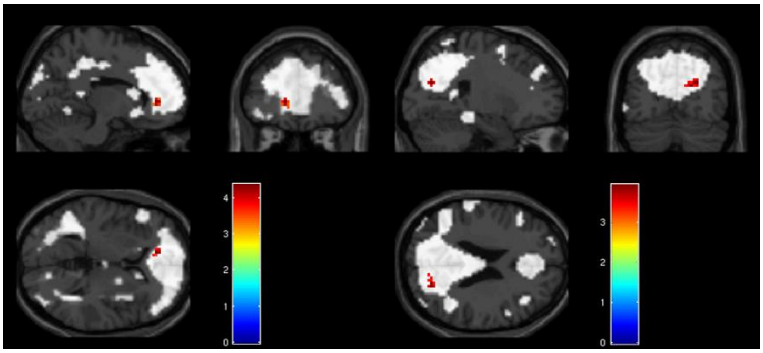

Figure 16 Group comparison of good vs. poor insight patients with the anterior component on the left showing the ACC, and the posterior component on the right showing the precuneus ($p < 0.001$, $k > 10$, masked with component image map), overlayed on the task-related deactivation, created by contrasting the fixation cross of a language task with task blocks

The anterior and posterior components were compared with a two-sample t-test. Patients with good insight showed stronger connectivity of the ACC to the rest of the anterior DMN component compared to patients with poor insight: $T = 4.37$, $Z = 3.94$, cluster size = 18, $p < 0.001$, xyz = -12 39 3 (Figure 16, left side). Subsequently, a voxel-wise regression between the image maps and the insight score was calculated. This revealed a cluster in the same location. In the two sample t-test of the posterior DMN component, a significant cluster was identified in the precuneus ($T = 3.94$, $Z = 3.62$, cluster size = 20, $p < 0.001$, xyz = 24 -72 24, see Figure 16, right side). The linear regression with insight score resulted in the same cluster. There was no significant cluster in the poor vs. good insight t-test comparison for both components.

A correlation between the time courses of the anterior and posterior DMN component was calculated and converted to Z-scores. These Z-scores were compared between healthy controls and all patients, and between patients with

good and poor insight. Z-scores are plotted per group in Figure 17. Whereas the Z-scores for the healthy controls were all above zero (with the exception for one subject), part of the patients showed a negative Z-scores with an overall mean around zero and a larger variation ($SD_{controls}$ = 0.20, $SD_{patients}$ = 0.66). This difference was significant (U = 388, z = -3.0, p = 0.003). Patients with poor insight showed the largest variation in Z-scores ($SD_{good\ insight}$ = 0.56, $SD_{poor\ insight}$ = 0.79), but did not differ significantly from the patients with good insight (U = 214, z = -0.56, p = 0.58).

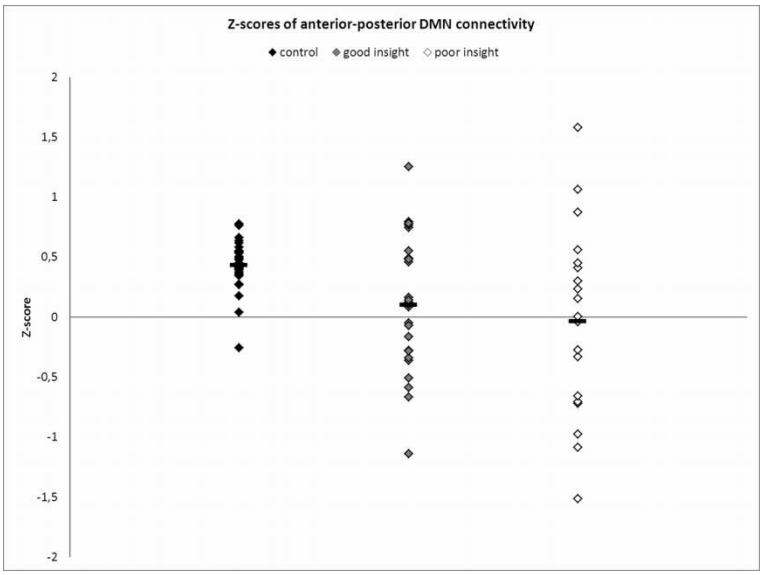

Figure 17 Z-scores of connectivity between the anterior and posterior DMN for healthy controls and schizophrenia patients with good and poor insight

Finally, adding the PANSS Positive symptoms subscale as a covariate to the group comparison between good and poor insight did not change the results. In addition, during the valence evaluation task deactivation of DMN regions was observed. The clusters that differed significantly between good and poor insight groups overlapped with the DMN regions showing significant deactivation during the task (Figure 16).

Discussion

In this study, the relationship between insight (awareness of illness) in schizophrenia and functional connectivity of regions in the default mode network (DMN) was investigated in patients with schizophrenia. The DMN connectivity pattern of patients clearly overlapped with the network in healthy control subjects, though the network was less extended (in accordance with e.g. Hill et al. 2004; Jang et al. 2011; Kuhn and Gallinat 2011; Ongur et al. 2010; Rotarska-Jagiela et al. 2010). Importantly, patients with poor insight showed a lower connectivity within the anterior cingulate and precuneus compared to patients with good insight. Group differences were found in DMN regions that indeed deactivated during task performance, supporting our interpretation. Moreover, although the poor insight group showed significantly more positive symptoms, these did not explain the group differences Connectivity between anterior and posterior DMN was lower in all patients compared to controls, but there was no significant difference between patients with good and poor insight.

The result of reduced connectivity in the precuneus and ACC/vMPFC of the DMN in poor insight patients was in accordance with our expectations that poor insight would be related to decreased DMN connectivity (Gusnard and Raichle 2001; Kuhn and Gallinat 2011; Schmitz et al. 2006; Van der Meer et al. 2010), although it may only concern part of the network. Studies assessing the overlap between self-referential processing and DMN activation demonstrated that the ACC/vMPFC was consistently activated (Qin and Northoff 2011; Whitfield-Gabrieli et al. 2011), and thus seems to be particularly important for self-referential thought. Lesion studies demonstrated that lesions in/around this area can result in a diminished self-referential processing (Philippi et al. 2012) and in a dysfunction of emotional self-control (Allman et al. 2001). This suggests that reduced connectivity in this region may indeed result in abnormal self-referential processing. Whereas the ACC/vMPFC may be specifically involved in self-related processing, research has shown that precuneus activation is less self-specific and also activates during thinking about other persons (Qin and Northoff 2011; Van der Meer et al. 2010; Whitfield-Gabrieli et al. 2011). Instead, the precuneus has been hypothesized to be involved autobiographical and episodic memory retrieval

and mentalizing, which has been confirmed by several studies (Cavanna 2006; Cavanna 2007; Gusnard and Raichle 2001; Kuhn and Gallinat 2011; Van der Meer et al. 2010). Consistent with this, structural neuroimaging results point towards a relationship between impaired insight and reduced grey (Cooke et al. 2008; Morgan et al. 2010) and white matter (Antonius et al. 2011) in this region among others. Taken together, this suggests that hampered self-processing through a lack of integration of self-related information may underlie impaired insight in schizophrenia (Van der Meer et al. 2010).

Schizophrenia patients had a lower, i.e. more negative, correlation between time courses of the anterior and posterior DMN. Though the mean connectivity was not significantly lower in patients with poor insight compared to good insight, the variation appeared to be higher in patients with poor insight. Disturbed connectivity between the frontal and posterior DMN could possibly have a modulating effect on insight. Patients with schizophrenia have shown decreased connectivity between the medial frontal cortex and other brain regions during self-reflective processing (Holt et al. 2011; Wang et al. 2011). Reduced communication between self-reflection areas may result in less transfer of self-related information (i.e. autobiographical or interoceptive information) of posterior areas to the anterior self-reflective areas.

One limitation of the study may be that insight was rated based on one item of a standardized interview. However, as we discussed above, this G12 item correlates highly with other more thorough measures of insight, suggesting that it can adequately index insight. Furthermore, it can be argued that subjects were not involved in self-reflective processing during resting state conditions. However, other studies have shown that self-referential processing is one of the major processes taking place during resting state (Buckner et al. 2008; Gusnard and Raichle 2001; Spreng and Grady 2009; Wicker 2003). And as this is spontaneous self-referential processing, it was exactly the type of processing we were interested in. More research is needed to elucidate the contribution of different cortical midline structures in more detail.

In conclusion, schizophrenia patients with relatively preserved insight showed stronger connectivity than patients with poor insight in the anterior cingulate cortex and precuneus, both key regions in self-reflective processing. These findings tentatively support the hypothesis that poor insight may be related to impaired self-related processing.

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6. Altered resting state connectivity of the default mode network in alexithymia

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Abstract

Introduction: Alexithymia is a trait characterized by a diminished capacity to describe and distinguish emotions and to fantasize; it is associated with reduced introspection and problems in emotion processing. The default mode network (DMN) is a network of brain areas that is normally active during rest and involved in emotion processing and self-referential mental activity, including introspection. We hypothesized that connectivity of the DMN might be altered in alexithymia. **Methods:** Twenty alexithymic and eighteen non-alexithymic healthy volunteers underwent a resting state fMRI scan. Independent component analysis was used to identify the DMN. Differences in connectivity strength were compared between groups. **Results:** Within the DMN, alexithymic participants showed lower connectivity within areas of the DMN (medial frontal and medial temporal areas) as compared to non-alexithymic participants. In contrast, connectivity in the high-alexithymic participants was higher for the sensorimotor cortex, occipital areas, and right lateral frontal cortex than in the low-alexithymic participants.

Discussion: These results suggest a diminished connectivity within the DMN of alexithymic participants, in brain areas that may also be involved in emotional awareness and self-referential processing. On the other hand, alexithymia was associated with stronger functional connections of the DMN with brain areas involved in sensory input and control of emotion.

Introduction

Alexithymia has been conceptualized as a personality trait that is associated with difficulties in emotion processing (Taylor et al. 1997). More specifically, alexithymia is characterized by difficulties in verbalizing one's emotions, diminished affect-related fantasy and imagery, difficulty to distinguish emotions from bodily sensations, and a tendency to focus on external events rather than internal experiences (Sifneos 1973; Taylor et al. 1991). The prevalence was around 10% in a Finnish sample (Salminen et al. 2007). Alexithymia has been associated with increased risk for psychosomatic complaints, anxiety disorders, and depression (Taylor et al. 1997), and the emotion regulation difficulties characteristic of alexithymia have been hypothesized to play a mediating role in these (Taylor 2000; Waller and Scheidt 2006). Unraveling the neurocognitive mechanisms underlying alexithymia may improve our understanding of this trait with possible clinical and societal implications.

In this study, we started from the observation that alexithymia is associated with difficulties in emotion processing, e.g. recognizing emotional facial expressions and deducing emotions of others from narratives (Meltzer and Nielson 2010; Swart et al. 2009), which may reflect a more general reduction of emotional awareness (Lane et al. 1997).The ability to recognize and experience emotions allows an individual to form a representation of his own emotions (Damasio 2003; Northoff et al. 2006). Such self-referential emotional processing and imagery have been suggested to take place in a network of brain areas called the 'Cortical Midline Structures' (CMS) (Northoff et al. 2006), which is a key part of the default mode network (DMN) (Gusnard and Raichle 2001). Indeed, parts of the DMN have been associated with emotion processing in general (Kober et al. 2008). The main regions within the DMN are the precuneus, posterior cingulate

cortex (PCC), anterior cingulate cortex (ACC), inferior parietal lobule (IPL), and medial prefrontal cortex (MPFC) (Gusnard and Raichle 2001). In a broader definition of the network, middle temporal gyrus (MTG), middle, superior, and inferior frontal gyrus (MiFG, SFG, and IFG), hippocampal formation, and cerebellar regions are also included (Buckner et al. 2008; He et al. 2004). The default mode network is also highly active during rest when self-referential processing apparently takes place (Gusnard and Raichle 2001) and shows synchronized slow fluctuations across its brain areas (Fransson 2006; Gusnard and Raichle 2001). Schilbach et al. proposed in their review that brain activation of DMN regions during the resting state is related to self-consciousness and self-processing and may thus be relevant for introspection (Schilbach et al. 2008). Indeed, D'Argembeau et al. showed that activation in the anterior part of the DMN is correlated to self-referential thoughts (D'Argembeau et al. 2005).

Several studies have shown a relation between emotional awareness, which may be impaired in alexithymia, and DMN brain areas (Gusnard and Raichle 2001; Northoff et al. 2006). Lower activation of the anterior cingulate cortex (ACC) and its connectivity to other brain areas have been related to lower emotional awareness and alexithymia (Lane et al. 1997; Lane et al. 1998). In alexithymic participants, the ACC and functionally related areas were less activated whereas the somatosensory cortex was more activated by emotionally valenced videos, emotional pictures, or imagery (Berthoz et al. 2002; Kano et al. 2003; Karlsson et al. 2008; Mantani et al. 2005; Moriguchi et al. 2006). Likewise, a structural MRI study found lower ACC and precuneus volumes in alexithymic participants (Borsci et al. 2008). Therefore, we hypothesized that alexithymic participants would show lower brain connectivity in areas implicated in emotional processing such as the ACC and higher somatosensory connectivity during rest, which may be related to less emotional awareness and a more action-oriented emotional coping style.

Because the DMN is highly active during rest and related to self-awareness, resting state analysis might, provide relevant information about the neural background of alexithymia. Resting state functional connectivity is considered as a more natural measure of brain function than task-based fMRI (Raichle and

Gusnard 2005), because it reflects intrinsic brain interactions (Van de Ven et al. 2004). These interactions may provide knowledge about overall brain function (Fox and Lancaster 1994) and predict task performance or behavior (Fox and Raichle 2007), without being biased by differences in task performance during the scanning (Calhoun et al. 2001; Van de Ven et al. 2004). If people with alexithymia in general devote less time to thinking about their feelings, this may have consequences for connectivity of relevant resting state areas, resulting in lower DMN connectivity.

Finally, alexithymia has been conceptualized as a disorder of emotion regulation, which warrants special interest for prefrontal areas known to be involved in emotion regulation (Ochsner et al. 2002; Taylor et al. 1997). Participants with alexithymia tend more to suppression of emotions than to use emotion reappraisal strategies (Swart et al. 2009). In reappraisal, participants use cognitive-linguistic strategies to downregulate emotional responses to arousing stimuli (Goldin et al. 2008; Reker et al. 2009; Silani et al. 2009). Effective control of emotions by reappraisal strategies has been related to activation of the medial and lateral prefrontal areas (Kim and Hamann 2007; Ochsner et al. 2002; Phan et al. 2005; Wager et al. 2008), which prevent excessive experience of negative emotions (Abler et al. 2010; Urry et al. 2009). Emotion regulation strategies such as suppression may involve right sided lateral frontal areas, but for a longer time period because suppression works on later stages of emotion processing than reappraisal (Abler et al. 2010; Goldin et al. 2008; Ochsner et al. 2002). We hypothesize that participants with alexithymia may show higher connectivity in the right lateral frontal and lower connectivity in the ventromedial prefrontal cortex, related to hampered emotion regulation.

In this study, the resting state DMN connectivity of high- vs. low-alexithymic participants was investigated. Because no such study has been conducted before, this study has an exploratory nature. We hypothesized that alexithymic participants would show diminished connectivity in areas implicated in awareness (DMN areas) and verbalizing of emotions (left frontal areas). In addition, we explored whether there might be higher connectivity in alexithymic participants of

areas implicated in emotion control (lateral prefrontal areas) and action-oriented processing (sensory and motor areas).

Methods

Participants

The study was approved by the local medical ethical committee and carried out in accordance with the latest version of the Declaration of Helsinki. 493 right-handed students of different disciplines from the local university filled out the Verbalizing subscale of the Bermond-Vorst Alexithymia Questionnaire (BVAQ). This sub-scale was chosen because reduced ability to verbalize emotions has been considered a central deficit of alexithymia (Aleman 2005). Further details of the questionnaire are given in the next section. Subjects scoring at the upper and lower extremes (25%) of the Verbalizing subscale of the BVAQ, i.e. showing high or low levels of alexithymia based on this measure, participated in the study.

All participants were normally functioning and showed no signs of psychiatric illness. Persons with a history of psychiatric or neurologic disorder for which they had received treatment were excluded from the study. Further exclusion criteria consisted of MRI incompatible implants, age above 50 years, pregnancy, claustrophobia, left-handedness and being a non-native Dutch speaker.

Twenty participants with a high and eighteen participants with a low Verbalizing score that fulfilled the inclusion criteria participated. All participants gave oral and written informed consent prior to testing after the procedure had been fully explained. An overview of the participant characteristics is given in Table 16. Groups did not differ in age (t-test; $T = -0.28$; $p = 0.78$). Because female participants may have stronger verbalizing skills, dissimilarity in general language skills due to different male/female ratios between groups might confound interpretation of findings and therefore our groups were matched on gender distribution (Chi-square test; $\chi^2 = 1.03$; $p = 0.16$).

On the day of the MRI-session participants filled out the complete BVAQ and the Positive And Negative Affect Schedule (PANAS) - (Watson et al. 1988).

Table 16 Mean and standard deviation of the demographic data of both subject groups, and the p-values of the t-test. The mean score on the BVAQ components and the two PANAS subscales are also shown; Subjects did differ significantly on the cognitive component of the BVAQ, but not on other subscales or demographic characteristics

	Low alexithymia mean (SD)	High alexithymia mean (SD)	p-value
Age (y)	22.3 (8.1)	21.6 (6.7)	0.77
Males/females	11/9	6/12	0.16
Cognitive component	42.9 (8.1)	63.2 (9.7)	< 0.0005
Emotional component	36.1 (8.1)	40.0 (9.7)	0.19
PANAS Positive affect	33.8 (5.5)	30.5 (6.3)	0.059
PANAS Negative affect	15.1 (3.5)	14.7 (4.1)	0.77

Questionnaires

For assessment of alexithymia, we used the Bermond-Vorst Alexithymia Questionnaire (BVAQ). Several studies have supported the criterion validity of the BVAQ in clinical samples, e.g. for eating disorders (Deborde et al. 2008), alcoholism (Sauvage and Loas 2006), autism spectrum disorders (Berthoz and Hill 2005), schizophrenia (Van 't Wout et al. 2007), and high risk for schizophrenia (Van Rijn et al. 2011). However, because the BVAQ includes self-assessment, which may be compromised in certain clinical samples, its validity may be attenuated in clinical groups characterized by reduced insight in their psychological functioning. This is not a problem in the present study, because we investigated nonclinical participants.

The BVAQ is a validated 40-item self-report scale that consists of five subscales: Verbalizing, Fantasizing, Identifying (Cognitive component), Emotionalizing, and Analyzing (Emotional component) (Bermond and Vorst 1993). Higher scores indicate a stronger degree of alexithymic characteristics. The scale measures alexithymic features as defined by Nemiah and Sifneos (Nemiah and Sifneos 1970; Sifneos 1973). Previous studies have shown that the BVAQ has good

psychometric properties (Berthoz et al. 2000; Berthoz et al. 2007; Zech et al. 1999).

The PANAS measures current affective positive and negative state (Watson et al. 1988). Positive affect refers to the extent to which a person feels enthusiastic, active, and alert, Negative affect addresses distress. The scale consists of ten Positive and ten Negative items, which can be scored on a 5-point scale (1 = certainly does not apply to me, up to 5 = certainly applies to me). The PANAS has shown good reliability and validity to measure positive (Cronbach's α = 0.89) and negative (α = 0.85) current mood states (Watson et al. 1988).

Groups were tested on differences in the Cognitive and Emotional component of the BVAQ and the Positive and Negative subscale of the PANAS with a two sample t-test ($\alpha < 0.05$).

Behavioral data

Participants also performed a language processing task in the same fMRI session. We report the performance on this task to provide an indication of language processing differences between groups. The task (Aleman et al. 2005) required participants to evaluate bisyllabic Dutch words for metrical stress followed by indicating the syllable that carried the metrical stress. In a second condition, participants rated the valence of a word (positive or negative).

Data acquisition

A resting state scan of 460 seconds was acquired at the end of an MRI-session that additionally consisted of three tasks and an anatomical scan. During the resting state scan, participants were asked to close their eyes, relax, and try to not fall asleep. There were no constraints on the content of their thoughts.

A 3 T Philips Intera MRI scanner (Best, The Netherlands) equipped with an eight-channel SENSE head coil was used to acquire 200 whole brain echo-planar functional images (EPIs) with a TR of 2.3 s and TE 28 ms. The volumes contained 39 (N = 3 participants), 41 (N = 29) or 43 slices (N = 4); 3.8x3.8x3 mm), interleaved, with a 0 mm slice gap and a 85^{o} flip-angle (FOV = 220x117x220 mm). The reason for a different number of slices is unspecified, but this is not expected to influence

study outcome. A high-resolution, transverse T1 anatomical was also acquired for overlay of statistic images (160 slices; voxel size 1x1x1 mm; FOV 256x220 x256 mm).

Preprocessing

The raw images were converted to ANALYZE format and analyzed using Statistical Parametric Mapping (SPM5; Wellcome Department of Imaging Neuroscience, London, UK) running on Matlab 7.1. Images were first corrected for slice-time differences and realigned to the first functional image. The mean image created during realignment was co-registered to the anatomy, together with the functional images, and the anatomy and functional images were normalized to the T1 template of SPM (voxel size 3x3x3 mm). Finally, images were smoothed with a 10 mm FWHM isotropic Gaussian kernel.

ICA procedure

Independent Component Analysis (ICA) is a data-driven method that can separate the fMRI signal into spatially independent networks (independent component; IC) that show shared temporal fluctuations (Calhoun et al. 2001; Jafri et al. 2008). An independent component consists of a time series and a spatial map per participant, which shows the contribution of every voxel in the brain to that time series, i.e. to that network (component). Those networks show a close correspondence to networks identified by activation studies (Smith et al. 2009). The size and strength of the identified networks may differ between individuals and groups sharing a specific trait (Calhoun et al. 2001; Van de Ven et al. 2005), i.e. a smaller network could represent altered connectivity of (the brain areas within) the network.

Images of all participants were decomposed into a set of independent components by the Group ICA FMRI Toolbox (GIFT) using the Infomax algorithm (Calhoun et al. 2001). We estimated the number of components by using the Maximum Likelihood and Akaike's criteria (Li et al. 2006), to prevent splitting or merging of components (Smith et al. 2009). The Infomax algorithm is a commonly used method to unmix the signal (Calhoun et al. 2001). To perform group ICA, dimensionality of the data was first reduced using Principle Component Analysis

(PCA), and afterwards the reduced subject data were concatenated over the time domain. Afterwards, individual image maps were reconstructed from the aggregated data based on matrices stored during PCA. Resulting image maps and time courses were converted into Z-scores to normalize the signal. Though the overall architecture of the networks generated by spatial ICA is similar due to the separation based on spatial location, subtle differences between individuals may be present. These can be investigated in a voxel-wise group comparison (Calhoun et al. 2001).

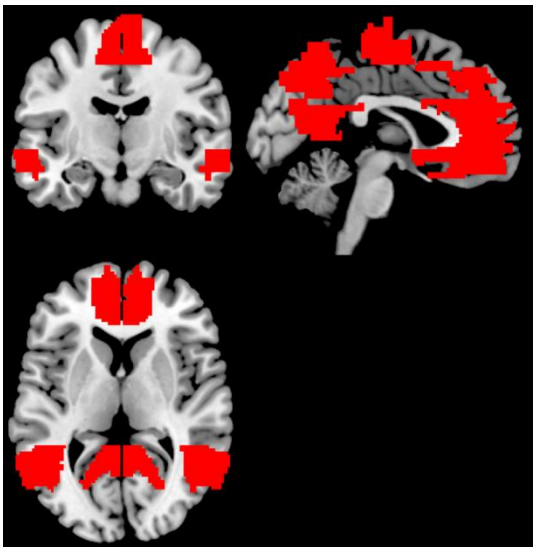

Figure 18 Mask of the DMN used for component selection

Independent components were first sorted based on the white matter and gray matter masks of SPM for exclusion of components with artifacts. Artifacts will generally represented be by separate components, which give the additional advantage of noise reduction in the data (Calhoun et al. 2001; Van de Ven et al. 2004). Selection of the component(s) of the DMN was based on spatial overlap with an anatomical mask of the DMN created with the WFU pickatlas (http://www.nitrc.org/projects/wfu_pickatlas/) - (Maldjian et al. 2003). The mask consisted of the PCC, precuneus, IPL, ACC, MPFC, and MTG. See Figure 18 for the outline of the mask. Components with a substantial overlap were visually

inspected for DMN brain areas also described in the introduction. Stability of the components of interest, i.e. whether components had the tendency to split or merge with another component, was confirmed by running the ICASSO toolbox (Himberg et al. 2004), which ran twenty iterations of the ICA. If the same component was identified during all iterations, this indicates the stable presence of that component in the data.

Group differences on questionnaires

Statistical analyses on questionnaires were performed using Statistical Package for Social Sciences (SPSS 16) and all tests were two-tailed. The Cognitive component: the sum of the Verbalizing, Identifying, and Analyzing subscale, and Emotional component: the sum of the Emotionalizing and Fantasizing subscales, of the BVAQ were calculated. A two-sample t-test was applied to test for significant differences between groups.

The Positive and Negative affect subscales of the PANAS were also calculated and compared between groups.

Group differences on behavioral data

Reaction time and accuracy on the language task were compared between groups. A two-way ANOVA was conducted separately on reaction times and accuracy, and separately for both task conditions. The analyses had reaction time or accuracy on the metrical stress or valence condition as independent variable, and group and gender as independent variables ($\alpha < 0.05$).

Statistical analysis of functional imaging data

The individual image maps of the identified components (networks) were entered into a separate second level analysis of SPM5, with a two sample t-test. First, a contrast was made of the main effect of interest, independent of group (FWE, $p < 0.05$, $k > 15$). Second, contrasts between both groups were made with a threshold of $p < 0.001$ uncorrected and a cluster-size threshold of 15 voxels. A mask of the contrast of the main effect of interest was used to restrict the analysis to DMN areas and to prevent false positive findings outside this area (inclusive mask, $p < 0.05$), as previously described (Garrity et al. 2007).

In an additional analysis, Positive and Negative affect (PANAS), and gender were entered as a covariate into the group analysis. The affect states were investigated to check for an effect of mood state on the group differences. Gender was controlled for because this might also have an effect on default mode connectivity (Bluhm et al. 2008).

Results

Questionnaire results

The scores on the two components of the BVAQ subscales and the Positive and Negative affect subscales of the PANAS are shown in Table 16. A two-sample t-test showed that groups differed significantly on the Cognitive component ($t(36) = 4.7$, $p < 0.0005$), but not on the Emotional component ($t(36) = 1.3$, $p = 0.19$). Further, there was a strong association between the Cognitive component and the Verbalizing scale used for selection ($r = 0.76$, $p < 0.0005$). Groups did not differ significantly on Positive ($t(36) = 1.9$, $p = 0.059$) nor on Negative affect ($t(36) = 0.3$, $p = 0.78$) as measured with the PANAS, although high alexithymic participants had a higher Negative and lower Positive affect than the low alexithymic participants.

Table 17 Mean and standard deviation of the reaction times and accuracy on the metrical stress task; Results are shown separately for males and females in both groups

	High alexithymia mean (SD)		**Low alexithymia mean (SD)**	
	Males	**Females**	**Males**	**Females**
Reaction time (s) metrical stress	1.53 (0.46)	1.45 (0.36)	1.44 (0.27)	1.46 (0.51)
Accuracy (%) metrical stress	78.1 (19)	76.4 (24)	75.3 (22)	80.8 (19)
Reaction time (s) valence evaluation	1.07 (0.43)	1.11 (0.47)	1.20 (0.16)	1.18 (0.42)
Accuracy (%) valence evaluation	78.1 (32.6)	68.4 (37.6)	87.4 (19.4)	80.0 (34.5)

Behavioral results

Reaction times and accuracy of the language task are presented in Table 17, separated for males and females. For the metrical stress condition, there was no significant effect of group ($F(1,34) = 0.11$, $p = 0.75$) or gender ($F(1,34) = 0.053$, $p = 0.82$) on reaction times, and also no interaction ($F(1, 34) = 0.18$, $p = 0.68$). There was also no significant effect on accuracy of group ($F(1,34) = 0.013$, $p = 0.91$), gender ($F(1,34) = 0.076$, $p = 0.79$) or interaction ($F(1,34) = 0.28$, $p = 0.60$).

For the valence evaluation condition, there was no significant effect or interaction of neither group nor gender on either reaction times or accuracy. The main effect of group on reaction times was $F(1,34) = 0.56$, $p = 0.46$, the effect of gender was $F(1,34) = 0.003$, $p = 0.95$, and their interaction was $F(1,34) = 0.057$, $p = 0.81$. The effect of group on accuracy was $F(1, 34) = 0.10$, $p = 0.96$, of gender $F(1,34) = 0.63$, $p = 0.43$, and their interaction $F(1,34) = 0.012$, $p = 0.93$.

Imaging results

After running the ICA, the DMN was unexpectedly represented in three separate components. The DMN was split in (1) an anterior part with ACC, medial frontal gyri, and lateral frontal areas, (2) a mainly middle/lateral part containing MTG, cingulate, insula, and hippocampal formation, and (3) a posterior part containing mainly PCC, precuneus, and IPL. We will refer to these subnetworks as (1) “anterior” component (2) “middle” component and (3) “posterior” component. See Figure 19. The anterior component had a spatial overlap of 21% with the DMN template while it contained mostly frontal areas but also some PCC, the middle component of 25%, and the posterior component 27%. One additional component showed an overlap of 23% but this component contained blood vessel artifacts. These components of interest were entered in the group comparison.

The contrast of alexithymic vs. non-alexithymic participants showed lower connectivity within the DMN for the following areas in alexithymic individuals; anterior component: cingulate gyrus, superior frontal gyri, and right medial temporal gyrus (MTG); middle component: right MiFG; posterior component: left medial frontal gyrus (MeFG) and right SFG (Table 18 ; Figure 20).

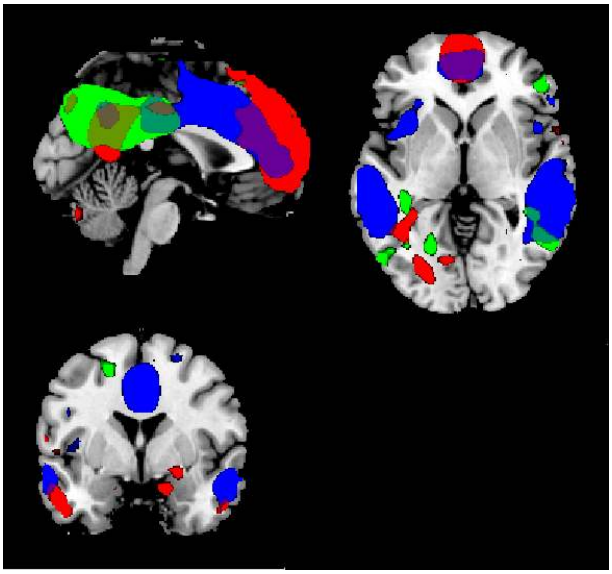

Figure 19 The three networks identified, the whole network is shown irrespective of group; All main areas of the default mode network are visible, including the anterior cingulate, posterior cingulate, medial middle/medial temporal gyrus, prefrontal cortex, precuneus and inferior parietal lobule; The anterior component is indicated in red, the middle DMN component in blue and the posterior component in green

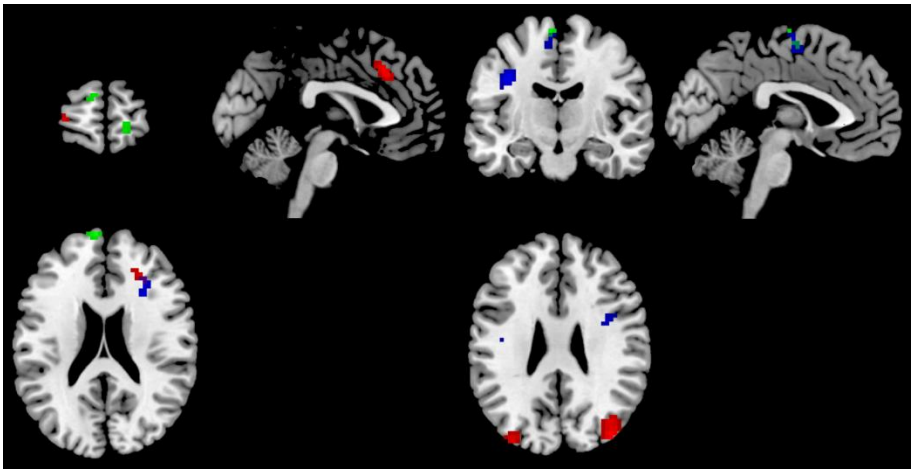

Figure 20 Left: Brain regions that show decreased connectivity in subjects with high alexithymia compared to low alexithymic subjects; Different components are indicated in different colors, green: anterior part, red: middle part; blue: posterior part; Right: Brain regions that show increased connectivity in subjects with alexithymia compared to control subjects; Different components are in different colors, green: anterior part; red: middle part; blue: posterior part

Table 18 Overview of clusters showing connectivity differences between groups ($p < 0.001$, $k > 15$, inclusive mask at $p < 0.05$); The first part of the table shows areas that are more connected in alexithymia, and the second half areas of decreased connectivity; Anterior, middle, and posterior refer to the different components of the DMN (L = left, R = right)

	Voxels	T	Z	x	y	z	Area
High alexithymia vs. low alexithymia							
Anterior	36	5.23	4.48	-33	-84	24	L superior occipital gyrus
	87	5.22	4.47	39	-81	27	R superior occipital gyrus
	22	4.08	3.67	-27	-75	-27	L declive
Middle	44	5.66	4.75	-36	-15	36	L precentral gyrus
	37	4.83	4.21	-6	-9	60	L precentral gyrus
	27	4.55	4.02	33	0	30	R IFG
Posterior	30	3.93	3.56	-6	-9	60	L precentral gyrus
	20	3.83	3.48	57	0	45	R MiFG
Low alexithymia vs. high alexithymia							
Anterior	47	4.93	4.28	0	24	39	cingulate gyrus
	23	4.59	4.05	27	36	24	R SFG
	16	4.33	3.86	-30	63	3	L SFG
	33	4.21	3.77	39	-3	-36	R MTG
Middle	42	4.61	4.06	30	27	27	R MiFG
Posterior	16	4.34	3.87	-9	66	18	L MeFG
	15	4.04	3.65	15	66	-6	R SFG

In contrast, higher connectivity with the DMN was observed for the following areas in alexithymic individuals; anterior component: occipital gyri and declive; middle component: precentral gyrus and right inferior frontal gyrus (IFG); posterior component: precentral gyrus and right middle frontal gyrus (MiFG) ($p < 0.001$, $k > 15$; Table 18, Figure 20).

Adding gender, Positive or Negative affect as a covariate did not influence the outcome of the study. Thus group differences could not be explained by these variables.

Discussion

The aim of this study was to investigate differences between alexithymic and non-alexithymic participants in default mode connectivity. Participants with high levels of alexithymia showed lower connectivity of DMN areas, including the cingulate gyrus, medial frontal gyrus, and medial temporal gyrus. In contrast, they showed higher connectivity to sensory areas and right lateral frontal areas. These group differences were not caused by differences in affect or gender distribution. Moreover, participants showed no difference in performance on a language task involving semantic emotional evaluation and stress placement, indicating that differences in such skills were not confounding interpretation of group differences. Networks identified with a resting state analysis have been shown to converge with networks resulting from task-induced activation (Fox and Raichle 2007; Fox and Lancaster 1994; Smith et al. 2009). However, analysis of resting state networks is not biased by differences in task performance between groups (Van de Ven et al. 2004).

The high and low alexithymic group showed no effect of Positive or Negative affect on imaging results. The TAS-20, measuring a trait, often shows a relation with Negative affect, which is a state characteristic (Lane et al. 1997). Because the TAS-20 may also tap aspects of affective state, the use of the BVAQ and the absence of an effect of the PANAS on our results may indicate that this study specifically measured trait alexithymia.

The two groups were initially selected based on the verbalizing subscale of the BVAQ. However, the high and low alexithymic group differed strongly on the Cognitive component at the day of scanning. Thus, selection based on the Verbalizing scale of the BVAQ was considered adequate for creating two rather extreme groups. Interestingly, the Cognitive component has shown a high correlation with the TAS-20 (Berthoz et al. 2000; Berthoz et al. 2007; Zech et al. 1999), thus this selection may be comparable to selection with the TAS-20.

The DMN was split into three subnetworks, while a test for component stability (ICASSO) showed a good stability of selected components. We did not expect the DMN to split into separate components. However, different components containing part of the DMN have been described by other studies as well (e.g. Damoiseaux et al. 2006; Garrity et al. 2007; Jafri et al. 2008). Indeed, our identified networks may fit the DMN model of Laird et al. (Laird et al. 2009) and three sub-domains described by Kim et al. (Kim 2010). The part containing MTG quite closely resembles the “action subnetwork” defined by Laird et al. and is involved in salience according to Kim et al. The anterior component (Laird: “emotion subnetwork”) could be the core domain of the DMN involved in cognitive emotional processing, and the posterior component (Laird: “perception subnetwork”) could be involved in monitoring of external cues and top-down memory (Kim 2010; Laird et al. 2009).

A key finding in the group comparison was that the alexithymic participants showed lower connectivity in anterior parts of the DMN, including cingulate gyrus, medial frontal regions, and MTG (Buckner et al. 2008; Gusnard and Raichle 2001). This finding is in accordance with our hypothesis of decreased emotional awareness in (Lane et al. 1997; Lane et al. 1998), and is consistent with earlier approaches (Lane et al. 1998).

The DMN is believed to reflect the baseline “idling” state of the brain that diminishes during specific goal-directed behaviors (Raichle et al. 2001). It has functions related to attending internal versus external state and consciousness (Raichle et al. 2001; Spreng and Grady 2009). Slow-wave fluctuations of the brain have shown to be related to short gaps of inattentiveness during task performance, which could be interpreted as a transient more internally oriented

focus (Singh and Fawcett 2008). Resting state fluctuations of the DMN may thus be related to the degree to which persons engage in introspective thinking (Singh and Fawcett 2008), which may be less pronounced in alexithymia. In a similar vein, research on subjects with meditation experience showed increased connectivity within attentional networks, as well as between attentional regions and medial frontal regions (Hasenkamp and Barsalou 2012). The authors suggested that these neural relationships may be involved in the development of cognitive skills, such as maintaining attention and disengaging from distraction, that are often reported with meditation practice. Thus, prolonged mental training or habits may have lasting influences on resting state networks.

Interestingly, lower DMN connectivity has also been shown in ASD (Assaf et al. 2010), implying that it may reflect a trait-characteristic associated with socio-emotional difficulties. Furthermore, lower connectivity of the MTG may relate to impaired ability to link external events to self-referential mental activity (Laird et al. 2009). Like the anterior cingulate, prefrontal regions, and temporal areas have also been implicated in language aspects of emotions (Anderson et al. 2010; Hesling et al. 2010), disturbances in these areas may also reflect more specific difficulties to put feelings into words (Aleman 2005).

In addition, the alexithymic group showed stronger connectivity to areas implicated in sensory input, namely the precentral gyrus and occipital areas. One could speculate that higher connectivity with sensory areas is consistent with the action-oriented tendencies of alexithymic people and a tendency towards strong bodily expressions of emotions (Sifneos 1973; Taylor et al. 1991; Taylor et al. 1997). Supporting our findings, alexithymic participants showed higher activation in sensory and motor areas (Karlsson et al. 2008), and altered activation of visual areas (Karlsson et al. 2008; Mantani et al. 2005) during viewing of emotional pictures. Participants with lower emotional complexity showed higher activation in action-oriented brain areas, such as the precentral gyrus, during animated 'social' interactions (Tavares et al. 2011).

The alexithymia group also showed higher connectivity in right-sided prefrontal regions. These areas have been implicated in emotional control

including suppression (Goldin et al. 2008; Reker et al. 2009; Silani et al. 2009). Ochsner hypothesized that cognitive reappraisal may involve verbalizing strategies resulting in more left sided activation whereas other emotion regulation strategies such as suppression - more often used by alexithymic persons (Swart et al. 2009) - may lead to right sided frontal involvement (Ochsner et al. 2002). Of note, it has been shown that reduction of emotional arousal by affect labeling is mediated by the right vLPFC (Lieberman et al. 2005; Lieberman et al. 2007), which does not fit our hypothesis. However, this topic should need further investigation in relation to alexithymia.

On a final note, some brain areas that showed altered connectivity in our study were not core parts of the DMN. Supporting our results, He et al. reported that these areas, such as precentral gyrus and lateral frontal areas, show a synchronized activation with the DMN (He et al. 2004).

In conclusion, the alexithymic group demonstrated a higher connectivity with right-sided prefrontal regions and sensory areas. These areas have been associated with emotion suppression and a more action-oriented focus. However, the high alexithymic group showed less connectivity with frontal areas of the DMN. We suggest that such distinct patterns of connectivity may be related to the diminished emotional awareness of alexithymic people.

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7. Two sub-domains of negative symptoms in schizophrenia: A two-factor model established and confirmed in two large cohorts

Submitted

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Abstract

Introduction: Negative symptoms of schizophrenia are normally grouped into a single category. However, the diversity of such symptoms suggests that they are actually made up of more than one dimension. The DSM-V proposes two negative symptom domains, namely expressive deficits and avolition/asociality. We investigated whether the negative symptoms do indeed have two dimensions. **Methods:** An exploratory factor analysis was carried out based on interviews with the PANSS (664 patients). We restricted our analysis to items that had been described as negative symptoms in previous factor analyses. The symptom structure was then tested for stability by performing a confirmatory factor analysis on PANSS interviews from a separate cohort (2,172 patients). **Results:** Exploratory factor analysis yielded a two-factor structure of negative symptoms. The first factor consisted of PANSS items Flat affect, Poor rapport, Lack of spontaneity, Mannerisms and posturing, Motor retardation, and Avolition. The second factor consisted of Emotional withdrawal, Passive/apathetic social withdrawal, and Active social avoidance. **Discussion:** The first factor could be related to expressive deficits, reflecting a loss of initiative, and the second factor to social amotivation, related to community interaction. This factor structure supports the DSM-V classification, and may be relevant for pathophysiology and treatment of schizophrenia and other psychotic disorders.

Introduction

The symptoms of schizophrenia and other psychotic disorders are often categorized into three main domains: positive symptoms, negative symptoms, and cognitive impairments (American Psychiatric Association 2000; Mueser and McGurk 2004). Negative symptoms have been defined as an absence of normal behaviors, including flattened emotional response, poverty of speech, lack of initiative, lack of pleasure, and social withdrawal (Andreasen and Flaum 1991). They are difficult to treat and are an important predictor for poor social outcome in schizophrenia (Pinkham et al. 2003).

The current DSM-IV considers negative symptoms as one dimension. However, instruments like the Scale for Assessment of Negative Symptoms (SANS)

or the Positive and Negative Syndrome Scale (PANSS) show considerable heterogeneity in items measuring negative symptoms (Andreasen 1983; Kay et al. 1987). This wide range of symptoms, hitherto classified as one group, may in fact reflect different subgroups, with each a different neural, social, or psychological etiology (Keefe et al. 1992). The new DSM-V proposes a two-subdomain model of negative symptoms, with one domain related to expressive deficits including affective, linguistic and paralinguistic expressions, and the second domain related to avolition for social activities (Kirkpatrick and Fischer 2006; Messinger et al. 2011). Such a classification with two subgroups could have important implications for research, diagnostics, and treatment (Blanchard and Cohen 2006; Messinger et al. 2011).

Negative symptoms have always been the 'pièce de résistance' in treatment. Recently some evidence is emerging that treatment with modafinil may have beneficial effects on negative symptoms (Arbabi et al. 2011), mainly restricted to the anhedonia-asociality item of the SANS (Bobo et al. 2011). Cognitive behavioral therapy is reported to be effective in improving motivation, apathy, and social participation (Grant et al. 2011). Thus, these treatments may address different biological and psychological issues of the group of negative symptoms. Instruments that reliably distinguish these two distinct subgroups of symptoms could be supportive for the research into treatment strategies aimed at negative symptoms.

One way to investigate whether negative symptoms comprise more than one symptom domain is to assess the correlational structure of the measures by factor analysis (Blanchard and Cohen 2006; Stevens 1996; Tabachnik and Fidell 2007). Factor analyses have already established that negative symptoms comprise a separate domain within the full symptom range seen in schizophrenia and related psychotic disorders (Blanchard and Cohen 2006; Van der Gaag et al. 2006a; Van der Gaag et al. 2006b). However, the concept of negative symptoms is still heterogeneous, and previous studies with factor analysis have shown that there may be two (or three) subdomains (Blanchard and Cohen 2006; Kirkpatrick and Fischer 2006; Kirkpatrick et al. 2006; Peralta and Cuesta 1995).

So far, most studies on the structure of negative symptoms have used the Scale for Assessment of Negative Symptoms (SANS) - (Andreasen 1983). Since inferences based on one symptom scale are limited (Blanchard and Cohen 2006), replication with the Positive and Negative Syndrome Scale (PANSS) – a widely used instrument (Foussias and Remington 2010) – could increase the construct validity. The PANSS and the SANS have a considerable overlap in how they measure symptoms, but the specific set of symptoms they measure differs (Lyne et al. 2012; Rabany et al. 2011), which makes the PANSS an interesting addition to factor analysis findings on the SANS. In addition, most previous factor analyses were performed on relatively small samples ($n < 200$) and only on patients with substantial evident negative symptoms.

Although negative symptoms often constitute one factor in factor analysis of the whole PANSS (Van der Gaag et al. 2006a; Van der Gaag et al. 2006b), this negative symptom factor appears to be unstable or sometimes even split (Blanchard and Cohen 2006; Lindström and Von Knorring 1993; Van den Oord et al. 2006). In factor analysis the number of factors is often predefined or based on variance measures. When the number of factors is set to low, this could force all negative symptoms in one factor, while they should actually constitute multiple factors {{244 Blanchard,J.J. 2006}}.

The aim of this study is to examine the negative symptom structure and its resemblance to the model proposed by the DSM-V in large, unselected groups of patients with a psychotic disorder. We focus on PANSS items already related to negative symptoms. Exploratory factor analysis (EFA) will be applied to reveal the underlying structure of the symptoms, and confirmatory factor analysis (CFA) will be performed in a separate, large sample to determine the robustness of the factor structure (Blanchard and Cohen 2006).

Methods

Study Samples

All data used in this study were handled anonymously, and all subjects gave oral and written informed consent. Research was approved by the local ethical committee. Most patients in the study samples were outpatient, recently

diagnosed with a psychotic disorder (American Psychiatric Association 2000). A diagnosis of schizophrenia could not always been given at this point, because of the often short duration of illness.

For the EFA, a cohort of 664 cases from the province of Groningen (Early Psychosis Outcome Groningen, EPOG), the Netherlands, was used. These patients followed a clinical assessment for diagnostic purposes at the department of psychotic disorder in the University Center Psychiatry in Groningen.

For the CFA, we used an independent sample of 2,172 cases, comprising three subsamples. The first group comprised a nationwide, longitudinal study: Genetic Risk and Outcome of Psychosis (GROUP) of persons aged 18 – 50 years, Dutch speaking, and on stable antipsychotic treatment (> 1 month). They all had a diagnosis of non-affective psychotic disorder (schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, psychotic disorder NOS; DSM-IV). The second group consisted of subjects with a first episode of psychosis and treated at the Academic Medical Centre, Amsterdam. The third group was a cohort from the University Medical Center Utrecht, the Netherlands, who undertook a PANSS interview for clinical or research purposes.

The demographic variables are presented per cohort to provide a general overview of the samples (Table 19). Given that the data was collected for diagnostic purposes in the first place, not all demographic information was fully available. Age and PANSS scores (not normally distributed) were tested with a Mann-Whitney U test between the EFA and CFA cohorts Gender and primary diagnosis were tested with a Chi-squared test for independence.

Study Design

The PANSS is a diagnostic interview with three parts: Positive symptoms (7 items), Negative symptoms (7 items) and General pathology (16 items) (Kay et al. 1987). The interviews were administered by experienced raters who had, at minimum, participated in an annual consensus training (inter-rater reliability > 0.8).

Table 19 Overview of the cohorts' demographic data; The EPOG cohort was used for the exploratory factor analysis, the GROUP cohort and the Utrecht (UTR) and Amsterdam (AMS) cohorts were combined for the confirmatory factor analysis; '-' indicates data was not available, some percentages do not reach 100% because only part of the data was available for these categories; 'X' indicates that a category was not present for that particular dataset

		EPOG N = 664	GROUP N = 1288	AMS N = 375	UTR N = 658
Age	mean (SD)	27.7 (8.9)	27.7 (8.1)	21.7 (5.5)	32.0 (9.8)
Gender	(% male)	73	76	78	60
Highest education level	primary school	18	12	2	1
	special education	x	12	2	7
	secondary school (low levels)	28	19	31	7
	high school	20	24	20	10
	vocational education	18	17	21	19
	vocational education (high)	8	9	8	17
	university	5	4	11	1
	none	1	1	x	2
Maritial status (%)	not married	90	82	-	42
	married	5	9	-	14
	divorced	4	3	-	1
Household (%)	independent alone	38	31	-	x
	with parent(s)	34	36	-	39
	with partner/family	12	9	-	79
	mental health institute	3	9	-	40
	other	12	6	-	x
Primary diagnosis (%)	schizophrenia	42	65	52	24
	schizoaffective	5	11	10	2
	schizophreniform	8	6	10	2
	psychotic disorder	20	14	16	4
	substance abuse	6	1	4	1
	depression/bipolar	9	2	5	9
	other	7	2	3	34
Employment (%)	employed	45	53	58	31
	unemployed	30	24	28	7
	student	16	37	x	16
	other	7	x	x	1
Antipsychotic (%)	none / not applicable	19	11	-	x
	risperidone	29	18	-	4
	olanzapine	28	22	-	10
	quetiapine	4	5	-	3
	clozapine	1	8	-	5
	aripiprazol	2	6	-	2
	strong DA-antagonist	16	10	-	3
PANSS total	mean (SD)	56.7 (12.6)	56.7 (16.1)	65.5 (20.3)	48.0 (18.9)
PANSS Positive	mean (SD)	12.6 (4.8)	12.6 (4.8)	16.2 (6.7)	11.8 (5.7)
PANSS Negative	mean (SD)	14.3 (6.0)	14.3 (6.0)	16.0 (6.7)	12.1 (6.1)
PANSS General	mean (SD)	29.7 (8.1)	30.0 (8.1)	33.3 (10.5)	24.3 (8.9)

We choose to do a data-driven, non-biased selection of items that reflect negative symptoms in the PANSS. To accomplish this, we selected items that had been identified as negative symptoms in factor analysis of the whole PANSS, and that also showed a moderate correlation with other negative symptoms. To identify items of previous factor analyses, a literature search was conducted in PubMed using the search terms: “factor analysis OR factor structure AND PANSS”. All retrieved studies were searched for cross-references: 33 studies that reported on a negative symptom factor in the PANSS were identified (Bell et al. 1992; Bell et al. 1994; Davis and Chen 2001; Dollfus and Petit 1995a; Dollfus and Petit 1995b; Drake et al. 2003; Emsley et al. 2003; Fitzgerald et al. 2003; Fredrikson et al. 1997; Fresan et al. 2005; Higashima et al. 1998; Kawasaki et al. 1994; Kay and Sevy 1990; Lancon et al. 1998; Lancon et al. 1999; Lancon et al. 2000; Lancon et al. 2000; Lee et al. 2003; Lindenmayer et al. 1994a; Lindenmayer et al. 1994b; Lindenmayer et al. 2004; Lindström and Von Knorring 1993; Loas et al. 1997; Lykouras et al. 2000; Lépine et al. 1989; Mass et al. 2000; Rapado-Castro et al. 2010; Reichenberg et al. 2005; Van der Gaag et al. 2006a; Vilaplana et al. 2007; White et al. 1997; Wolthaus et al. 2000). PANSS items N5 Abstract thinking and N7 Stereotyped thinking from the original Negative subscale of the PANSS, were seldom (both 3 times) reported as a negative symptom by these factor analyses and showed a correlation of < 0.3 to the other negative symptoms, and were therefore not considered further in our analysis.

Further selection was based on correlations of N1, N2, N3, N4 or N6 with other PANSS items. A factor analysis requires items to have a moderate, positive inter-correlation (Stevens 1996; Tabachnik and Fidell 2007). A correlation matrix with Spearman’s correlations of all items from the EPOG-database was created. Items showing a correlation of > 0.3 for at least three times with N1, N2, N3, N4 or N6 were selected for further analysis. Based on the above criteria, the following were selected for factor analysis: N1 Flat affect, N2 Emotional withdrawal, N3 Poor rapport, N4 Passive/apathetic social withdrawal, N6 Lack of spontaneity, G5 Mannerisms and posturing, G7 Motor retardation, G13 Avolition, and G16 Active social avoidance.

Exploratory factor analysis

Items selected according to the above criteria were entered into an EFA (Principal Axis Factoring) using Statistical Package for Social Sciences (SPSS 16). The factor analysis was based on the correlation matrix of the items. The Kaiser-Meyer-Oklin (KMO) and Bartlett`s test for sphericity were calculated. The number of factors was not fixed beforehand, but factors were only retained when they showed an eigenvalue of > 1. Items within a factor were only retained with a factor loading of > 0.3. After factor estimation, both Direct Oblimin rotation with Kaiser Normalization and Varimax was applied. The Oblimin solution was reported because we expected the factors to be correlated (Tabachnik and Fidell 2007).

Confirmatory factor analysis

We then performed a CFA in LISREL 8 (Jöreskog and Sörbom 2011) to investigate the fit of the model identified by EFA. Because of non-normality, an asymptotic covariance matrix was used for estimation and comparative fit indices were used instead of the traditional Chi-square values (Hu and Bentler 1998; Lei and Lomax 2005; Powel and Schafer 2001; Yuan and Bentler 1998). The factors identified by EFA were entered as latent variables in the CFA and the PANSS items were entered as observed variables. The maximum likelihood method was used for estimation (Van der Gaag et al. 2006a). We used multiple indices to measure goodness-of-fit: the Comparative Fit Index (CFI > 0.9), the Goodness-of-Fit index (GFI > 0.9), the Root Mean Square of Approximation (RMSEA < 0.06), the Root Mean Square of Residuals (RMR < 0.05), and an unstandardized factor loading > 2 * standardized factor loading (Albright and Park 2009; Hu and Bentler 1998; Marsch et al. 2004). Correlated measurement errors were introduced into the model based on significant correlated residuals indicated by modification indices. Improvement of the model and the impact of correlated measurement errors were assessed in this way.

Many factor analyses on the PANSS focused on schizophrenia, while our focus was on psychotic disorders. To investigate whether this broader diagnostic inclusion affected the structure of symptoms, the CFA was repeated with patients with a DSM-IV diagnosis of schizophrenia from the GROUP database. Correlated residuals were also introduced in the resulting CFA model, but similar to the

model with all diagnoses included. The goodness-of-fit measures both CFA models on schizophrenia were compared to the original models without and with correlated residuals respectively.

Results

First, socio-demographic data of the cohorts were inspected and the EFA and CFA groups were compared (Table 19). The age of the subjects ranged mostly between 20 and 30 years, and 60 - 78% were male. Most subjects had a primary diagnosis of schizophrenia or a psychotic disorder. Subjects from the Amsterdam cohort were generally younger and subjects from the Utrecht cohort had lower PANSS scores. The cohorts for EFA and CFA showed no significant difference in age (p = 0.20), gender (p = 1), or diagnosis (p = 0.23). PANSS original subscales (Positive symptoms, Negative symptoms and General Pathology, defined by Kay et al. (Kay et al. 1987) were significantly different between the various samples (all p < 0.005), but the differences were not regarded as clinically relevant.

Table 20 Factor Structure of Factor Analysis on Items N1, N2, N3, N4, N6, G5, G7, G13, and G16 of the PANSS after Varimax Rotation; Bold values indicate that the item loaded strongest on this factor

	Factor 1		**Factor 2**	
	Unrotated loading	**Rotated loading**	**Unrotated loading**	**Rotated loading**
N6 Lack of spontaneity	**0.756**	**0.807**	0.357	0.202
N3 Poor rapport	**0.744**	**0.759**	0.297	0.257
N1 Flat affect	**0.713**	**0.594**	0.080	0.403
G7 Motor retardation	**0.645**	**0.571**	0.124	0.325
G5 Mannerisms and posturing	**0.443**	**0.460**	0.189	0.144
G13 Avolition	**0.435**	**0.406**	0.117	0.194
N4 Passive/apathetic social withdrawal	0.807	0.287	**-0.503**	**0.906**
N2 Emotional withdrawal	0.777	0.386	**-0.315**	**0.744**
G16 Active social avoidance	0.431	0.158	**-0.261**	**0.478**

Exploratory factor analysis

Inspection of a histogram of the data and a Q-Q plot showed a non-normal, left-skewed distribution. Factor analysis on EPOG (n = 644) resulted in a Kaiser-Meyer-Oklin (KMO) of 0.85 (excellent) and a significant result for the Bartlett`s test for sphericity (Chi = 2598.9; p < 0.005), indicating that the correlation matrix was suitable for factor analysis. A two-factor solution indicated an eigenvalue > 1 (60% of the variance explained) with all factor loadings above 0.3. Communalities were all above 0.3, indicating that all items explained a substantial amount of variance. The two factors had a strong, negative correlation of –0.64, indicating the Oblimin solution should also be reported. The Varimax solution (Table 20) showed that, after rotation, items loaded preferably either on Factor 1 or Factor 2. The Oblimin rotation (Table 21) resulted in one factor with items loading the strongest in the positive direction, while Factor 2 items loaded the strongest in the negative direction.

Table 21 Factor Structure of Factor Analysis on Items N1, N2, N3, N4, N6, G5, G7, G13 and G16 of the PANSS after Oblimin Rotation; The unrotated solutions are identical to the unrotated Varimax solution; Bold values indicate that the item loaded strongest on this factor

	Factor 1		**Factor 2**	
	Pattern coefficient	**Structure coefficient**	**Pattern coefficient**	**Structure coefficient**
N6 Lack of spontaneity	**0.896**	**0.833**	0.099	-0.472
N3 Poor rapport	**0.822**	**0.801**	0.033	-0.491
N1 Flat affect	**0.577**	**0.697**	-0.219	-0.575
G7 Motor retardation	**0.563**	**0.649**	-0.135	-0.494
G5 Mannerisms and posturing	**0.503**	**0.481**	0.034	-0.286
G13 Avolition	**0.416**	**0.449**	-0.510	-0.316
N4 Passive/apathetic social withdrawal	-0.033	0.586	**-0.971**	**-0.950**
N2 Emotional withdrawal	0.158	0.623	**-0.729**	**-0.830**
G16 Active social avoidance	-0.10	0.315	**-0.510**	**-0.504**

Confirmatory factor analysis

The CFA was based on a merged sample of three databases (GROUP, Amsterdam, Utrecht) of 2,172 cases. A model was created based on the results of the EFA (Figure 21). The CFA by LISREL indicated a moderate fit if correlated residuals were not introduced into the model. The following goodness-of-fit indices were obtained (with criteria for a good fit given in brackets): CFI = 0.99 (> 0.9), GFI = 0.99 (> 0.9), RMSEA = 0.063 (< 0.06), RMR = 0.071 (< 0.05), and unstandardized factor loading/standardized factor loading > 2 (> 2). Next, significantly correlated residuals (measurement errors) were introduced into the model to improve the fit (Cole et al. 2011; Gerbing and Anderson 1984), see Table 22 for factor loadings and Figure 21. This model resulted in the following fit: CFI = 1.0 (> 0.9), GFI = 1.0 (> 0.9), RMSEA = 0.015 (< 0.06), RMR = 0.015 (< 0.05), and unstandardized factor loading/standardized factor loading > 2 (> 2). These indices indicate a good fit of the model when correlated residuals were introduced.

Table 22 Factor Loadings of the CFA with the included correlated measurement errors; Bold values indicate that the item loaded strongest on this factor

	Factor 1 loading	**Factor 2 loading**
N6 Lack of spontaneity	0.83	-
N3 Poor rapport	0.85	-
N1 Flat affect	0.87	-
G7 Motor retardation	0.75	-
G5 Mannerisms and posturing	0.57	-
G13 Avolition	0.75	-
N4 Passive/apathetic social withdrawal	-	0.96
N2 Emotional withdrawal	-	1.02
G16 Active social avoidance	-	0.76

The CFA was repeated in a sample of 845 cases with a DSM-IV diagnosis of schizophrenia from the GROUP database. The following goodness-of-fit indices were obtained in the model without introduced correlated residuals: CFI = 0.98, GFI = 0.99, RMSEA = 0.070, RMR = 0.079. In the model with correlated residuals the following values were obtained: CFI = 1.0, GFI = 1.0, RMSEA = 0.0082, RMR =

0.019. The CFA analyses with the schizophrenia group showed similar results to the analyses on the whole sample, both with and without correlated residuals.

Discussion

We found that a two-factor model represents negative symptoms better than a single factor, albeit that the two factors are correlated. We confirmed this two-factor model by CFA in a separate cohort and demonstrated that the model is not restricted to a diagnosis of schizophrenia, but also fits for psychotic disorders. The first factor of the model comprises items that show similarity to the "expressive deficits" domain of DSM-V, with the highest factor loadings on Flat affect (N1), Poor rapport (N3), and Lack of spontaneity (N6). In the second factor, the items resembled aspects of the "social amotivation" domain of DSM-V, with the highest loadings on Emotional withdrawal (N2) and Passive/apathetic social withdrawal (N4).

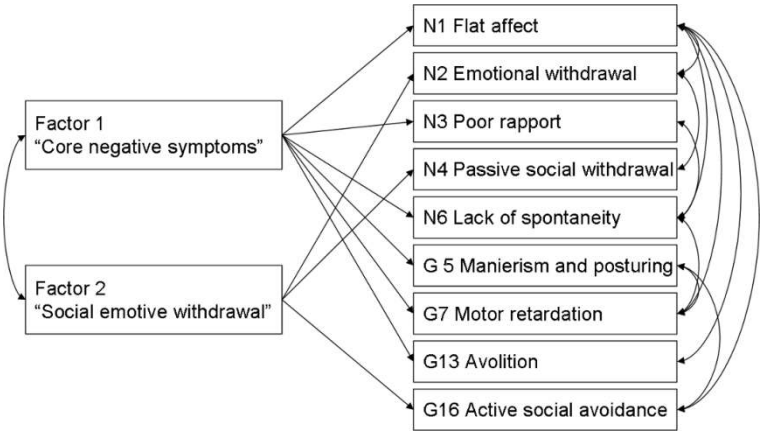

Figure 21 The factor model created for the confirmatory factor analysis (CFA) based on the results of the exploratory factor analysis (EFA); The two boxes on the left indicate our factors, the boxes on the right indicate the PANSS items connected to their corresponding factor by arrows, and the arrows connecting the right-hand boxes indicate the correlated residuals introduced into the model; Each item also has its own error term, but these are not shown for simplicity

Our two-dimension structure of negative symptoms provided good support for the two negative symptom domains proposed in the DSM-V (Messinger et al. 2011) and agrees with earlier proposed symptom models (Keefe et al. 1992; Kirkpatrick et al. 2001). Moreover, the two-factor division determined by PANSS

robustly extends the results of other studies suggesting two negative symptom domains that were mainly based on SANS (Bell et al. 2011; Blanchard and Cohen 2006; Foussias and Remington 2010; Keefe et al. 1992; Kimhy et al. 2006; Kirkpatrick et al. 2006; Lindström and Von Knorring 1993; Messinger et al. 2011; Peralta and Cuesta 1995; Van den Oord et al. 2006).

Of note, Avolition (G13) would conceptually also fit Factor 2, social avolition/amotivation. Indeed, Avolition loaded relatively high on Factor 2 of our EFA. Factor analysis is a data-driven method, and multiple aspects may influence the factor loading of items. In this case, the rating of PANSS item G13 Avolition is merely based on observed behavior during the interview, and the item may be rated as disturbance in willful initiation of behavior and thereby load the "expressive behavior factor".

For the negative symptom model as identified in our study, the CFA showed a low loading or poor fit of PANSS item Mannerisms and posturing (G5). But as excluding it did not improve the CFA fit and the item showed a loading of > 0.4 in the EFA, we retained the item in the model. In the DSM-V, this item would probably fit better in the abnormal psychomotor behavior. In addition, the Motor retardation (G7) and Avolition (G13) items also loaded lower on Factor 1, possibly because they originate from the General Pathology subscale of the PANSS.

The fit of the CFA improved when we added a correction for measurement errors to the model. An explanation could be that, although the interviewers were well-trained, some PANSS items may have a common origin that is difficult to disentangle and thus rated in multiple items (Cole et al. 2007; Gerbing and Anderson 1984), e.g. reduced movement could be rated as Flat affect (N1), Mannerism and posturing (G5), or Motor retardation (G7).

Some authors have speculated that the "expressive deficits" factor may reflect directly apparent symptoms that change quickly over time, while the "social amotivation" factor reflects the status of social relationships that may change more slowly (Blanchard and Cohen 2006; Foussias and Remington 2010; Keefe et al. 1992). Moreover, the first group of symptoms is rated as directly observed behavior, while the social items are based on reports from family

members and nursing staff (Messinger et al. 2011). Indeed, directly observed behavior – Poor rapport and Lack of spontaneity – show the highest loading on Factor 1 and thus have the strongest impact in this factor.

"Social amotivation" may be due to a diminished capacity of patients to anticipate pleasurable events, despite intact hedonic consumption (Foussias and Remington 2010; Oorschot et al. 2011). This explanation finds support in the strong loading of Emotional and apathetic withdrawal. Moreover, the "social amotivation factor" could, besides interest, also include aspects of social performance, based on engagement in social situations (Keefe et al. 1992; Oorschot et al. 2011). This factor was first discerned during treatment with atypical antipsychotics, whereas (high dosage) classic antipsychotics may have obscured the two subdomains (Van den Oord et al. 2006).

Negative symptoms and depressive symptoms are often considered to be associated (Fitzgerald et al. 2002; Lako et al. 2011). Additional analysis in this study showed no association between depression and negative symptoms (results not shown), while previous factor analyses also showed no loading of Depression (G6) on the negative symptom factors. Thus, the "expressive deficits" factor may be more a reflection of apathy than of depression. Research using scales specifically designed for assessing apathy (Clarke et al. 2011) or depression (Lako et al. 2011) could further corroborate this.

A unique strength of our study is its large sample size and its replication in large, independent cohorts. CFA is a complicated procedure and depends strongly on the underlying data structure (Van der Gaag et al. 2006a), thus our confirmation of the negative symptom structure can be considered quite robust. In addition, this study is the first to replicate findings of studies on the SANS by using the PANSS. This is a useful addition, as the PANSS is more frequently used in research settings and clinical practice, and it also covers a broader range of symptoms (Fitzgerald et al. 2001; Van den Oord et al. 2006).

However, some limitations should be mentioned. The two-factor structure may be an artifact, because the first factor includes symptoms rated by the interviewer during the interview, while the second factor includes social activities outside the interview room (Blanchard and Cohen 2006). In this study, patients

were relatively young and often in the early stages of their illness, with only 25% suffering from more severe negative symptoms (PANSS items > 3). This limits our ability to draw conclusions about symptom dimensions in, for example, chronically ill samples. Lastly, the two factors show a considerable association with each other and may partly overlap. But because of the extensive support from earlier findings, the two factors have good construct validity.

In conclusion, our results support the two subdomains proposed in the DSM-V. The first subdomain is related to the "expressive deficits", while the second could be described as a "social amotivation" factor. Negative symptoms are difficult to treat and the pathophysiology remains poorly understood. By acknowledging the two dimensions that have now emerged robustly from the factor structure of systematic assessments, the effects of interventions may be assessed with greater precision (Blanchard and Cohen 2006; Kirkpatrick et al. 2006). Research into their differential pathophysiology, e.g. using neuroimaging, could advance our understanding of these debilitating symptoms further (Bell et al. 2011).

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8. Antipsychotic medication and prefrontal cortex activation: A review of neuroimaging findings

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Abstract

Introduction: Decreased prefrontal activation (hypofrontality) in schizophrenia is thought to underlie negative symptoms and cognitive impairments, and may contribute to poor social outcome. Hypofrontality does not always improve during treatment with antipsychotics. We hypothesized that antipsychotics, which share antagonism at dopamine receptors, with a relatively low dopamine receptor affinity and high serotonin receptor affinity may have a sparing effect on prefrontal function compared to strong dopamine receptor antagonists. **Methods:** We systematically investigated the relation between serotonin and dopamine antagonism of antipsychotics and prefrontal functioning by reviewing neuroimaging studies. **Results:** The weight of the evidence was consistent with our hypothesis that antipsychotics with low dopaminergic receptor affinity and

moderate to high serotonergic affinity were associated with higher activation of the prefrontal cortex. However, clozapine, a weak dopamine and strong serotonin antagonist, was associated with decrease in prefrontal activation. **Discussion:** Future studies should further elucidate the link between prefrontal activation and negative symptoms using prospective designs and advanced neuroimaging techniques, which may ultimately benefit the development of treatments for disabling negative symptoms.

Introduction

Schizophrenia is a severe and complex psychiatric disorder that causes pervasive impairments in social and occupational functioning. The disorder is characterized by positive symptoms, negative symptoms, and cognitive impairments (Mueser and McGurk 2004). Positive symptoms include hallucinations and delusions. Negative symptoms can be described as the absence of normal behavior, such as a flattened emotional response, poverty of speech, lack of initiative, lack of pleasure, and social withdrawal (Andreasen 1982). Cognitive impairments pertain to memory, attention, verbal fluency, executive function, and social-emotional function (Aleman et al. 1999; Aleman 2005; Heinrichs and Zakzanis 1998; Pinkham et al. 2003).

Although positive symptoms generally respond well to pharmacological interventions, negative and cognitive symptoms do not: they show minimal improvement, no change or even a worsening due to treatment with antipsychotic drugs. Importantly, negative symptoms and cognitive impairments predict persistent difficulties in social interactions, vocational functioning, and independent living (Barch et al. 1998; Gold et al. 1997).

Brain imaging techniques like functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and single photon emission computed tomography (SPECT) are valuable tools to deduce abnormal activity of large cerebral areas such as the frontal lobe. Using these techniques, negative symptoms and cognitive impairments have both been associated with hypoactivation of the prefrontal cortex (PFC) (Wang et al. 2008; Weinberger and Berman 1996). This review focuses specifically on hypofrontality because it

appears to be the basis of the often treatment resilient negative and cognitive symptoms. Frontal hypoactivation is defined as an impaired increase in blood flow during cognitive tests that require frontal function in fMRI, HMPAO-SPECT or H_2O-PET studies, or as a decrease of glucose metabolism in ^{18}F-FDG PET imaging studies.

Early studies imaging blood flow have shown that both medication free and chronically medicated patients with schizophrenia had less activation in the dorsolateral prefrontal cortex (Ingvar and Franzen 1974; Weinberger et al. 1986). This so-called hypofrontality was confirmed in a number of subsequent studies (Hazlett and Buchsbaum 2001; Molina et al. 2005; Rieheman et al. 2001), but others failed to find it or even reported hyperfrontality (e.g. Parellada et al. 2003; Schneider et al. 2005; Soyka et al. 2005). Three meta-analyses (Davidson and Heinrichs 2003; Glahn et al. 2005; Hill et al. 2004) concluded that hypofrontality is a feature of schizophrenia, both during rest and during task performance. Differences between individual studies have been related to difficulty of tasks used, because hypofrontality is often shown for moderately difficult tasks, but less frequently for simple or difficult tasks (Carter et al. 1998; Liddle and Pantelis 2003; Perlstein et al. 2001).

The prefrontal cortex is very rich in dopaminergic receptors and they are thought to play a crucial role in the action of antipsychotics, which all have antagonistic action at dopamine (DA) receptors. Weinberger et al. showed that higher DA levels in the cortex of patients were related to higher prefrontal activation (Weinberger et al. 1988). Moreover, the DA releaser D-amphetamine improves task performance and PFC function in patients (Daniel et al. 1991). Likewise, subjects with a certain gene polymorphism, resulting in less efficient DA metabolism, showed more efficient prefrontal activation (Egan et al. 2001). Overall, these findings are consistent with the notion that impaired prefrontal DA transmission may be related to hypofrontality (Chen et al. 1997).

So-called first generation or classical antipsychotics such as chlorpromazine and haloperidol are potent blockers of DA receptors, especially postsynaptic D_2 receptors, but the prefrontal cortex also contains a high concentration of D_1

receptors, blockade of which may also hamper prefrontal activation (Tausscher et al. 2004). Antipsychotic reduction of DA signaling in the brain affecting D_2 receptors is thought to underlie reduction of positive symptoms, and have no influence or detrimental effect on negative symptoms. These effects inspired dopamine hypotheses of schizophrenia: a hyperdopaminergic state in mesolimbic pathways (projecting to the striatum), combined with a hypodopaminergic state mesocortical pathways (projecting to the prefrontal cortex). Because the prefrontal cortex possibly already has low dopamine levels, additional D_2 receptor blockade may contribute to negative symptoms and cognitive impairments (Abi-Dargham and Laruelle 2005).

Clozapine, a weak dopamine antagonists but potent 5-HT_{2A} antagonist that targets many other receptors, was the first antipsychotic demonstrating appreciable efficacy against negative symptoms and possibly cognitive impairments (Bishara and Taylor 2008; Sharafi 2009). Clozapine's receptor profile presumably holds the key to its special effectiveness, but the exact mechanisms have remained elusive. All antipsychotics developed since clozapine are often grouped as ‘atypical’ or second-generation antipsychotics, though the receptor profiles within this group are very diverse. Some mimic the low D_2 receptor affinity of clozapine (quetiapine), others are stronger postsynaptic DA antagonists (risperidone, olanzapine). The primary uniting property of this generation of ‘atypical’ drugs is strong antagonism at serotonin (5-HT) receptors (Kapur et al. 1999; Meltzer et al. 2003). 5-HT2A antagonism may directly (Amargós-Bosch et al. 2006; Goldman-Rakic and Selemon 1997) or indirectly via dopamine (Busatto and Kerwin 1997; Lee et al. 1994; Weinberger et al. 1986) enhance prefrontal activation.

Three alternative neuropharmacological hypotheses for efficacy against hypofrontality and ultimately negative symptoms have been proposed. First, the antipsychotics should have a low dopamine receptor affinity (Abi-Dargham and Laruelle 2005; Jarskog et al. 2007) or show rapid dissociation from the D_2 receptor (Kapur and Seeman 2001). A second hypothesis was that high 5-HT receptor affinity relative to dopamine receptor affinity was sufficient (Sipes and Geyer 1995). However, this effect was only tenable in animal studies (Gozzi et al. 2010)

but not in human studies (Nyberg and Farde 1997). Thirdly, an interaction of weak D_2 and stronger 5-HT_{2A} receptor antagonism was thought to relieve both positive and negative symptoms (Abi-Dargham and Laruelle 2005; Da Silva Alves et al. 2008). Blockade of serotonin leads to increased dopamine levels in especially the mesocortical dopamine system (Busatto and Kerwin 1997) and induces prefrontal DA release and prefrontal activity in animal studies (Pehek 1996).

We conducted a literature review of imaging studies in frontal functioning. We expected that antipsychotics with high D_2 receptor affinity would decrease activation of the prefrontal cortex while antipsychotics with low D_2 affinity would increase it. Secondly, we expected that high 5-HT_{2A} receptor affinity in addition to lower dopamine receptor affinity would also help to preserve prefrontal activation. In sight in mechanisms underlying pharmacological influence on hypofrontality may ultimately facilitate improvement of negative symptoms and cognition.

Methods

The scientific literature was searched for studies on the effects of antipsychotics on prefrontal activity, using fMRI measuring blood oxygen level dependent (BOLD) effects, or with PET and SPECT measuring regional cerebral blood flow (rCBF) or fluorodeoxyglucose (FDG) uptake. PET with [^{18}F]-FDG measures glucose consumption, while BOLD fMRI, [^{15}O]-H_2O PET and HMPAO SPECT measure blood flow. Blood flow is a more indirect measure of metabolism than glucose consumption, and may therefore give different results. Time resolution is also different. fMRI can measure effects in seconds, while rCBF PET may take minutes, and [^{18}F]-FDG PET and SPECT only give static pictures of a whole acquisition. Differences in imaging result due to imaging modality were evaluated.

The main topic of the studies had to be the effect of antipsychotics on brain activation and cover information regarding activation of the prefrontal cortex, or regarding cognitive functions that have been implicated in frontal cortex functioning (working memory, learning, emotion processing, attention, verbal fluency, and executive functioning). The study population had to include patients

with schizophrenia or related disorders (e.g. schizophreniform disorder, schizoaffective disorder) that were treated with antipsychotics. Single dose studies and depot treatment were excluded, as were studies that included subjects taking both strong and weak DA antagonists in one group, or studies that did not report antipsychotic drug dosage. PubMed and Web of Science (ISI, Thomson Reuters) were searched until May 2010 with the following search terms: antipsychotic* AND (*MRI OR PET OR SPE*T) AND schizophren*. Studies that met the criteria were scanned for cross-references and eventually 31 studies fulfilled the criteria (See Table 23).

To characterize the binding profile of antipsychotics for our purposes, D_2 and 5-HT_{2A} receptor affinity were considered. Affinity was considered a useful measure of receptor effects because all antipsychotics except aripiprazole lack intrinsic activity at D_2 and 5-HT_{2A} receptors: i.e. they are antagonists. Receptor affinity was defined as the dopamine dissociation constant K_i measured as the equilibrium concentration at which dissociation of the antipsychotic is equal to a dopamine antagonist, in most cases the specific D_2 ligand raclopride. A lower K_i thus value means a stronger binding of the antipsychotic to the receptor.

Table 23 Overview of study characteristics included in this review; Articles are sorted based on cognitive function, and within this order on imaging modality (Technique and Measure); A clarification of abbreviations is listed below; Patients: AP = acute psychosis, CS = chronic schizophrenia, FE = first episode, S = schizophrenia, SF schizophreniform psychosis, TRS = treatment resistant schizophrenia, DF = drug free, DN = drug naive, M = medicated, PT = pretreatment, W = washout; Group/Study design: HC = healthy control, MP = medicated patient, NP = non-medicated patient, P = placebo; Study design: B = baseline, F = follow-up, S = single scan, W = wash-out; Antipsychotics: AMI = amisulpride, ARI = aripiprazole, CHLOR = chlorpromazine, CLOZ = clozapine, FLUP = flupentixol, FLUPH = fluphenazine, HAL = haloperidol, OLA = olanzapine, QUE = quetiapine, RISP = risperidone, SER = sertindole, SULP = sulpiride, THIO = thiothixene; Results: APFC = anterior prefrontal cortex, DLPFC = dorsolateral prefrontal cortex, IFG = inferior frontal gyrus, IPFC = inferior prefrontal cortex, MPFC = medial prefrontal cortex, LPFC = lateral prefrontal cortex, OPFC = orbito-prefrontal cortex, PFC = prefrontal cortex, SPFC = superior prefrontal cortex, VLPFC = ventrolateral prefrontal cortex, arrow up = higher activation, arrow down = lower activation

See next pages for table

Article	Cognitive function	Tasks	Tech.	Meas.	Patients	Group	Study design	Antipsychotics	Haldol euivalalents	Study result
Cohen e.a., 1988	attention & executive functioning	auditory discriminat. task	PET	FDG	S, DN or DF	8 MP, 16 DF	MP vs DF	FLUPH (mean: 26.1 mg)	mean: 26.1 mg	SFC ↓
Cohen e.a., 1997	attention & executive functioning	continuous performance task	PET	FDG	S, M	22 MP, 12 MP, 12 DFP, 30 HC	S, 69.6 ± 8.0, 473.8 ± 121.7, or 91.5 ± 76.4 day T	FLUPH (25.4 ± 12.5 mg), FLUPH (22.5 ± 11.6 mg), CLOZ (431.2 ± 200.8 mg)	FLUPH (25.4 + 12.5 mg), FLUPH (22.5 ± 11.6 mg), CLOZ (5.7 ± 2.7 mg)	SPFC ↓, IPFC ↓ CLOZ
Ngan e.a., 2002	attention & executive functioning	continuous letter sequence recognition task	PET	FDG	S or SF, DN	8 MP	B + 6 week F	RISP (max 6 mg)	max 6 mg	MPFC & LPFC ↓
Potkin e.a., 1994	attention & executive functioning	continuous performance task	PET	FDG	S	9 MP	B + 10 week F	CLOZ (460 mg)	6.1 mg	PFC ↓, normalized assymetrical activity
Lahti e.a., 2004	attention & executive functioning	auditory discriminat. task	PET	H_2-^{15}O	CS, 4 DF	6, (5 F)	B + F at 12 weeks + F at 11 weeks (crossover)	HAL (12 ± 4.5 mg) vs CLOZ (280 ± 135 mg)	HAL (12 ± 4.5 mg), CLOZ (3.7 ± 1.8 mg)	-
Molina e.a., 2008	attention & executive functioning	Stroop task	SPECT	rCBF	TRS	10 MP, 10 HC	4 weeks PT RISP, 6 month F	CLOZ (mean: 449.2 mg)	5.3 - 8 mg, mean: 6.6 mg	MPFC ↓
Zhao e.a., 2004	attention & executive functioning	Winconsin Card Sorting test	SPECT	rCBF	S, DF	21 MP, 40 HC	S, 8 week T	CLOZ (290 + 5 mg)	3.9 + 0.07 mg	-

Article	Cognitive function	Tasks	Tech.	Meas.	Patients	Group	Study design	Antipsychotics	Haldol equivalents	Study result
Blasi e.a., 2009	emotional processing	emotion recognition task	fMRI	BOLD	S, DN or DF	12 MP, 12 HC	4 & 8 week F	OLA (16 mg + 7 mg)	2.3 + 1 mg	VLPFC ↑↓
Fahim e.a., 2005	emotional processing	negative IAPS pictures	fMRI	BOLD	CS, M	12 MP	B + 22 week F	QUE (200 - 700 mg)	2.7 + 9.3 mg	DLFPC ↑
Stip e.a., 2005	emotional processing	sad movie	fMRI	BOLD	S, M	12 MP	B + 5.5 month F	QUE (mg; 529 + 138.9 mg)	2.7 - 9.3 mg, 7.1 + 1.9 mg	PFC ↑
Walter e.a., 2009	emotional processing	monetary reward task	fMRI	BOLD	S	16 MP, 16 HC	S, 2 week T	OLA (18 + 6.1 mg)	2.6 + 0.9 mg	VLPFC ↓
Buchsbaum e.a. 2007	learning	serial verbal learning task	PET	FDG	FE, DN	30, 22 compl.	B + 8 - 9 week F	HAL, OLA (max 20 mg)	HAL max 20 mg, OLA max 6.7 mg	PFC ↑ OLA
Buchsbaum e.a., 2009	learning	serial verbal learning task	PET	FDG	S, MP or DF	15 MP, 33 DFP, 55 HC	6 week F + 6 week F (crossover)	SER (12 - 24 mg), HAL (4 - 16 mg)	SER ?? mg, HAL 4 - 16 mg	MPFC ↑, DLPFC & APFC ↑ SER, OPFC ↑ HAL
Barlett e.a., 1991	resting state	rest	PET	FDG	CS	8 vs 12	B + 4 - 6 week F, 2 week W	HAL (max 80 mg), THIO (30 - 100 mg)	HAL max 80 mg, THIO 15 - 50 mg	PFC ↓ HAL

Article	Cognitive function	Tasks	Tech.	Meas.	Patients	Group	Study design	Antipsychotics	Haldol equivalents	Study result
Holcomb e.a. 1996	resting state	rest	PET	FDG	CS, M	12 MP	B + F at 5 and 30 days withdrawal	HAL (pre 0.3 mg/kg)	24 mg (weight 80 kg)	PFC ↑ (withdrawal)
Molina e.a., 2003	resting state	rest	PET	FDG	TRS, M, 3 weeks HAL PT	25 MP	B + 6 month F	CLOZ (600 mg)	8 mg	DLPFC ↓ correlated to improved neg.
Molina, 2005/7	resting state	rest	PET	FDG	M, 4 weeks HAL PT	23 MP, 17 NMP, 18 HC	B + 6 month F	CLOZ (477.56 ± 109.25 mg)	4 - 8 mg, mean: 6.3 ± 1.5 mg	PFC ↓
Wik e.a., 1989	resting state	rest	PET	FDG	S, DN or DF	17 MP	B + 5 - 6 week F	SULP (800 mg), CHLOR (400 mg)	SULP 7.5 mg, CHLOR ??	-
Lahti e.a., 2003	resting state	rest	PET	H_2-^{15}O	CS, DF	6, 5 at F	B + F at 12 weeks, , F at 11 weeks SG, 4 week W	HAL (12 ± 4.5 mg) vs CLOZ (280 ± 135 mg)	HAL (12 ± 4.5 mg), CLOZ (3.7 ± 1.8 mg)	VLPFC ↓, DLPFC ↑ CLOZ
Miller e.a., 2001	resting state	rest	PET	H_2-^{15}O	S or CS, DF	19, 13 MP	B + 3 week F, 3 week W	HAL (4.9 ± 2.8 mg: 0.5 –12 mg), RISP (11.2 ± 5 mg: 3 - 20 mg)	HAL (4.9 ± 2.8 mg: 0.5 –12 mg), RISP (11.2 ± 5 mg: 3 - 20	HAL: DLPFC ↓, RISP: -
Gonul e.a., 2003	resting state	rest	SPECT	rCBF	S, M	24 M	B + 6 week F, 3 week W	OLAN (10 mg)	1.4 mg	-

Article	Cognitive function	Tasks	Tech.	Meas.	Patients	Group	Study design	Antipsychotics	Haldol equivalents	Study result
Molina e.a., 1997 (1996)	resting state	rest	SPECT	rCBF	TRS	39 MP	B + 6 month F	CLOZ (600 mg)	8 mg	responders PFC ↓
Sharafi e.a., 2005	resting state	rest	SPECT	rCBF	AP, DN or DF	20 MP (10 F)	B + 7 month F (3 month W)	CLOZ (300 mg), classic (600 mg	CLOZ 5.3 mg, classic 600 mg	PFC ↑ CLOZ
Yildiz e.a., 2000	resting state	rest	SPECT	rCBF	S, DN or 1 month W	15 MP, 10 HC	B + 4 month F	HAL (according to clinician)	??	-
Meizenzahl e.a., 2006	working memory	N-back memory task	fMRI	BOLD	S	12 MP, 12 HC	B + 12 week F	QUE (566.7mg + 242.5)	7.6 ± 3.2 mg	VLPFC ↑
Jones e.a., 2004	verbal fluency	verbal fluency and passive auditory stimulation	fMRI	BOLD	FE, DN	8 MP, 7 DFP, 8 HC	S, 3 month T	QUE (364 ± 103 mg)	4.6 ± 1.4 mg	IFG ↑
Vaiva e.a., 2002	verbal fluency	trail making test	SPECT	rCBF	S, DN or DF	19 MP	B + 4 week F	AMI (100 mg)	??	DLFPC ↑
Honey e.a., 1999	working memory	N-back memory	fMRI	BOLD	CS, M	10 vs 10 MP, 20 HC	B + 6 week F	RISP (4.6 ± 1.7 mg)	4.6 ± 1.7 mg	right PFC ↑ RISP
Slagenhauf e.a., 2008	working memory	N-back memory	fMRI	BOLD	S	10 MP, 10 HC	B + 4 week F	HAL (10.0 ± 5.0 mg, FLU 7.5 ± 4.7	HAL 10.0 ± 5.0 (5 - 15 mg), FLU 7.5 ±	DLPFC ↓
Slagenhauf e.a., 2010	working memory	N-back memory	fMRI	BOLD	S, M	11 MP, 11 HC	B + 3-4 week F	ARI (14.1 ± 5.8 mg)	-	-
Bertolino e.a., 2004	working memory	N-back memory task	fMRI	BOLD	CS & AP, DN	20 MP	4 + 8 week F	OLA (21.1 ± 7.6 mg)	3 ± 1 mg	PFC ↑↓

Affinities were determined in receptor binding studies (Allison et al. 1999; Arnt and Skarsfeldt 1998; Burstein et al. 2005; Bymaster 1996; Kapur and Seeman 2006; Kapur and Seeman 2001; Reimold 2007; Schotte 1996; Seeman 1993). When different K_i values were reported, an average of these values was used.

The studies included in the review showed a large heterogeneity in study population, treatment design, and imaging protocol. For this reason, it was deemed impossible to conduct a quantitative comparison with effect sizes of studies. We therefore used a Chi-square test to investigate whether D_2 and 5-HT_{2A} binding strength had an effect on prefrontal activation (Baas et al. 2004). Antipsychotics were categorized in strong D_2 antagonists, strong D_2/strong 5-HT antagonists, and strong D_2/weak 5-HT antagonists. Prefrontal effect was categorized in increased, equal or decreased prefrontal activation. If there would be no effect of antipsychotic on prefrontal actuation, the frequency of different prefrontal effects should be equal across categories of antipsychotics.

Summary of studies

An overview of all studies can be found in Table 24 and Figure 22. The graph in Figure 22. shows the percentages of studies that found decreased, equal, or increased prefrontal activation during treatment per antipsychotic category. It shows that strong D_2 antagonists mostly caused decreased activation, weak D_2 and 5-HT_{2A} antagonists show mostly lower activation. The special effects of clozapine are shown separately.

A Chi-square test showed that there was no effect of antipsychotic category on prefrontal activation ($\chi^2 = 5.61$, $p = 0.23$). However, clozapine decreased activation in most studies and has an idiosyncratic receptor profile. Therefore, an additional Chi-square test was performed with clozapine as a separate category. This test showed a significant effect of antipsychotic on prefrontal activation ($\chi^2 = 13.8$, $p = 0.032$), with strong D_2 antagonists and clozapine showing mostly decreased activation, and weak D_2 antagonists showing mostly increased activation.

Table 24 Overview of the receptor affinities of the antipsychotics used in the studies and their effect on prefrontal activation; The column "frontal activation" indicates the effect on activation, being increased (+), unchanged (=) or decreased (-); Results are ordered according their expected frontal activation (decreased for strong D_2 antagonists, equal for strong D_2/strong 5-HT_{2A} antagonists, increased for weak D_2/strong 5-HT_{2A} antagonists) showing that most studies show results according to the expectations, except for clozapine

	Medication	D_2 affinity	5-HT_{2A} affinity	Frontal activation
Cohen e.a., 1988	fluphenazine	+	-	-
Cohen e.a., 1997	fluphenazine	+	-	-
Barlett e.a., 1991	haloperidol	+	-	-
Holcomb e.a. 1996	haloperidol	+	-	-
Lahti e.a., 2003	haloperidol	+	-	-
Lahti e.a., 2004	haloperidol	+	-	-
Miller e.a., 2001	haloperidol	+	-	-
Buchsbaum e.a. 2007	haloperidol	+	-	=
Yildiz e.a., 2000	haloperidol	+	-	=
Barlett e.a., 1992	thiothixene	+	-	=
Buchsbaum e.a., 2009	haloperidol	+	-	+
Wik e.a., 1990	chlorpromazine	+	+	=
Bertolino e.a., 2004	olanzapine	+	+	=
Gonul e.a., 2003	olanzapine	+	+	=
Miller e.a., 2002	risperidone	+	+	=
Wik e.a., 1989	sulpiride	+	+	=
Vaiva e.a., 2002	amisulpride	+	+	+
Buchsbaum e.a. 2008	olanzapine	+	+	+
Honey e.a., 1999	risperidone	+	+	+
Buchsbaum e.a., 2010	sertindole	+	+	+
Ngan e.a., 2002	risperidone	+	+	-
Slagenhauf e.a., 2008	olanzapine	+	+	-
Blasi e.a., 2009	olanzapine	+	+	-
Fahim e.a., 2005	quetiapine	-	+	+
Jones e.a., 2004	quetiapine	-	+	+
Meisenzahl e.a., 2006	quetiapine	-	+	+
Stip e.a., 2005	quetiapine	-	+	+
Lahti e.a., 2005	clozapine	-	+	+
Sharafi e.a., 2006	clozapine	-	+	+
Cohen e.a., 1998	clozapine	-	+	-
Potkin e.a., 1994	clozapine	-	+	-
Zhao e.a.,	clozapine	-	+	=
Molina e.a., 1997(6)	clozapine	-	+	-
Molina e.a., 2003	clozapine	-	+	-
Molina e.a., 2005/7	clozapine	-	+	-
Molina e.a., 2008	clozapine	-	+	-
Lahti e.a., 2004	clozapine	-	+	=
Slagenhauf e.a., 2010	aripiprazole	-	+	=

Thus, according to our results antipsychotics with a strong D_2 antagonism do not increase or even decrease activation of the prefrontal cortex. In contrast, weaker D_2 and strong 5-HT_{2A} antagonists preserve or increase activation of the prefrontal cortex in the majority of the studies. Clozapine, not in line with other antipsychotics, decreased activation in most studies.

Below, studies are ordered according to the cognitive functions evaluated. This classification was chosen because most studies investigated a particular cognitive function, rather than a specific brain area. Within this order, studies are ordered according to imaging method, because this could have a large influence on study outcome. Detailed information about the study characteristics is shown in Table 23.

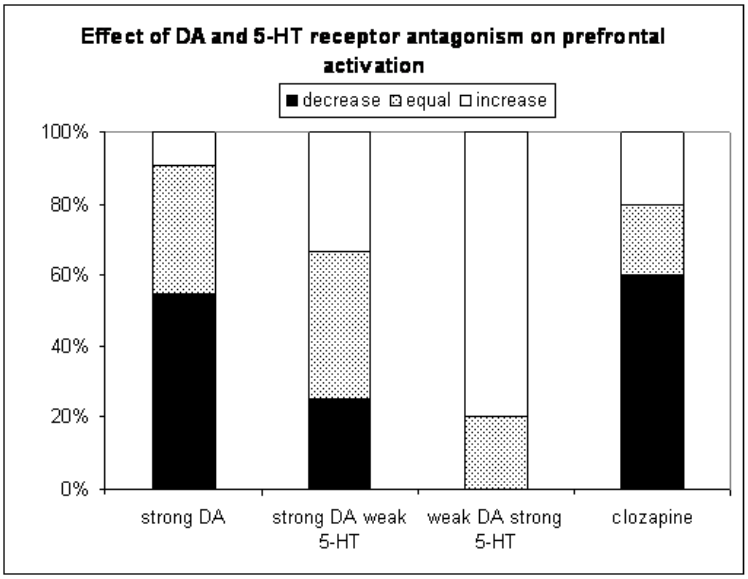

Figure 22 Graph showing the percentage of studies that showed an decreased, equal or increased prefrontal activation after treatment with antipsychotics with different DA and 5-HT binding properties, clozapine is shown separately

Resting state

In resting state studies, brain activation is measured during rest, i.e. the subject is not required to do a particular task. An early PET study compared the effect of sulpiride (N = 11) and chlorpromazine (N = 6) in patients with healthy controls (N =

7). There were no effects of either treatment on frontal rCBF (Wik et al. 1989). Similarly, in fifteen patients treated for four months with haloperidol there were no SPECT measured changes in frontal activation compared to ten healthy controls (Yildiz et al. 2000). A PET study compared the effects of 4-6 weeks treatment with haloperidol or thiothixene (Barlett et al. 1999). Haloperidol decreased prefrontal metabolism while thiothixene had no effects. In another PET study (N = 19) haloperidol decreased perfusion in the left DLPFC, after treatment for three weeks (Miller et al. 2001). In a similar vein, withdrawal from haloperidol increased glucose metabolism in the dorsolateral prefrontal cortex (DLPFC) and superior frontal cortex (SFC), as shown with PET in twelve medicated subjects (Holcomb et al. 1996). Finally one PET study reported increased DLPFC perfusion but decreased ventrolateral prefrontal (VLPFC) perfusion, when patients were first scanned non-medicated (N = 6) and then after twelve weeks of haloperidol treatment (N = 5) (Lahti et al. 2003).

Antipsychotics with additional high affinity antagonist action at 5-HT receptors have less influence on resting state brain activity than first generation drugs. A PET study on risperidone treatment (three weeks, N = 13) found no prefrontal perfusion changes (Miller et al. 2001). Similarly, a SPECT study found no differences in (prefrontal) rCBF between pre and post-olanzapine treatment (six weeks, N = 24) (Gonul et al. 2003).

Clozapine has been extensively studied, both with and without pretreatment with antipsychotics with dopamine receptor antagonism. An aforementioned PET study (Lahti et al. 2003) showed increased perfusion in DLPFC, and a decreased VLPFC and superior frontal (SFC) perfusion after clozapine treatment for five weeks. An early article on treatment resistant patients (N = 24) found no effects of clozapine on prefrontal rCBF (Molina et al. 1996). In a subsequent analysis on the same data, it was shown that responders to clozapine had high prefrontal rCBF at baseline, which decreased after treatment (Molina et al. 1997). Molina et al. 2003 showed in 25 patients that activity of the prefrontal cortex decreased after treatment with clozapine (Molina et al. 2003). Patients with a high baseline metabolism of the DLPFC were more likely to improve on negative symptoms during treatment with clozapine. This finding of decreased

prefrontal activation after treatment with clozapine was replicated in a more recent study in the medial prefrontal (MPFC) and left DLPFC (Molina et al. 2005; Molina et al. 2007). Contrary to the aforementioned studies, a cross-over study (N = 20) reported that prefrontal perfusion increased after several months of treatment (N = 10 at follow-up) with clozapine in comparison to strong DA antagonists (Sharafi 2009).

Taken together, the above studies suggest that haloperidol may decrease resting activity of the prefrontal cortex. Likewise, clozapine showed a decreased metabolism of prefrontal regions in treatment-resistant patients, although all studies were of the group of Molina et al. Other strong 5-HT antagonists, although underrepresented in this section, appear to have little effect.

Resting state studies have the disadvantage that brain activity is undirected and may be highly variable between persons. This might be even more pronounced in patients, as resting state activity may reflect abnormal self-generated activity related to their symptoms (Liddle and Pantelis 2003). Such confounds may be less pronounced in studies that measure task related activations.

Working memory

Only studies on more recent antipsychotics that used working memory tasks to measure prefrontal activation were available to include in this review. When risperidone was substituted for first generation antipsychotics (types not specified, N = 10) and taken for ten weeks, activation during an N-back task increased in the right dorsolateral prefrontal cortex, but task performance did not change (Honey et al. 1999).

Another fMRI study found decreased prefrontal activation after successful treatment with olanzapine (Bertolino et al. 2004). They created three patient groups (total N = 20), based on alleles of the COMT gene. One homozygous group (Met/Met) showed a better task performance with decreased PFC activation, while the other homozygous group (Val/Val) showed an opposite pattern, comparing eight with four weeks of treatment (no baseline). This may imply that frontal activation effects of antipsychotics are partially dependent on genotype.

In contrast, after a switch from strong DA antagonists to olanzapine (4 weeks), 25 patients showed hypofrontality during the 0-back baseline condition (strong DA antagonists) and increased activation of the DLPFC after treatment with olanzapine (Slagenhauf et al. 2010). The 2-back condition resulted in deactivation, possibly because of high task load (see General discussion).

In an fMRI study (12 weeks, N = 25) with the N-back task, frontal cortex activation of patients increased after quetiapine in the VLPFC and DLPFC (Meisenzahl et al. 2006). Activation in the VLPFC reached levels comparable to healthy controls.

Aripiprazole is partial agonist of the dopamine D_2 receptor, and is hypothesized to stabilize dopamine transmission and increase prefrontal activation (Lieberman 2004; Slagenhauf et al. 2010). However, eleven patients switched from strong DA antagonists to aripiprazole showed no increased prefrontal fMRI activation during the N-back task after 3-4 weeks of treatment (Slagenhauf et al. 2010).

To conclude, most studies show a consistent pattern of increased PFC activity induced by working memory tasks after treatment with strong serotonin antagonists, partially such effect might be dependent on genotype however (Bertolino et al. 2004).

Learning

An [^{18}F]-FDG-PET study showed in a randomized trial that haloperidol decreased activation of the frontal cortex compared to baseline (N = 22 at follow-up) (Buchsbaum et al. 2007) . This is in contrast to another study (Buchsbaum et al. 2009), in which haloperidol (N = 15) increased metabolism in the MPFC and orbitofrontal cortex after six weeks.

Both aforementioned studies investigated besides haloperidol also a weak dopamine and strong serotonin antagonist. The first (Buchsbaum et al. 2007) found that olanzapine increased activation of the frontal cortex compared to baseline. In the other study (Buchsbaum et al. 2009), sertindole increased metabolism in the DLPFC and anterior PFC together with performance on the learning task. Again, it appears that serotonin antagonists increase PFC activation relative to haloperidol.

Emotional processing

Emotional processing has also been related to prefrontal functioning (Berthoz et al. 2002). A PET study (N = 12) showed that olanzapine treatment lowered VLPFC activation during implicit face processing after four weeks. Activation was higher after eight weeks, but it was lower during explicit processing of emotional faces (Blasi et al. 2009). Since no baseline scan was included, it is difficult to draw conclusions from this complicated pattern. Walter et al. also studied the effect of olanzapine, but their study focused on reward mechanisms, using a monetary reward task (Walter et al. 2009). After two weeks of treatment (N = 16; fMRI), activation in the VLPFC was increased.

A PET study with quetiapine (N = 12) showed that 22 weeks treatment increased activation in the DLPFC during viewing of emotional pictures (Fahim et al. 2005). This finding was replicated in another PET study after 5.5 months of treatment (N = 12) (Stip et al. 2005) using a sad movie, which is according to our expectations.

To conclude, weak dopamine antagonists increase DLPFC activation. Activity changes of the ventral frontal areas by olanzapine are less clear, as one study showed a complicated picture of activation and deactivation (Blasi et al. 2009). However, in the other study it increased frontal activation as expected based on olanzapine's high affinity 5-HT receptor antagonism (Walter et al. 2009).

Attention and executive function

In an early SPECT study, subjects (N = 8) had to perform an auditory discrimination task after treatment with fluphenazine (Cohen et al. 1988). They showed a lower rCBF in the SFC. While task performance was related to higher MFC rCBF values in medicated patients, this was not the case in unmedicated patients (N = 16). A more recent glucose-PET study also showed that fluphenazine (N = 22) lowered glucose metabolic rates in the SFC (Cohen et al. 1997).

Risperidone (6 weeks; N = 8) decreased activation in the left lateral frontal cortex and the MFC during a letter recognition task. Reduction in MFC activity was related to a decrease of positive symptoms (Ngan et al. 2002).

A more recent SPECT study investigated the effect of clozapine on frontal activation during performance on the Wisconsin Card Sorting task. After eight weeks of treatment in 21 subjects, there was no change in frontal activation (Zhao et al. 2006). In contrast, in another PET study clozapine lowered the metabolic rate in the frontal cortex during a Stroop task (N = 9; 10 weeks) (Potkin et al. 1994). Clozapine (N = 12) also decreased activation of the SFC and IFG during an auditory discrimination task (Cohen et al. 1988). A SPECT study (Molina et al. 2008) with ten subjects treated for six months showed that substituting clozapine for risperidone extended hypoactivation of the MFC during the Stroop task. Concluding, clozapine appears to decrease frontal activation during tasks of attention and executive functioning.

Verbal fluency

During a verbal fluency test, subjects have to name as many words of a certain category as possible. This test activates selectively the frontal and temporal lobes (Baldo et al. 2006). After four weeks of treatment with amisulpride, prefrontal rCBF increased with concurrently increased performance on a verbal fluency task (Vaiva et al. 2002). In a similar vein, eight patients receiving quetiapine (three months) showed increased activation of the left inferior frontal cortex compared to medication-free patients (Jones et al. 2004).

General discussion

After reviewing the neuroimaging studies concerning antipsychotics and prefrontal activation in schizophrenia, the weight of evidence indicated that antipsychotics with relatively weak D_2 antagonism combined with strong 5-HT_{2A} antagonism are overall associated with increased prefrontal activation, in contrast to strong DA antagonists. Clozapine showed an unexpected effect on prefrontal activation, as it appeared to cause a decrease in prefrontal activation in most studies, despite an improvement in negative symptoms and task performance.

Our finding of mostly decreased or unaltered brain activation with strong DA antagonists and increased activation by weak DA antagonists supports our theory that strong D_2, and possibly D_1, blockade decreases prefrontal activation. Moreover, treatment with strong 5-HT_{2A} receptor antagonists combined with

strong D_2 antagonism was also associated with increased or preserved frontal activation in the majority of the studies. This effect of strong 5-HT_{2A} antagonism on prefrontal activation is possibly mediated by indirect effects of the serotonin system on DA levels (Abi-Dargham and Laruelle 2005; Lee et al. 1994).

The unique effect of clozapine on prefrontal activation is one of the most notable findings of this review. Strikingly, most studies on clozapine that showed decreased PFC activation used higher doses of clozapine (400-600 mg) and used PET or SPECT imaging. However, these studies also reported concurrent improvement in PANSS subscales and task performance, thus the effect seems desirable for the patient. Potentially, clozapine does not increase task related activation. Instead it could have a positive effect by selectively decreasing aberrant activity observed during rest periods (Molina et al. 2003; Molina et al. 2005; Molina et al. 2007). Similarly, clozapine may help to selectively increase activation in task relevant areas (Lahti et al. 2003), such as ACC activation during the Stroop task (Molina et al. 2008).

The effect of clozapine on PFC activation is possibly associated with its unique high D_1/D_2 affinity ratio compared to other antipsychotics (Kapur et al. 2002; Tausscher et al. 2004). Another explanation may be that clozapine's broad receptor profile is hypothesized to enhance NMDA receptor transmission (Abi-Dargham and Laruelle 2005; Advocat 2005; Davies et al. 2005; Onali and Olianas 2007; Tausscher et al. 2004) and PFC activation (Wittmann et al. 2005). Ultimately both mechanisms could contribute to ameliorating negative symptoms and cognitive impairments (Abi-Dargham and Laruelle 2005).

The current review has a number of caveats that limit applicability of our conclusions to the clinic. One is that decreases in brain activation can be the result of decreased activation during task performance or increased activation during resting conditions (Davis et al. 2005). It has been reported that, during task performance, patients with schizophrenia fail to deactivate the prefrontal cortex, which is part of the so called default mode network (Kim et al. 2009; Polli et al. 2005; Pomarol-Clotet et al. 2008). This network, which is involved in introspection, is highly active during rest, and deactivation facilitates effective

task performance (Kim et al. 2009; Pomarol-Clotet et al. 2008). Moreover, treatment with antipsychotics has shown to affect activation of the default mode network (Abbott et al. 2011) even specifically the prefrontal regions (Sambataro et al. 2010). Also the relation between task load and PFC activation could not be linear and not the same in patients and controls. Patients may activate their prefrontal cortex maximally at a lower task load than controls, and show decreased activation at higher task loads (Jansma et al. 2004; Liddle and Pantelis 2003; Mendrek et al. 2004; Mendrek et al. 2007).

Although increased PFC activity may be an indicator of a favorable antipsychotic effect, it does not reliably predict symptom improvement (Da Silva Alves et al. 2008) and our results tend to confirm this. Although behavioral studies show that cognitive performance can be improved with antipsychotic treatment (Abi-Dargham and Laruelle 2005; Lee et al. 1994; Meltzer et al. 1994), studies that show a direct link with brain activation are relatively scarce.

Except for the receptor profile of the administered antipsychotic, other factors could also confound conclusions about prefrontal activation. Study outcome can depend on the paradigm, task difficulty, dose of the antipsychotic, and the patient characteristics (e.g. age, duration of illness, diagnosis, symptom severity, and previous medication) (Chung and Remington 2005; Davidson and Heinrichs 2003).

We were unable to find evidence for a systematic influence on frontal activation of the aforementioned factors, but a number of factors will be considered in some more detail because they may contribute to study outcome.

First, studies on strong DA antagonists often used relatively high doses compared to studies on strong 5-HT (and weak DA) antagonists, as shown by their haloperidol equivalents (Table 23 ; before-last column). This could thus be a confound that exaggerated the conclusions. However, we found no evidence that the dose of the antipsychotic was a dominant factor in determining the effect on prefrontal activation: typical antipsychotics and clozapine induced hypofrontality across their dose range while atypical drugs, irrespective of dose, generally did not.

Similarly, treatment with antipsychotics at baseline versus medication free status may have a substantial contribution to study outcome, as is shown by other studies (Davidson and Heinrichs 2003; Hill et al. 2004). We did not observe an effect of medication status. Part of the studies did not report medication status at baseline, and other studies used in most cases medication free patients or switched from typical to atypical medication, which is expected to have a positive effect on the prefrontal cortex.

Moreover, the severity of negative symptoms may have an effect on the choice of antipsychotic treatment. Clozapine is often prescribed to patients with more severe negative symptoms. Indeed, most studies on clozapine performed by Molina et al., studied treatment resistant patients which may have more severe negative symptoms. Additionally, diagnosis and duration of illness could have their effect (Glahn et al. 2005) showed indeed that chronicity influences prefrontal activation. Patients with a longer duration of illness or who were older had a lower prefrontal activation. Besides, males with schizophrenia have shown stronger prefrontal responses than females (Davidson and Heinrichs 2003). Patients with bipolar disorder also show different brain activation than patients with schizophrenia (McIntosh et al. 2008). However, the effect of diagnosis on prefrontal activation has not been investigated in psychotic disorders specifically.

Of a different note, task was linked to study outcome: While there was no systematic difference in study outcome between different cognitive tasks, half of the studies that showed results not supporting our hypothesis were resting state studies. Resting state is characterized by undirected brain activation (Davis et al. 2005), and we postulate that this may result in a very low intrinsic sensitivity of this technique to detect hypofrontality in psychiatric patients.

Imaging modality may also have had its influence. As indicated, [^{18}F]-FDG PET is based on metabolism, while fMRI, HMPAO SPECT, and H_2-^{15}O PET methods are based on perfusion. Also the time resolution is different. However, imaging modality had no apparent effect on study outcome in our study, as was previously found (Hill et al. 2004).

Of a final note is the direct effect that antipsychotics can exert on blood vessels (Da Silva Alves et al. 2008). Abler et al. showed that a single dose of olanzapine in healthy controls decreases activation of the IFC, ACC, and ventral striatum during a monetary reward task, but that these effects were partially mediated by general effects of olanzapine on blood flow (Abler et al. 2007). On the other hand, a recent review showed that the effect of antipsychotics on the BOLD signal is possibly limited (Röder et al. 2010).

Summarizing the results of this review, antipsychotics with a weak D_2 antagonism and strong 5-HT_{2A} antagonism seem to increase or preserve prefrontal activation more than strong DA antagonists do. Clozapine shows an opposite picture of decreased activation associated with clinical improvement. Future studies should address the question whether increased prefrontal capacity by antipsychotics is beneficial for treatment of negative symptoms and cognitive impairments. Improvement of these negative symptoms would implicate a large gain in quality of life for patients with schizophrenia.

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9. An open randomized pilot trial on the differential effects of aripiprazole versus risperidone on anhedonia and subjective well-being

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Abstract

Introduction: Negative symptoms of schizophrenia often predict an unfavorable clinical outcome. Disturbed dopamine transmission in different brain parts may underlie different aspects of negative symptoms, and the effect of antipsychotics on them may also differ. This pilot study investigated the potentially therapeutic effects of the partial dopamine agonist aripiprazole on different negative symptoms. **Methods:** This pilot study randomly assigned patients with schizophrenia (N = 40) to either aripiprazole or risperidone. After 6 weeks of treatment, the severity of negative symptoms was determined by the PANSS. Subscales of self-report questionnaires were used to assess differences in

initiative, anhedonia, social functioning and subjective well-being. **Results:** Patients treated with aripiprazole showed a significant improvement on measures for anhedonia and subjective well-being. Negative symptoms in general, lack of initiative, and social inhibition were also lower in the aripiprazole treated group, but without reaching statistical significance. **Discussion:** According to this pilot study, aripiprazole appears to specifically improve anhedonia and subjective well-being compared to risperidone. This may be caused by a specific effect of aripiprazole on the limbic branch of the dopamine system. Future studies should replicate this finding with a larger sample size.

Introduction

Schizophrenia is a disabling psychiatric illness, which strikes about 1 % of the population, often in early adulthood. The disorder is characterized by positive and negative symptoms, and cognitive impairments (Mueser and McGurk 2004). Positive symptoms include hallucinations and delusions. Negative symptoms include emotional flatness, speech impairments, lack of initiative, anhedonia, and social inhibition (Andreasen 1982). Negative symptoms have a large impact on social functioning and a satisfactory integration in the community (Gold et al. 1997).

Dopamine (DA) pathways are thought to play a major role in the symptomatology of schizophrenia (Grace 2000). According to the dopamine hypothesis, positive symptoms are caused by a hyperdopaminergic state in the striatal and mesolimbic dopamine pathways, whereas negative symptoms may reflect a hypodopaminergic state in the mesocortical pathways, which include the prefrontal cortex (Abi-Dargham and Moore 2003; Abi-Dargham and Laruelle 2005; Jarskog et al. 2007).

In this model, the origin of all negative symptoms is attributed to prefrontal functioning, while the functions underlying the symptoms (e. g., emotion, initiative, speech) are very diverse. Some studies indicate that, for example, lack of initiative and lack of social dysfunction may indeed originate from prefrontal dysfunction (Goldman-Rakic 1994), while emotional flatness (anhedonia) may

originate from disturbances in the limbic dopaminergic branch and the nucleus accumbens (Gur et al. 2007; Juckel et al. 2006).

Antipsychotic drugs have shown to be effective in reducing positive symptoms by blocking DA receptors. However, their effects on negative symptoms are controversial. Because negative symptoms possibly have different neuroanatomical and neurochemical backgrounds, effects of anti-psychotics on e.g., lack of initiative (Chan et al. 2007) or anhedonia (Lambert et al. 2003), and other negative symptoms may also be differential.

The primary mechanism of action of the earliest, first-generation, antipsychotics concerns strong blockade of dopamine receptors (Bortolozzi et al. 2007; Jordan et al. 2004). By blocking the prefrontal and limbic dopamine system, dopaminergic output may decrease, and result in exacerbation of negative symptoms (Brown et al. 2003; De Haan et al. 2006).

More recent antipsychotics share a high serotonin (5-HT) antagonism, sometimes with a low dopamine antagonism, and are referred to as atypical or second-generation antipsychotics. 5-HT receptor antagonism (and low DA antagonism) may help to preserve endogenous dopamine transmission (Abi-Dargham and Moore 2003; Da Silva Alves et al. 2008; Jarskog et al. 2007; Kapur et al. 2000; Lee et al. 1994). According to some authors, this receptor profile may result in a limited improvement of negative symptoms and subjective well-being (Green et al. 1999; Lambert et al. 2003; Van Nimwegen et al. 2008).

In 2001 aripiprazole, a partial dopamine receptor agonist, became available for clinical use (McGavin and Goa 2002). Aripiprazole acts either as a functional dopamine agonist or a functional antagonist, depending on the surrounding levels of dopamine (Lieberman 2004). Thus given its putative working mechanism, aripiprazole may stabilize dopaminergic transmission in different brain regions (Bortolozzi et al. 2007; Jordan et al. 2004; Semba et al. 1995) and in this way improve negative symptoms. Previous studies showed that aripiprazole has a beneficial effect on negative symptoms (Janicak et al. 2009; Kane et al. 2007; Riedel et al. 2010a), cognitive functioning (Riedel et al. 2010a; Riedel et al. 2010b), and quality of life (Kane et al. 2007; Kane et al. 2009), but that these effects are

not superior to those of other atypical antipsychotics (Janicak et al. 2009; Kane et al. 2007; Riedel et al. 2010a). These studies addressed a broad domain of symptoms while the effects of aripiprazole may be more specific.

It would be of interest to study the clinical effects of aripiprazole on different symptom domains (e.g. initiative, social functioning, or hedonia) compared to a strong DA and 5-HT antagonist (risperidone).

This could give some insight in whether negative symptoms indeed consist of different domains and whether antipsychotics affect them differently. It was hypothesized that aripiprazole in comparison to risperidone will have a more beneficial effect on domains of negative symptoms, but that the strength of this effect may differ between domains.

Patients and Methods

This pilot study included inpatients and outpatients diagnosed for schizophrenia (DSM-IV) or related psychotic disorders. They had to start or switch to a new antipsychotic for clinical reasons, e. g. side effects like weight gain or exacerbation of symptoms, without a preference for aripiprazole or risperidone. Participants gave written and oral consent in accordance with the local ethical committee for research. Patients could take any antipsychotic before entering the study except depot antipsychotics, aripiprazole or risperidone. Patients were randomly assigned to either open-label aripiprazole (starting dose 15 mg) or risperidone (starting dose 3 mg). Dosage could be adjusted weekly, as deemed necessary by the clinician (aripiprazole, 7.5-30 mg/day; risperidone, 1-6 mg/day). The patients were informed that effects of the switch would be assessed but they were blinded with regard to any hypothesis.

Part of the study investigated the effects of antipsychotics on sexual functioning (De Boer et al. 2011), while other questionnaires addressed the effects of antipsychotics and subjective well-being of the patient. In the current study, an interview and two questionnaires were used as a measure for different domains of negative symptoms (initiative, social functioning, hedonia). The Positive and Negative Syndrome Scale (PANSS) - (Kay et al. 1987) measures three domains of symptoms, namely Positive and Negative symptoms and General

pathology. Patients received the interview at baseline and after six weeks of treatment. The interview was performed by an experienced rater who followed a course for the interview and yearly did a consensus training. After six weeks, patients also filled out the Subjective Well-being on Neuroleptics (SWN) - (Naber et al. 2001), which measures subtle subjective changes, such as restrictions in emotionality, clarity of thinking, and spontaneity. The questionnaire correlates with quality of life and other self-ratings of mood (Wolters et al. 2009). Scores per item range from 1-6 (strongly disagree - strongly agree). Furthermore, patients received the Subject 's Response to Antipsychotics (SRA) at week 6, which consists of 10 subscales (Wolters et al. 2003). This questionnaire measures both desired and undesired effects of antipsychotics. Scores per item range from 0 – 2 (no, yes to some extent, yes to a great extent). A Negative symptom factor of the PANSS (N1, N2, N3, N4, G7, and G16) - (Van der Gaag et al. 2006b) acted as a general measure of negative symptoms, and the SWN total score as a measure for subjective well-being. The SRA and SWN were scanned for subscales that could act as a measure for specific negative symptoms. When at least 2/3 of the questions within a subscale addressed one of the symptom domains (emotional flatness, speech impairments, lack of initiative, anhedonia, and social inhibition) this subscale was used as a measure. We used existing subscales, because they have shown a good internal consistency (Naber et al. 2001). When subscales of two questionnaires evaluate one symptom domain, they could be used as a control of each other in a group comparison. Largely different p-values of subscales measuring one domain would indicate that they mea sure different aspects. We included the SWN subscale Emotion regulation (e. g. "My emotions and sensations are dull. Nothing matters to me"; "I am interested in what is happening around me, and it is important to me.") and the SRA subscale Flat affect (e. g. "My emotions are flat"; "I have less feeling") as measures for anhedonia/subjective well-being. The SWN subscale Social integration and the SRA subscale Social inhibition were taken as a measure for social functioning. The SWN subscale Functioning of thinking ("My thoughts stay unrealized.") and the Sedation subscale of the SRA ("I react more slowly.") were used as measures of

initiative. Other symptoms could not be assessed with these questionnaires. No PANSS subscale or factor from a factor analysis was found to measure negative symptom domains.

Groups were first tested for significant differences in demographic characteristics. Age and baseline PANSS scores (Positive, Negative, General) were compared with a t-test and gender with a Chi-square test for independence. DSM-diagnosis previous medication (none, classical antipsychotic, clozapine, olanzapine, quetiapine, classical + olanzapine) duration previous treatment (none, < 1 week, 1-2 weeks, 2-6 weeks, 6 weeks-3 months, > 3 months), reason for switch of medication (new psychosis, insufficient effect, side effects, scientific research, other reasons), and co-medication (antidepressants, benzodiazepines, lithium and anticholinergics, antidepressant + benzodiazepine, antidepressant + lithium and lithium + benzodiazepine) were considered as categorical variables and tested with Chi-square test for independence. Average dose and dose range of aripiprazole and risperidone at week 6 were also reported, but were not statistically compared because their effect on the dopamine receptor is so different. Group comparison of the symptom domains consisted of a Mann-Whitney U-test for the different subscales separately ($\alpha = 0.05$).

Results

40 patients (20 in each group) participated in the study. 3 patients (1 woman) treated with risperidone and 5 patients treated with aripiprazole did not complete the study but discontinued the study before the second week. Subjects discontinued because of subjective restlessness (reported by 5 patients), sometimes combined with akathisia (N = 1), sleeplessness (N = 2), suicidal behavior (N = 1). Two other patients stopped because of non-compliance of medication, and one for unknown reasons.

Patients characteristics are listed in Table 25. Groups did not differ significantly in age, baseline PANSS scores, gender, DSM-diagnosis previous medication, duration previous treatment, reason for switch of medication, and co-medication during the study. At week 6 the risperidone group was using an average of 3.2 mg risperidone (*SD* 1.2; range 1-5 mg). The average dose of

Table 25 Demographical data of the aripiprazole and risperidone groups, which showed no significant differences

		Aripiprazole		Risperidone			
Variable		**Mean**	**SD/%**	**Mean**	**SD/%**	**Test**	**p-value**
Age (SD)		29.2	8.8	29.0	6.0	t-test	0.95
Gender (m/f)		16/4	-	13/5	-	Chi-square	0.86
diagnosis (freq.):	297.1	1	33.3	2	66.7	Chi-square	0.53
	295.10	0	0	2	100		
	295.20	0	0	1	100		
	295.30	10	52.6	9	47.4		
	295.40	2	66.7	1	33.3		
	295.60	0	0	1	100		
	295.70	2	100	0	0		
	295.90	2	66.7	1	33.3		
	298.90	1	50	1	50		
PANSS (SD)	Positive symptoms	12.6	4.3	11.3	4.5	t-test	0.41
	Negative symptoms	13.6	4.8	15.5	4.4	t-test	0.26
	General pathology	26.7	6.0	27.0	6.3	t-test	0.90
Antipsychotic (freq.):	Strong DA antagonist	2	50	2	50	Chi-square	0.97
	Olanzapine	11	57.9	8	42.1		
	Quetiapine	2	66.7	1	33.3		
	Strong DA + Olanzapine	1	50	1	50		
Duration previous treatment (freq.):	Not applicable	3	33.3	6	66.7	Chi-square	0.41
	2-6 weeks	2	50	2	50		
	6 weeks - 3 months	1	25	3	75		
	> 3 months	11	61.1	7	39.9		
Reason switch (freq.):	Treatment unsatisfactory	7	58.3	5	41.7	Chi-square	0.59
	Side effects	1	33.3	2	66.7		
	Scientific research	0	0	1	100		
	Other	6	60	4	40		
Coeducation (freq.):	None	11	45.8	13	54.2	Chi-square	0.310.34
	Antidepressant	5	83.3	1	16.7		
	Benzodiazepine	2	40	3	60		
	Lithium	1	100	0	0		
	Anticholinergic	1	100	0	0		
	Antidepressant + lithium	0	0	1	100		

aripiprazole was 12.6 mg (*SD* = 5.8, range 5-30 mg). After treatment with aripiprazole or risperidone, subjects failed to show a difference in negative symptoms measured by the PANSS, but patients on aripiprazole reported a significant better subjective well-being as shown by the SWN total score (*Md* = 143, N = 15; *Md* = 129, N = 16), *U* = 64.5, *z* = 2.2, *p* = 0.027, *d* = 0.87.

Furthermore there was a significant difference in the SWN measure for anhedonia between risperidone (*Md* = 24, N = 17) and aripiprazole (*Md* = 29.5, N = 16), *U* = 71, *z* = 2.35, *p* = 0.019, *d* = 0.86, and trend for significance for the SRA Flat affect subscale (*Md* = 2.0, N = 17; *Md* = 1.0, N = 15 resp.), *U* = 83.5, *z* = 1.70, *p* = 0.090, *d* = 0.62. The aripiprazole group also showed a lower incidence of other symptom domains measured by the subscales, but these differences were not significant. The p-value levels for the two different questionnaires within one symptom domain showed a fairly consistent pattern. For a complete overview, see Table 26.

Discussion

The aim of this pilot study was to compare the effects of a partial dopamine agonist and an antagonist on different domains of negative symptoms. Symptoms domains were assessed by sub-scales of validated questionnaires and compared between groups. We expected that aripiprazole would have a superior effect on different domains of negative symptoms.

In line with the hypothesis, a differential effect of aripiprazole on subjective well-being and anhedonia was observed compared to risperidone. Concurrently, aripiprazole also showed a subtle better improvement of other symptom domains and the PANSS Negative symptom factor, although not reaching statistical significance. This implies that aripiprazole may have a preferential effect on anhedonia (and well-being).

Aripiprazole has been shown to increase dopamine release in medial prefrontal regions (Bortolozzi et al. 2007; Li et al. 2004). An increased dopamine release is suggested to improve negative symptoms. However, in line with earlier studies, this study did not show a superior effect of aripiprazole on negative symptoms (Janicak et al. 2009; Kane et al. 2007; Riedel et al. 2010a). It might be

effects of aripiprazole are only apparent at certain sub-domains, as is suggested by our study.

Table 26 Comparison between aripiprazole and risperidone on the measures for hedonia, initiative, and social interaction, a significant effect was found for the SWN emotion regulation subscale; N = number of subjects, *Md* = median, *U* = Mann-Whitney U-value, *d* = effect size

Subscale	Aripiprazole		Risperidone					
	N	*Md*	N	*Md*	*U*	*Z*	*p*	*d*
Negative symptoms								
PANSS Negative scale	14	12.5	16	14.5	82	1.25	0.21	0.39
Subjective well-being								
SWN total score	15	143	16	129	64.5	2.2	0.027	0.87
Hedonia								
SWN Emotion regulation	16	29,5	17	24	71	2.34	0.019	0.86
SRA Flat effect	15	1.0	17	2	83.5	1.70	0.090	0.62
Initiative								
SWN Functioning of thinking	16	29.0	17	27	110	0.94	0.35	0.43
SRA Sedation	16	4.5	18	3.5	133	0.38	0.72	0.14
Social interaction								
SWN Social integration	16	31.0	16	29	95.5	1.20	0.22	0.52
SRA Social inhibition	12	1.0	18	2	87.5	0.89	0.40	0.38

In line with Mizrahi et al. (Mizrahi et al. 2009), this study showed that aripiprazole increased subjective well-being and hedonia more than a strong DA antagonist (Naber et al. 2001). Moreover, aripiprazole has also shown good treatment effects on depression and bipolar disorder (McIntyre 2010; Pae et al. 2008), and the same receptor effects may alleviate or stabilize (an)hedonic mood (Pae et al. 2008). DA receptor occupancy of aripiprazole appears to be uncorrelated with subjective well-being, while this is the case for strong DA

antagonists (Naber et al. 2001). This may be an indication that aripiprazole acts in a different way on the dopamine system than other antipsychotics.

These specific effects of aripiprazole may be related to the partial agonistic properties on the dopamine receptor. Experiments in rats showed that atypical antipsychotics selectively block DA receptors and decrease DA output of the mesolimbic system and the shell of the nucleus accumbens (involved in reward) (Han et al. 2009).In contrast, aripiprazole does not influence or even augments DA output, decreases DA reuptake, and increases DA receptor expression in the mesolimbic system and decreases nigrostriatal output (Han et al. 2009; Pae et al. 2008). Moreover, 5-HT_{2C} antagonism (stronger in aripiprazole than in risperidone) may result in increased serotonin induced dopamine release in the nucleus accumbens (Pae et al. 2008). Possibly, absence of limbic down-regulation during treatment with aripiprazole causes increased or preserved experience of emotions.

This study was designed as a pilot and therefore suffers from some limitations. The number of subjects was low and the study did not include baseline measurements of SRA and SWN. However, since both groups showed equal baseline characteristics and were randomized, comparable baseline conditions may be assumed. Additionally, the SWN and SRA showed a consistent picture, as both p-values for anhedonia were (almost) significant, but the other results were not. This study may therefore be considered a first step in disentangling different domains (initiative, hedonia) of negative symptoms and the effects of antipsychotic treatment on these symptoms.

In conclusion, this pilot study shows that aripiprazole in comparison to risperidone may have a differential and for patients a preferable effect on anhedonia and subjective well-being. This effect may be related to a specific effect on the dopaminergic output of the limbic system. Future studies using larger study populations and repeated measurements are needed to confirm these findings and to focus on details.

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10. Discussion

In this thesis different brain networks were investigated in relation to network function in patients with schizophrenia. Schizophrenia patients show symptoms and behavioral impairments that may be caused by disturbances in networks that include the prefrontal cortex. Chapter 2 and 3 show that schizophrenia patients indeed have altered connectivity between prefrontal regions and more posterior language and auditory regions, both during rest and performance of a task. Chapter 4 shows that decreased abilities of patients to make associations between words and emotions, i.e. linking language and emotion, may also relate to altered prefrontal network connectivity. Self-reflection problems may cause multiple symptoms of schizophrenia. As an example of one of these symptoms, Chapter 5 shows that patients with poor insight in their illness have decreased connectivity in default mode network (DMN) regions involved in self-reflection. Healthy subjects with relatively low capacity to evaluate and describe emotions also show altered DMN connectivity, as can be read in Chapter 6. This impaired ability to evaluate and describe emotions is called alexithymia, which overlays to certain extent with negative symptoms of schizophrenia (e.g. both involve reduced emotional expression). Negative symptoms may originate from impaired prefrontal function, and it has been hypothesized that newer antipsychotics may be superior to older ones in that they stimulate prefrontal activation. According to Chapter 8, prefrontal activation indeed increases after treatment with weaker DA antagonists, however symptoms did not improve. Interestingly, Chapter 7 showed that negative symptoms may consist of different subgroups, and Chapter 9 that only specific symptoms may improve due to treatment with a new antipsychotic. These findings could encourage research on improved symptom definitions, which in turn could act as a starting point for neuroimaging research and development of novel treatment options. For now, I will start with general conclusion concerning the findings in this thesis, before I discuss the findings in more detail.

Prefrontal networks

The prefrontal cortex is a highly complex brain region with intimate connections to all other brain regions. Because of its high complexity, changes in prefrontal function may lead to complex changes in behavior (Goldberg 2009). As is shown in this thesis, schizophrenia is indeed a disorder with complex manifestations of symptoms that in multiple facets relate to prefrontal network functioning.

Current fMRI investigations often report on dysfunctions of separate brain regions and their implications (Fletcher et al. 1999; Glahn et al. 2005). However, brain regions do not function as isolated entities, thus the effect of disturbances in one brain region should preferably be considered within the network of brain regions it is part of (Fuster 2009; Goldberg 2009). In this framework, brain connectivity studies may add to our current knowledge of brain functioning as well as pathology in certain psychiatric conditions.

The brain network that receives most attention in this thesis is the DMN, although multiple brain networks are important for brain function (Damoiseaux et al. 2006; Jafri et al. 2008). However, some researchers have proposed that the DMN may be the key hub of interactions with other networks and "facilitate the retrieval and integration of relevant informational components, stored in their modality-specific cortical areas, the product of which has a coherent spatial context, and can then later be manipulated and visualized" (Hassabis and Maguire 2007; Kim 2010). The DMN may in this respect have a key role in anticipating on future events based on input from other networks (Buckner et al. 2008). On the other hand, the DMN deactivates during cognitive performance and a "task-positive network", which contains the dorsolateral prefrontal cortex (DLPFC), becomes increasingly active (Fransson 2006), see Figure 23. Possibly, an interplay between both networks with the PFC as a prominent player orchestrates brain function across different mental states (Fransson 2006). It may be interesting to incorporate this task-positive network in future analyses of brain function.

Besides focusing on the implications of observed slow-wave fluctuations, the exact meaning of slow-wave fluctuations and brain connectivity should receive more attention (Auer 2008). In their influential paper, Raichle and

Gusnard consider a network of brain areas that shows coherent BOLD-signal changes as neuronal network with specific functions (Raichle et al. 2001).

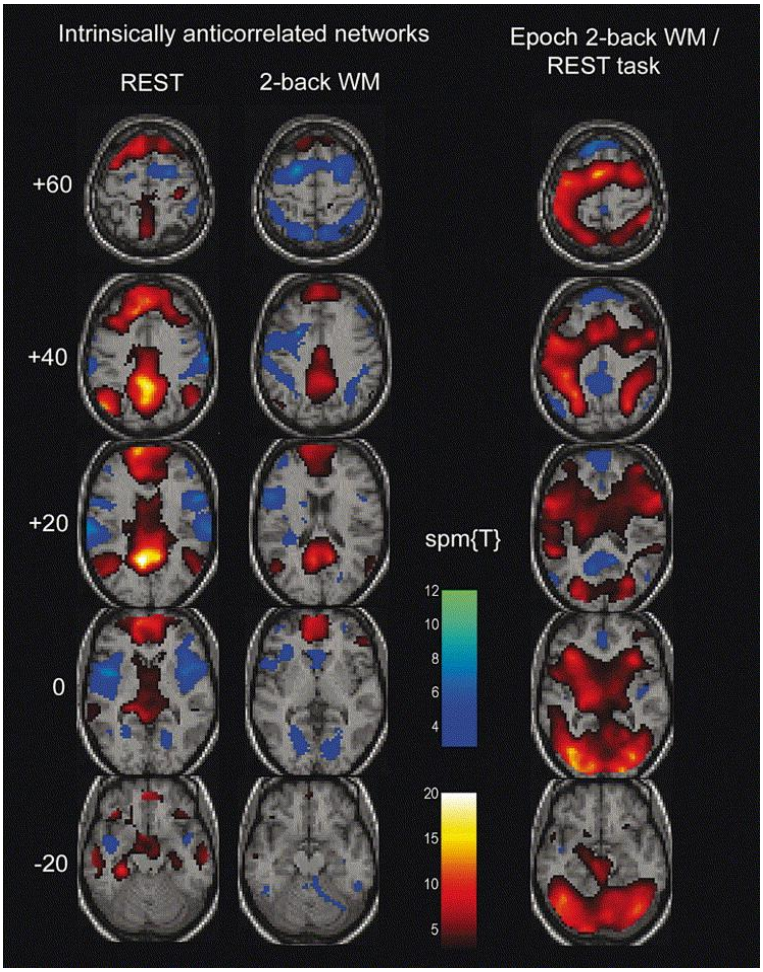

Figure 23 Default mode network identified as task-negative network in red and task-positive network in blue, based on N-back task (Fransson 2006)

However, some authors have concluded that default mode fluctuations may represent non-neuronal, e.g. vascular, signals, or neural signals that may not be informative concerning cognitive function (Boly et al. 2008; Morcom and Fletcher 2007). Other authors concluded that the DMN indeed has a neuronal origin and supports cognitive functions, and thus can provide important information about

brain physiology and disease states (Auer 2008; Broyd et al. 2009; Buckner et al. 2008; Spreng and Grady 2009). However, the exact meaning of the fluctuations remains to be elucidated, and non-neural sources may still confound the observed signal (Auer 2008). Although not everything is known about the measured fMRI signal, it can provide important information about brain function in certain disorders.

Prefrontal networks in schizophrenia

The DMN may be an important network to understand the pathology behind schizophrenia (Kuhn and Gallinat 2011; Schilbach et al. 2008). It has been shown that patients with schizophrenia have a stronger local connectivity of the DMN both within the network and to other brain regions (Jafri et al. 2008). On the other hand, they have decreased long-range connectivity (Lynall et al. 2010; Van den Heuvel and Hulshoff Pol 2010). This may result in a decreased ability to switch states and to coordinate the activation of specific networks, including successful deactivation of the DMN during task performance (Garrity et al. 2007; Jafri et al. 2008; Kim et al. 2009; Sambataro et al. 2010). Degraded prefrontal connectivity may be an important cause for a disturbed controlling function of the DMN on the level of awareness (Van et al. 2010). This supports the hypothesized role of the DMN as a conductor of brain networks, with the PFC at the top of the hierarchy, and may explain symptoms patients experience in schizophrenia like disorganized thinking, impaired attention, negative symptoms and lack of insight into their illness.

Other interesting aspects of brain development and function also point to an important role for the DMN and specifically the PFC in schizophrenia. For example, healthy children show connectivity between posterior DMN regions, but not with the PFC (Bluhm et al. 2008). These prefrontal connections develop in early adulthood, which typically is also the life phase when full-blown schizophrenia may develop. Moreover, while schizophrenia is more prominent in males, frontal connections appear to be stronger in females (Bluhm et al. 2008). This could imply that their more robust prefrontal connections may protect women to some extent against schizophrenia. On a neurotransmitter level, it has

been suggested that decreased dopaminergic input to the PFC may cause a disturbed modulation and synchronization of the DMN (Sambataro et al. 2010) or fronto-temporal connectivity (Fletcher et al. 1999), which would fit the most often reported brain dysfunctions in schizophrenia. These aspects could be interesting starting points for future research.

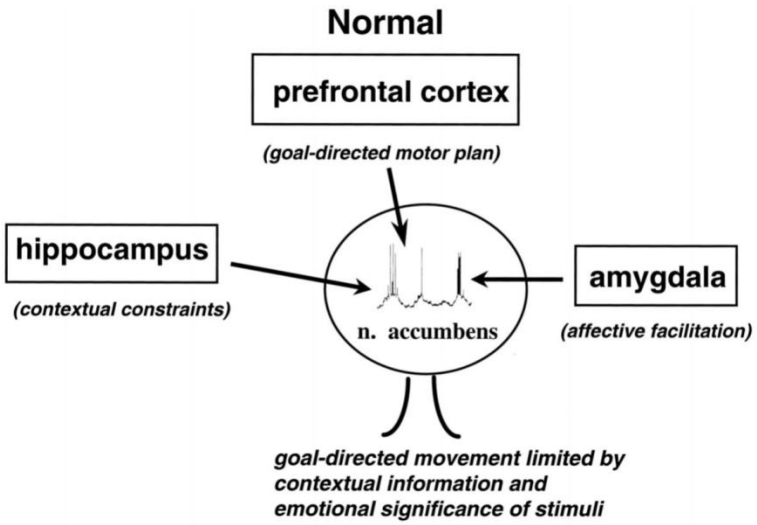

Figure 24 The prefrontal cortex provides multiple motor plans by which it drives goal-directed behavior and the most effective plan is then selected within the nucleus accumbens via the facilitatory effects of hippocampal and amygdalar influences; Under normal conditions, the hippocampus selects behavioral output based on the current context of the situation or past experiences with the stimulus; However, should a stimulus with a high affective valence - e.g. a threatening object - come into play, the amygdala can over-ride the hippocampal influence, and instead direct behavior in a manner that can effectively deal with the threatening stimulus (Grace 2000)

Apart from DMN dysconnectivity being related to symptomatology in schizophrenia, additional imbalance in activity of other brain networks may exist. Dysfunction of one region, such as the prefrontal cortex may cause relative hyperactivity or impaired function of other regions (Glahn et al. 2005; Goldberg 2009; Minzenberg et al. 2009). It has been hypothesized that schizophrenia is caused by a dysfunctional cerebellar-thalamic-temporal-striatal-prefrontal-network (Frith et al. 2009). The cerebellum shows interactions with the PFC (Goldberg 2009) and is part of the DMN in its broader definitions (Buckner et al.

2008; He et al. 2004). In this context the cerebellum is involved in complex planning and working memory (Goldberg 2009; Kim et al. 2009; Rieheman et al. 2001). Unfortunately, the cerebellum is often neglected in the interpretation of MRI data and also not covered in this thesis. This brain area should be an important candidate for future fMRI studies of schizophrenia.

Grace proposed another interesting model of brain network dysfunction in schizophrenia, involving the amygdala (Grace 2000). See Figure 24 and Figure 25. In this model, emotional drive from the amygdala competes with the normal goal-directed behavior of the PFC and in this way disturbs normal executive functioning (Grace 2000). Based on the discussed literature and our own findings, I would propose that not only the amygdala may be overactive, but that PFC dysfunction may lead to a relatively submissive state of the PFC to other brain areas and functions, including the amygdala.

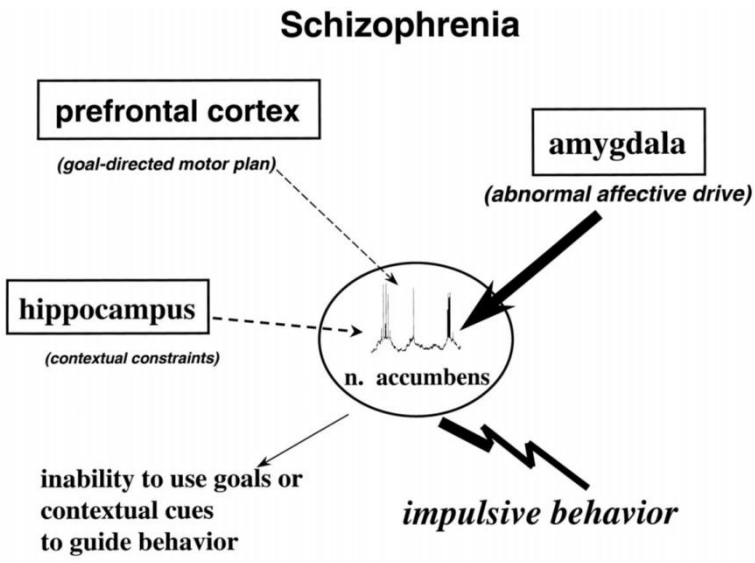

Figure 25 In schizophrenia, the amygdala not only fails to facilitate prefrontal cortical throughput, but in this condition actually competes with it for driving accumbens cell activity; Therefore, instead of selecting response strategies based on the goal-directed motor plan by the prefrontal cortex, the system is biased to react exclusively based on the affective valence of the stimulus; As a result, the planned behavior is replaced by impulsive responses based solely on the emotional state of the subject (Grace 2000)

In conclusion, a general model for the pathology of schizophrenia is slowly gaining shape. The prefrontal cortex and the DMN may have an important role in

this model, in close association with other brain areas. However, to gain more insight into the pathology, a more specific focus on the neural background of certain symptoms is important.

Networks abnormalities in relation to different symptoms of schizophrenia

Language is important for executive and social functioning (Fuster 2009; Goldberg 2009). Disturbances in brain networks involved in language processing could have widespread consequences for patients with schizophrenia (Crow 2008). In Chapter 2 and 3, the function of language networks in schizophrenia is covered. Both studies report decreased connectivity between temporal and frontal language areas, consistent with other studies (Ford et al. 2010; Hashimoto et al. 2010; Jeong et al. 2009; Karlsgodt et al. 2008). But whereas, the resting state analysis in Chapter 2 failed to show a difference in connectivity between hallucinating and non-hallucinating patients, Chapter 3 on task fMRI using Dynamic Causal Modeling (DCM) did report differences between these two groups. Possibly, resting state analysis with ICA taps more into trait characteristics, whereas DCM is more sensitive to trait aspects of functioning (Meyer-Lindenberg 2009). These findings show that different approaches to study a certain phenomenon may have additive value.

Another interesting finding in Chapter 2 was an increased connectivity between language areas and the ACC, which is also part of the DMN. Earlier studies have related disturbed ACC function to impaired source monitoring in schizophrenia (Allen et al. 2007; Allen et al. 2008). In patients, self-generated speech is often tagged as coming from a non-self source (Allen et al. 2007), possibly caused by defective self-monitoring (Simons et al. 2010; Stephane et al. 2001; Wang et al. 2011) related to ACC and MPFC dysfunction (Brüne et al. 2008).

Another cognitive process that may be related to disturbed self-processing is associative emotional learning (Parnas and Handest 2003; Sass and Parnas 2003). This process is used to make associations between emotional stimuli and other stimuli, for instance, one's emotional state and a word to describe it.

Generation of inappropriate associations has been regarded as a risk-factor for developing certain symptoms of schizophrenia (Bleuler 1911). Chapter 4 shows that schizophrenia patients may show impaired prefrontal connectivity in a network of brain areas activated during associative emotional learning. Unexpectedly, the results were weak and no differences between schizophrenia patients and healthy controls were observed in connectivity of amygdala and hippocampus to PFC. Earlier studies also report controversial findings, so the role of these areas in emotional learning needs further investigation.

Associating and verbalizing of emotions are language processes important for adequate social and psychological functioning (Swart et al. 2009). Alexithymia is a trait that is characterized by problems to interpret and verbalize emotions (Sifneos 1973; Taylor et al. 1991) and results in a higher risk to develop psychiatric symptoms (Taylor et al. 1997). Emotional awareness may also be dependent on good self-reflective capacities (Lane et al. 1997) and thus DMN capacities (Qin and Northoff 2011). Chapter 6 describes that students scoring high on alexithymia (but without psychiatric history) indeed show decreased DMN connectivity, and instead show higher connectivity to non-DMN brain areas during resting state. Other studies showed that when subjects with alexithymia are explicitly asked to rate emotions, they give similar ratings as non-alexithymic participants (Berthoz et al. 2002). It is suggested that alexithymia may occur as a result of being hyporesponsive to automatically self-processed emotions (Reker et al. 2009). In a similar way, decreased self-processing, i.e. evaluating information relevant for the self, may lead to higher levels of alexithymia in schizophrenia patients.

Self-reflective problems are also widely observed in schizophrenia (Amador and David 2004). Impaired self-awareness may lead to a diminished awareness of symptoms, and eventually to impaired insight in schizophrenia and also in other psychiatric disorders (Flashman and Roth 2004; Lysaker et al. 2005; Van der Meer et al. 2010). Chapter 5 shows a link between poor insight and reduced connectivity of the ACC and de precuneus within the DMN. In the literature, specific attention is often given to self-awareness and insight in relation to prefrontal function (Johnson et al. 2002; Van der Meer et al. 2010). However, an association between insight or self-referential processing and the precuneus,

which can be found in the posterior brain, has also been reported (Carter et al. 2001; Kuhn and Gallinat 2011; Morgan et al. 2010). Thus, also posterior DMN functions such as autobiographical memory may be important for insight in schizophrenia (Cooke et al. 2008; Whitfield-Gabrieli et al. 2011).

In general, the findings reported in this thesis show that brain networks involved in self-processing and language processing may be important in understanding aspects of dysfunction in schizophrenia, both in executive and social cognitive domains (Crow 2008; Nelson et al. 2009; Parnas and Handest 2003; Sass and Parnas 2003; Stirling et al. 2001). It has even been suggested that self-processing and language disturbances may even have diagnostic validity for schizophrenia (Raballo et al. 2011). Integrating the findings in this thesis and earlier findings, we could conclude that disturbances of the DMN may relate to a broad spectrum of deficits observed in schizophrenia (Brüne et al. 2008; Cooke et al. 2008; Schilbach et al. 2008).

Thus far this thesis focused on brain function and connections. With regard to schizophrenia symptoms, the negative symptoms may be most strongly caused by prefrontal dysfunction. Symptoms that often occur together may even have a shared (neural) background. The next part of the discussion focuses on the nature of the construct of negative symptoms.

Symptom dimension approach

Negative symptoms may be the most disabling symptoms in schizophrenia, but often receive less attention than positive symptoms. It has often been debated whether negative symptoms constitute one domain (Kirkpatrick and Fischer 2006; Messinger et al. 2011; Sass and Parnas 2003). Chapter 7 shows with factor analysis and subsequent confirmation in a separate cohort that negative symptoms may consist of two sub-domains, namely emotional deficits and social amotivation. Emotional deficits and social amotivation could thus be seen as two separate though related problems within the negative symptoms domain. A revised view on certain symptoms could have important implications for diagnostics and treatment, as discussed below.

A more fundamental question would be if these two sub-domains actually represent problems recognized by patients and whether they would relate to different aspects of functioning and therapeutic interventions. Based on the expressive deficit factor, one could conclude that patients encounter emotional problems in their daily life situations. However, patients with schizophrenia may in fact have intact experience of emotion, while only expression of emotion is impaired (Kirkpatrick and Fischer 2006; Messinger et al. 2011; Sass and Parnas 2003). Other studies suggested that patients may show deficits in anticipatory experience of pleasant emotions, while consumatory experience, thus at the moment itself, may be intact (Messinger et al. 2011). A first step in a better definition of symptoms would be to start with more accurate monitoring of what patients are really able to achieve, or what problems they encounter from their own perspective (Foussias and Remington 2010).

Better definitions and criteria are also needed for research using cognitive tasks. Some studies on schizophrenia do not show impaired performance on cognitive tasks, but meanwhile patients fail to run a household or work in a job setting (Goldberg 2009). There may be a large gap between experimental conditions used to measure symptoms, not biased by motivation or environmental distracters, and daily life settings. Moreover, there may be little overlap between objectively rated life circumstances and subjective quality of life experience of patients (Fitzgerald et al. 2001). Better and more realistic measures of daily functioning may be required (Messinger et al. 2011). For example, in current working memory tasks used in clinical research the participant is asked to remember specific stimuli, but in real life, an important aspect of executive function is the autonomous selection of relevant stimuli and omission of irrelevant ones (Goldberg 2009).

A better mapping of actual dysfunctions related to schizophrenia may also help to answer the question whether schizophrenia is a uniform disorder, or a syndrome with different clinical representations (Glahn et al. 2005; Keefe et al. 1992; Nelson et al. 2009). The current understanding of certain symptom domains may be constrained by instrumental limitations to measure symptoms (Blanchard and Cohen 2006).

A more general discussion point would be the strict distinction between diagnoses such as depression, schizophrenia and anxiety disorder. It has been observed by some clinicians (personal communications) that diagnosis may even partly depend on which symptoms patients report as most invalidating, on behavior most apparent during observation, or even on the psychiatric department a patient is admitted to. Moreover, symptoms belonging to different psychiatric diagnoses as classified in the DSM-IV strongly overlap (Borsboom et al. 2011). A more symptom-cluster based approach of symptoms may help to find shared origins for certain groups of symptoms.

It would be interesting to not only investigate domains of related symptoms, but also incorporate causation of one symptom to the other. For example, in this thesis disturbances in language processing and self-reflection are seen as symptoms that may contribute to various other symptoms. An interesting model that explains relations between symptoms has been proposed by Green: perceptual impairments > social cognitive dysfunction > defeats beliefs > experience of negative symptoms > decreased functional outcome (SIRS Conference 2012, Florence). Ultimately, more complex models could be formulated where disturbances in one function may lead to a cascade of other dysfunctions (Cramer et al. 2010). These cascades may then even interact with the personality of an individual, and help to unravel the question why some persons develop a psychiatric disorder, and others do not (Cramer et al. 2010).

Well defined domains of symptoms may be a good starting point for further investigation of their neuroanatomical background (Glahn et al. 2005; Kirkpatrick and Fischer 2006). Symptoms that cluster together on a phenotypical level may also have a shared neural background (Bell et al. 2010; Goghari et al. 2010). E.g. concerning our two factor model of negative symptoms, social amotivation may be an important core cause for negative symptoms (Foussias and Remington 2010) and may be caused by DLPFC dysfunction (Goldberg 2009; Kimhy et al. 2006). On the other hand, expressive deficits may be linked to the inferior parietal lobule (Kimhy et al. 2006). More studies are now on their way linking data-

determined symptom dimensions to their neural background, and they may be an important step forward for the field.

Schizophrenia may well be a multidimensional disorder, with different neuroanatomical substrates per subtype (Davidson and Heinrichs 2003; Pinkham et al. 2003). Some disease-linked brain abnormalities may be present in one subgroup of patients, while other abnormalities are present in others (Kirkpatrick et al. 2001). While some patients with schizophrenia do not shows cognitive dysfunctions (Keefe 2007), and may not show prefrontal abnormalities, others do show prefrontal abnormalities (Davidson and Heinrichs 2003). Or, patients with paranoid symptoms have shown abnormalities in their social cognitive brain network and a related social cognitive dysfunction, but non-paranoid patients do not (Pinkham et al. 2008).

Treatment of negative symptoms and other prefrontal dysfunctions

Better characterization of symptoms has important implications for adequate diagnostics and treatment, and this is also the case for negative symptoms (Kirkpatrick et al. 2006; Messinger et al. 2011). When drugs always affect two symptoms similarly, measuring both symptoms has no additive value (Laughren and Levin 2011). On the other hand, negative symptoms of schizophrenia are now often used as one entity to evaluate treatment effects (Bell et al. 2011). But as Chapter 9 shows, only specific symptoms improve after treatment with a antipsychotic with a specific receptor profile, while the total negative symptom cluster does not. In this case, aripiprazole (a partial DA agonist) led to a specific improvement of feelings as measured by different questionnaires, while no effects were found for initiative or social interactions.

Illness outcome should be the primary variable of interest in clinical research. An interesting approach to investigate antipsychotic effects is to focus on brain activation. Chapter 8 shows that dopamine and serotonin binding strength of antipsychotics influence prefrontal activation. A high dopamine receptor affinity caused in general a decrease in prefrontal activation, which has been linked to negative symptoms and cognitive impairments. Weaker dopamine

binding and serotonin antagonism more often increased or preserved prefrontal activation. However, most reviewed studies overlooked or failed to show concurring clinical and behavioral effects of treatment, (e.g. Bishara and Taylor 2008; Honey et al. 1999). This controversy should receive more attention in the future. Whereas Chapter 8 only focused on activity in the PFC, future studies should focus on other brain areas and focus on different measure of brain function. For example, other studies have shown that the DMN and motor network show decreased fluctuations in response to antipsychotics (Abbott et al. 2011).

Furthermore, antipsychotics with different receptor profiles (Arnt and Skarsfeldt 1998) are often classified as one group of 'atypicals' (Bell et al. 2011). Besides dopamine, serotonin has important effects on prefrontal brain circuits (Bishara and Taylor 2008; Gozzi et al. 2010; Meltzer et al. 2003), as have glutamate (Belsham 2001; Laruelle et al. 2003), acetylcholine (Jarskog et al. 2007; Meltzer et al. 1999), and noradrenaline (Di Pietro and Seamans 2008; Goldman-Rakic and Selemon 1997). Targeting these neurotransmitters has already shown to influence cognitive performance, e.g. glutamate (Yurgelun-Todd et al. 2005), serotonin (Meltzer et al. 2003; Yurgelun-Todd et al. 2005) or acetylcholine (Nahas et al. 2003) may provide potential targets. Moreover, noradrenaline appears to be equally important for cognitive function as dopamine (Fuster 2009). By focusing on these neurotransmitters systems, and possibly others as well, treatment resistant symptoms, such as negative symptoms and cognitive impairments, may be amenable to treatment (Vita and De Peri 2007).

Besides pharmacological interventions, other, non-pharmacological ways to treat negative symptoms deserve further investigation. At the University Medical Center Groningen an ongoing study is investigating whether applying magnetic pulses to the prefrontal cortex by Transcranial Magnetic Stimulation (TMS) may ameliorate negative symptoms (Dlabac-De Lange et al. 2011). Other effective treatment strategies of negative symptoms may be psychological interventions, such as Behavioral Activation Therapy (Mairs et al. 2011). These methods may be as effective as medication, but cause less side effects. Most probably, in view of

the complex nature of negative symptoms in schizophrenia, an integrated treatment program should include combination of pharmacological, psychological, social, and vocational interventions.

Thus, because multiple neurotransmitter systems are implicated in schizophrenia, individually tailored and integrated treatment strategies could be a large step forward in treatment. As the majority of clinical trials evaluates only one intervention to prove a treatment principle, integrated and individualized treatment strategies imply a challenging rethinking of clinical trial design and evaluation.

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12. Summary

The prefrontal cortex has an important leading role in brain functions. These regulating brain functions include executive function, goal-directed behavior, memory processes, initiative, and social behavior. To regulate all its brain functions, the prefrontal cortex operates within brain networks, as information is collected from all parts of the brain, and newly planned behavior is redirected to all parts of the brain. Different brain networks exist, which show slow fluctuations in the BOLD signal. These fluctuations possibly represent intrinsic neural activity and are related to cognitive function.

Dysfunction of the prefrontal networks may lead to disorders in which its higher order brain functions are impaired, such as schizophrenia. This thesis discusses different cognitive functions in relation to prefrontal network connectivity in patients with schizophrenia. In addition, the thesis focuses on the treatment options of negative symptoms, which may also originate from prefrontal dysfunction.

Language impairments and lateral prefrontal connectivity are disussed during resting state in Chapter 2 and during task performance in Chapter 3. These chapters show that schizophrenia patients indeed have altered connectivity between prefrontal regions and more posterior language and auditory regions, both during rest and performance of a task. In resting state, additional increased connectivity was observed between the anterior cingulate cortex, involved in source monitoring, and language regions.

Chapter 4 discusses a process with both emotional and language aspects; it focuses on the relation between associative emotional learning and prefrontal connections. The results of the study indicate that decreased abilities of patients to make associations between words and emotions, i.e. linking language and emotion, may relate to altered prefrontal network connectivity. However, the observed effects were weak.

Emotion processing such as self-reflection is one of the functions of the default mode network. Self-reflection problems may cause multiple symptoms of schizophrenia. Chapter 5 reports on the link between poor insight in schizophrenia and default mode network (DMN) resting state connectivity, because impaired self-reflective capacities may underlie poor insight. Patients with poor insight indeed have decreased connectivity in DMN regions involved in self-reflection and auto-biographical memory, namely the anterior cingulate cortex and precuneus.

Self-reflection may also be important for a good awareness of emotional state. An impaired ability to evaluate and describe emotions is called alexithymia. Chapter 6 reports on disturbed DMN function in healthy subjects with alexithymia. Persons with alexithymia show decreased connectivity of DMN areas within the network, and instead increased connectivity to other brain areas such as sensory and motor areas.

Alexithymia overlaps to certain extent with negative symptoms of schizophrenia, e.g. both involve reduced emotional expression. The construct of negative symptoms as one group has been debated. Chapter 7 indeed shows that negative symptoms may consist of two sub-domains, expressive deficits and social amotivation, which may have relevance for research into the neural correlates and into treatment.

Negative symptoms may originate from impaired prefrontal function, and it has been hypothesized that newer antipsychotics may be superior to older ones in that they stimulate prefrontal activation. Chapter 8 investigates whether antipsychotics with different receptor profiles may have a different effect on prefrontal activation by reviewing the published neuroimaging literature. Prefrontal activation indeed increases after treatment with weaker DA antagonists, however symptoms do not improve concurrently.

Chapter 9 expands on the construct of negative symptoms and antipsychotic treatment by investigating effects of aripiprazole (a partial dopamine agonist) on different negative symptoms. The chapter shows that only specific symptoms may improve due to treatment with this new antipsychotic. These findings may act as a good starting point for future research.

13. Nederlandse samenvatting

Achtergrond

De prefrontale cortex (het voorste gedeelte van de hersenen) speelt een belangrijke rol in dit proefschrift. De prefrontale cortex (PFC) heeft een rol in complex gedrag, zoals sociale interactie, geheugen, aandacht, het starten en stoppen van activiteiten en het wisselen van activiteiten (Fuster 2009; Goldberg 2009). Deze functies van de PFC hebben allen te maken met het evalueren van gedrag uit het verleden, en het creëren of aanpassen van doelen en gedrag op basis van deze evaluaties. De prefrontale cortex zorgt er voor dat mensen kunnen leven in complexe, sociale situaties, en geavanceerde vaardigheden beheersen om te overleven (Goldberg 2009).

Om zijn complexe functies te kunnen uitvoeren, heeft de prefrontale cortex verbindingen met het hele brein (Fuster 2009) en vervult hij een rol als een soort dirigent van een orkest (Goldberg 2009). De PFC is geen uniform geheel, maar bestaat uit verschillende sub-gebieden met elk een andere functie. Deze sub-gebieden hebben in die functie ook andere verbindingen met specifieke delen van het brein. De onderste en middelste delen van de PFC (ventromediale PFC) zijn vooral betrokken bij de emotionele regulatie van gedrag. Ze zijn het sterkst verbonden met een emotioneel systeem midden in de hersenen, het limbisch systeem (Fuster 2009; Goldberg 2009). De zijkanten van de PFC (dorsolaterale prefrontale cortex) zijn meer betrokken bij planning en werkgeheugen, en hebben verbindingen met hersengebieden die daar meer mee te maken hebben, zoals de pariëtaalkwab (Fuster 2009; Goldberg 2009). Zowel de ventromediale als de dorsolaterale prefrontale gebieden zijn verbonden met de anterieure cingulate cortex (ACC). Deze bevindt zich in het midden van de hersenen achter de ventromediale PFC, en is betrokken bij zelfevaluatie en het aanpassen van gedrag bij veranderende situaties (Allman et al. 2001).

Al in 1974 bleek uit onderzoek dat de prefrontale cortex tijdens rust actiever is dan de rest van het brein (Ingvar and Franzen 1974). Hersenonderzoek

met functional Magnetic Resonance Imaging (fMRI) richtte zich tot dat moment vooral op veranderingen van hersenactiviteit tijdens het uitvoeren van een bepaalde taak (Wicker 2003). Echter, het lijkt er op dat de PFC een belangrijk onderdeel van een netwerk van hersengebieden is dat juist heel actief is tijdens rust (Gusnard and Raichle 2001), en minder actief wordt tijdens een taak. Dit netwerk is betrokken bij het verwerken van informatie die te maken heeft met een persoon zelf (Gusnard and Raichle 2001) en wordt het "default mode netwerk" (DMN), vrijvertaald het "rustbrein" genoemd.

Het default mode network is een netwerk van hersengebieden die samen een gelijktijdige toe- en afname van activiteit laten zien (Beckmann et al. 2005; Buckner et al. 2008; Raichle and Gusnard 2005). Naast het DMN zijn meer van deze netwerken, bijvoorbeeld voor zintuiglijke waarneming (zien, horen), motorisch gedrag (bewegen) of geheugen (Beckmann et al. 2005; Damoiseaux et al. 2006; Van de Ven et al. 2004). Ze overlappen met al bekende groepen hersengebieden die tijdens een bepaalde fMRI taak actief worden (Smith et al. 2009; Van den Heuvel and Hulshoff Pol 2010).

De prefrontale cortex lijkt een coördinerende rol te hebben in het functioneren van de netwerken. Dit is met name het geval bij het DMN, maar ook voor andere netwerken lijkt dit te gelden (Northoff and Bermpohl 2004; Northoff et al. 2006). Zo heeft de mediale prefrontale cortex een regulerende rol bij zelfevaluatie (Gusnard and Raichle 2001; Northoff and Bermpohl 2004; Raichle et al. 2001). Bij andere cognitieve processen, zoals taal en geheugen, lijkt de vooral laterale PFC een belangrijke rol te spelen als schakel tussen zelfevaluatie en het verwerken van informatie uit de buitenwereld (Northoff and Bermpohl 2004; Northoff et al. 2006; Qin and Northoff 2011).

Waar de prefrontale cortex binnen het DMN een regulerende functie vervult, lijkt het DMN op zijn beurt weer de rol te hebben andere netwerken te reguleren (Hassabis and Maguire 2007; Kim 2010). Het DMN werkt hierbij samen met een ander netwerk dat juist actiever wordt tijdens cognitieve uitdaging (uitvoeren van taken), met de dorsolaterale prefrontale cortex (DLPFC) als belangrijk onderdeel (Fransson 2006). Beide netwerken wisselen elkaar waarschijnlijk af in het reguleren van hersenactiviteit.

Het bestuderen van de samenwerking (interacties) tussen hersengebieden in een netwerk wordt connectiviteit analyse genoemd. Deze analyse vormt een belangrijke aanvulling op huidig fMRI onderzoek naar activatie van hersengebieden met cognitieve taken (Fox and Raichle 2007; Van den Heuvel and Hulshoff Pol 2010). Vaak wordt nu in MRI analyses naar afwijkende activiteit van losse hersengebieden gekeken (Fletcher et al. 1999; Glahn et al. 2005), maar bestudering van netwerken met connectiviteit analyses lijkt biologisch ook waardevol (Fuster 2009; Goldberg 2009). Bovendien heeft het ook een aantal voordelen om connectiviteit tijdens rust, oftewel resting state, te bestuderen. Zo worden resultaten niet beïnvloed door verschil in cognitieve capaciteiten tussen groepen, bijvoorbeeld in onderzoek met patiënten (Fransson 2006; Smith et al. 2009).

Een populaire techniek om te kijken naar samenwerking tussen hersengebieden is Independent Component Analysis (ICA) (Beckmann et al. 2005; Calhoun et al. 2001). Deze techniek probeert 'originele' signalen te filteren uit het gemeten signaal dat bestaat uit een mix van verschillende signalen. Een simpel voorbeeld is een microfoon die een signaal opvangt van twee pratende mensen. In dat geval stelt ICA in staat om uit het samengestelde opgevangen geluid, de twee oorspronkelijke stemmen te reconstrueren. Op dezelfde manier kan ICA het signaal van verschillende netwerken in de hersenen herleiden uit een gemeten MRI signaal tijdens rust, en kan er verder onderzoek naar deze netwerken worden gedaan (Damoiseaux et al. 2006; Fox and Raichle 2007).

Een groot voordeel van deze ICA techniek is dat iemand niet van te voren hoeft te voorspellen hoe de netwerken er uit zien (Van de Ven et al. 2004; Van den Heuvel and Hulshoff Pol 2010). De techniek is daarom heel geschikt om naar netwerken te kijken bij psychiatrische aandoeningen zoals schizofrenie, waarbij niet van te voren bekend is welke veranderingen er in het brein te verwachten zijn.

Prefrontale netwerken in schizofrenie

Schizofrenie is een psychiatrische aandoening met een verscheidenheid aan symptomen, zoals het horen van stemmen, het hebben van overtuigingen die moeilijk te begrijpen zijn en verwardheid in het denken. Daarbij hebben veel mensen met schizofrenie problemen met het richten van de aandacht, het geheugen (o.a. werkgeheugen) en het oplossen van problemen. Deze problemen worden samen cognitieve functieproblemen genoemd. Zoals hiervoor beschreven, speelt de prefrontale cortex een belangrijke rol bij de uitvoering van verschillende cognitieve functies (Aleman et al. 1999; Goldberg 2009; Goldman-Rakic 1994; Rissling et al. 2010; Wible et al. 2009). Mogelijk speelt een verstoring in de PFC een belangrijke rol bij de cognitieve beperkingen en veranderingen in gedrag die optreden bij mensen met schizofrenie (Goldberg 2009; Goldman-Rakic 1994; Weinberger and Berman 1996). Ook zou een verminderde regulerende rol van de prefrontale cortex kunnen leiden tot ontremming van andere hersengebieden en het ontstaan van bepaalde symptomen (Frith et al. 2009; Goldberg 2009).

Mensen met schizofrenie laten verminderde activiteit zien van de prefrontale cortex (Davidson and Heinrichs 2003; Hill et al. 2004; Weinberger and Berman 1996), dit wordt ook wel ook wel hypofrontaliteit genoemd (Ingvar and Franzen 1974). Preciezer geformuleerd, bij eenvoudige taken laten patiënten meer activiteit zien in de PFC dan mensen zonder schizofrenie (controles), terwijl ze vergelijkbaar presteren. Maar wordt de opdracht te moeilijk, dan laat de PFC bij mensen met schizofrenie juist minder activiteit zien en zijn ook de prestaties slechter vergeleken met mensen zonder schizofrenie (Jansma et al. 2004; Liddle and Pantelis 2003; Mendrek et al. 2004; Mendrek et al. 2007).

Er lijkt bij schizofrenie sprake te zijn van een verstoring in de feedbackmechanismen tussen de PFC en andere hersengebieden (Fusar-Poli et al. 2007). Anders gezegd, er is een verstoorde connectiviteit van de PFC met andere hersengebieden, waarbij ook de verbindingen van het DMN zijn aangedaan (Auer 2008; Buckner et al. 2008; Greicius 2008). Vooral de de verbindingen tussen ver uit elkaar gelegen hersengebieden zijn aangedaan (Lynall et al. 2010; Van den Heuvel and Hulshoff Pol 2010). Het DMN speelt bovendien een rol in functies die vaak verstoord zijn bij schizofrenie, zoals zelfreflectie (Kuhn and Gallinat 2011;

Van der Meer et al. 2010) en het niet weten waar de eigen gedachten of waarnemingen vandaan komen (misattributie) (Buckner et al. 2008; Northoff and Bermpohl 2004). Ook heeft het DMN een belangrijke rol in de regulatie van activiteit van andere hersennetwerken (Fransson 2006). Een verstoorde (prefrontale) DMN activiteit kan leiden tot overactiviteit in andere netwerken (Buckner et al. 2008; Van et al. 2010), wat weer kan samenhangen met sommige symptomen van schizofrenie.

Ook het functioneren van die andere hersennetwerken en hun onderlinge interactie spelen een rol bij schizofrenie (Glahn et al. 2005; Goldberg 2009; Minzenberg et al. 2009). Mogelijk is een sprake van veranderde functie van een zogenaamd cerebellair-thalamisch-temporaal-striataal-prefrontaal–netwerk (Frith et al. 2009). Een ander interessant model gaat er van uit dat de amygdala, of amandelkern, mogelijk overactief is, en de functie van de PFC overschaduwt (Grace 2000). Dit hersengebied geeft relevantie aan belangrijke, vaak bedreigende stimuli uit de omgeving. Het zou ook zo kunnen zijn dat de PFC te weinig actief is, waardoor de amygdala te weinig wordt geremd, waardoor te sterke ervaring van emoties als angst zouden kunnen ontstaan.

Belangrijk om te vermelden is dat in dit proefschrift het cerebellum (kleine hersenen) en ook de amygdala (amandelkern) weinig aandacht krijgen, terwijl de eerste betrokken is bij planning en werkgeheugen en de tweede bij emotieverwerking, en beiden een onderdeel van het DMN zijn in ruimere definities. In vervolgonderzoek zou dit deel van de hersenen meer aandacht moeten krijgen.

Naast een algemene benadering van afwijkingen in netwerkinteracties in schizofrenie, is het ook interessant om te kijken naar de relatie tussen specifieke symptomen en verstoorde hersengebieden. Dit is het onderwerp van de volgende sectie.

Prefrontale netwerken en hun relatie met symptomen van schizofrenie

Een beter inzicht in de neurale achtergrond van cognitieve symptomen zou kunnen leiden tot betere behandelopties (Heinrichs and Zakzanis 1998; Palmer et al. 2009; Rissling et al. 2010). Cognitie is een brede term, en kan worden verdeeld in neurocognitie en sociale cognitie (Foussias and Remington 2010). Schizofreniepatiënten laten afwijkingen in verschillende neurocognitieve processen zien (Fusar-Poli et al. 2007; Glahn et al. 2005). Een verstoring in de dorsolaterale PFC (DLPFC) is mogelijk verantwoordelijk voor deze problematiek (Fusar-Poli et al. 2007; Goghari et al. 2010; Goldman-Rakic 1994; Minzenberg et al. 2009; Minzenberg et al. 2009). De mediale prefrontale cortex is mogelijk juist meer betrokken bij emotionele en sociale cognitieve problemen (Chemerinski et al. 2002; Goghari et al. 2010), die verderop zullen worden besproken.

Taal is waarschijnlijk een belangrijk aspect van executief of neurocognitief functioneren (DeLisi 2001; Goldberg 2009). In veel onderzoek is aangetoond dat schizofreniepatiënten taalproblemen hebben (Crow 2008; Stephane et al. 2001; Wible et al. 2009). Mogelijk worden deze veroorzaakt door een verminderde controle van de prefrontale cortex over meer naar achter gelegen hersengebieden (Allen et al. 2008; Goldberg 2009; Wible et al. 2009).

Hoofdstuk 2 en 3 onderzoeken connectiviteit in taalnetwerken tijdens respectievelijk een taal taak en resting state. Beide studies tonen aan dat er een verminderde connectiviteit is tussen temporale en prefrontale hersengebieden, consistent met andere studies (Ford et al. 2010; Hashimoto et al. 2010; Jeong et al. 2009; Karlsgodt et al. 2008). Hoewel hoofdstuk 3 een verschil aantoont tussen schizofrenie patiënten met en zonder (auditieve) hallucinaties, doet hoofdstuk 2 dit niet. Dit kan komen doordat in het laatste geval een techniek gebruikt wordt die stabiele kenmerken van het brein meet, en in het eerste geval de gebruikte techniek meer gevoelig is voor veranderlijke kenmerken. Ook toont hoofdstuk 2 een verminderde connectiviteit tussen taalgebieden en de anterieure cingulate cortex aan. Een verstoorde evaluatie van zelfgegenereerde taal, bijvoorbeeld als iemand in zichzelf denkt, is hier een mogelijk gevolg van (Brüne et al. 2008; Simons et al. 2010; Stephane et al. 2001; Wang et al. 2011).

Taal is een cognitief proces met zowel neurocognitieve als sociaal cognitieve aspecten (Hashimoto et al. 2010; Li et al. 2009; Stephane et al. 2001; Wible et al. 2009), en waarschijnlijk spelen de prefrontale en DMN gebieden hier een belangrijke rol in (Li et al. 2009; Stephane et al. 2001; Wible et al. 2009). Een verstoorde representatie van de 'zelf', kan leiden tot problemen in de interpretatie van dagelijkse sociale situaties en activiteiten (Nelson et al. 2009), hetgeen kan zorgen voor een verstoorde sociale cognitie (Frith 1995; Sass and Parnas 2003). Problemen met zelf-evaluatie kunnen leiden tot zowel een excessieve focus op de zelf (hyperreflexiteit), als tot een verminderde zelf-evaluatie (Parnas and Handest 2003; Sass and Parnas 2003). Beiden kunnen onderstaande problemen tot gevolg hebben.

Hyperreflexiteit in schizofrenie kan leiden tot het vormen van niet correcte associaties (Parnas and Handest 2003; Sass and Parnas 2003), bijvoorbeeld tussen gevoel en daarbij passende woorden (Murray et al. 2010). Dit wordt associatief emotioneel leren genoemd. Een prefrontaal netwerk dat ook andere emotionele hersengebieden bevat, speelt hier een belangrijke rol bij (Achim and Lepage 2005). Hoofdstuk 4 laat zien dat een verstoorde connectiviteit van een prefrontaal netwerk met de emotionele hersengebieden mogelijk te maken heeft met een verstoord associatief emotioneel leren.

Een verminderde zelfreflectie kan ten grondslag liggen aan een verminderd bewustzijn van bepaalde symptomen en dus een verminderd ziekte-inzicht (David 1990; Northoff et al. 2006; Van der Meer et al. 2010). Dit is een veel voorkomend probleem bij schizofrenie (Amador and David 2004). Zelfevaluatie is één van de belangrijkste functies van het DMN (Buckner et al. 2008; Van der Meer et al. 2010). Aangezien patiënten met schizofrenie een verstoorde functie van DMN gebieden laten zien, zou dit ook kunnen leiden tot verminderd ziekte-inzicht. Hoofdstuk 5 beschrijft dat patiënten met slecht ziekte-inzicht inderdaad verminderde connectiviteit in bepaalde DMN gebieden hebben. Vaak wordt gezegd dat vooral prefrontale gebieden te maken hebben met inzicht in zelfreflectie (Johnson et al. 2002; Van der Meer et al. 2010), maar deze studie lijkt

aan te tonen dat ook posterieure gebieden zoals de precuneus betrokken kunnen zijn (Carter et al. 2001; Kuhn and Gallinat 2011; Morgan et al. 2010).

Een verstoord zelfbewustzijn vertoont ook samenhang met negatieve symptomen van schizofrenie en een verstoorde ervaring van emoties (Sass and Parnas 2003). Het vermogen om te kunnen reflecteren is van belang voor goed emotioneel besef (Lane et al. 1997) en het goed kunnen beschrijven van emoties (Swart et al. 2009). Indien iemand verminderd is staat is om gevoelens te ervaren, herkennen en beschrijven, wordt er gesproken van alexithymie (Aleman 2005). Dit persoonskenmerk kan leiden tot psychiatrische problematiek (Taylor et al. 1997). Er is een sterke relatie aangetoond tussen alexithymie en negatieve symptomen van schizofrenie gemeten met vragenlijsten (Cedro et al. 2001; Van 't Wout et al. 2007; Yu et al. 2011). Ook op neuraal niveau lijkt deze relatie er te zijn, aangezien er hersengebieden zijn die zowel bij alexithymie als bij negatieve symptomen een rol spelen (Van 't Wout et al. 2007; Yu et al. 2011). Het DMN zou hierbij van belang kunnen zijn, vanwege zijn betrokkenheid bij zelfreflectieve processen (Qin and Northoff 2011).

Hoofdstuk 6 beschrijft de betrokkenheid van het DMN bij alexithymie in gezonde studenten. Dit is een interessante onderzoekspopulatie om kennis over schizofrenie en negatieve symptomen op te doen, zonder een bias van andere psychopathologie of medicatie. Personen met alexithymie hebben inderdaad een verminderde connectiviteit van DMN gebieden binnen het netwerk, en juist een versterkte connectiviteit naar andere gebieden. Interessant om te vermelden is dat personen met alexithymie mogelijk wel in staat zijn om emoties te beoordelen als ze hier expliciet om gevraagd worden (Berthoz et al. 2002), maar niet wanneer ze automatisch, zelfbewust emoties te moesten beoordelen (Reker et al. 2009).

In het algemeen laten bovenstaande resultaten zien dat zelfevaluatie en taal belangrijk zijn voor veel dysfuncties bij schizofrenie (Crow 2008; Nelson et al. 2009; Parnas and Handest 2003; Sass and Parnas 2003; Stirling et al. 2001). Ook kan geconcludeerd worden dat het DMN en prefrontale gebieden hierin een belangrijke rol hebben (Brüne et al. 2008; Cooke et al. 2008; Schilbach et al. 2008).

Negatieve symptomen en hun behandeling

Hoewel er tot dusver is gekeken naar hersenfunctie, is ook een goede definitie van symptomen van belang als uitgangspunt voor verder onderzoek. Het volgende gedeelte focust op het construct negatieve symptomen, en behandeling daarvan.

Negatieve symptomen, mogelijk de meest belangrijke symptomen van schizofrenie (Andreasen and Flaum 1991; Foussias and Remington 2010), worden nu vaak gezien als een coherente groep symptomen. Al in de jaren 80 werd gesuggereerd dat er mogelijk meerdere subgroepen negatieve symptomen bestaan (Goghari et al. 2010; Kirkpatrick et al. 2001). Een manier om de samenhang tussen symptomen te bestuderen is factoranalyse (Blanchard and Cohen 2006; Peralta and Cuesta 1995). Met deze techniek is al aangetoond dat er waarschijnlijk twee subgroepen negatieve symptomen bestaan, namelijk 'expressieve afwijkingen' en 'sociale demotivatie' (Blanchard and Cohen 2006; Foussias and Remington 2010; Peralta and Cuesta 1995). Een vergelijkbaar concept wordt nu zelfs voorgesteld voor de nieuwe versie van het diagnostisch handboek DSM-V (Messinger et al. 2011).

De meeste studies die het construct negatieve symptomen onderzochten zijn niet recent en bovendien werd er gebruik gemaakt van kleine steekproeven (Blanchard and Cohen 2006; Foussias and Remington 2010; Peralta and Cuesta 1995). Hoofdstuk 7 laat zien hoe de structuur van negatieve symptomen wordt onderzocht in een grote steekproef, en hoe deze structuur wordt bevestigd in een onafhankelijke steekproef.

Een herziende visie op het construct van negatieve symptomen zou belangrijke implicaties voor diagnostiek en behandeling kunnen hebben. In een breder kader zou kunnen worden onderzocht of schizofrenie een uniforme of multidimensionale aandoening is (Glahn et al. 2005; Keefe et al. 1992; Nelson et al. 2009). Wellicht kan zelfs het onderscheid tussen verschillende diagnoses worden bekeken. Het lijkt er op dat symptomen van verschillende aandoeningen sterk overlappen (Borsboom et al. 2011), wat zou pleiten voor een betere categorisering van symptomen. Daarvoor zouden misschien wel betere meetinstrumenten ontwikkeld moeten worden (Blanchard and Cohen 2006).

Een vraag van nog fundamentelere aard is of gevonden symptoomconstructen daadwerkelijk problemen zijn die door patiënten worden ondervonden. Zo heeft onderzoek aangetoond dat patiënten wel gevoelens op het moment zelf kunnen ervaren, maar geen voorpret ervaren of niet kunnen nagenieten van mooie momenten (Kirkpatrick and Fischer 2006; Messinger et al. 2011; Sass and Parnas 2003). Het perspectief van de patiënt zou een belangrijke rol moeten spelen bij het in kaart brengen van hun problemen (Foussias and Remington 2010). Een ander voorbeeld van een betere omkadering van problematiek is het presteren op cognitieve taken. Vaak tonen patiënten goede prestaties, maar zijn er toch problemen met functioneren in het dagelijks leven (Goldberg 2009). Aandacht, motivatie, afleiding door stressoren, een verkeerd beeld van functioneren, en problemen met selectie van relevante informatie zouden hierin een rol kunnen spelen, en moeten beter onderzocht worden (Fitzgerald et al. 2001; Goldberg 2009; Horan et al. 2006; Messinger et al. 2011).

Nieuwe constructen van symptomen kunnen een goede basis vormen voor onderzoek naar hun neuroanatomische achtergrond (Glahn et al. 2005; Kirkpatrick and Fischer 2006). Symptomen die vaak samen voorkomen delen mogelijk hun oorsprong (Bell et al. 2010; Goghari et al. 2010). Zo zou de factor “expressive deficits” uit hoofdstuk 7 kunnen samenhangen met dysfunctie van pariëtale hersengebieden, en de "social amotivation" factor meer met de DLPFC (Goldberg 2009; Kimhy et al. 2006).

Een verbeterde karakterisering van negatieve symptomen en andere klachten kan ook belangrijke consequenties hebben voor diagnostiek en behandeling (Kirkpatrick et al. 2006; Messinger et al. 2011). Als medicatie altijd een vergelijkbaar effect op symptomen heeft, hoeven niet beiden gemeten te worden in een experiment, omdat de uitkomst voor beiden gelijk is (Laughren and Levin 2011). Anderzijds, verschillende constructen zoals gevonden in dit proefschrift zouden niet samengenomen moeten worden (Bell et al. 2011).

Een adequate behandeling van negatieve symptomen en cognitieve beperkingen bij schizofrenie zou wel eens de sterkste uitkomstmaat kunnen zijn (Horan et al. 2010). Medicamenteuze behandeling bij schizofrenie bestaat meestal uit behandeling met antipsychotica. De eerste generatie antipsychotica die op de

markt kwamen, blokkeerden de receptor van de neurotransmitter dopamine (Jarskog et al. 2007). Een neurotransmitter is een stofje dat signalen doorgeeft tussen verschillende hersencellen. Uit de gunstige effecten die deze middelen hadden op positieve symptomen, zoals het horen van stemmen, ontstond de dopamine hypothese. Volgens deze hypothese over schizofrenie is er te weinig dopamine in de prefrontale cortex, wat kan leiden tot negatieve symptomen (Di Pietro and Seamans 2008; Fuster 2009; Lieberman 2004). Anderzijds veroorzaakt dit een overschot aan dopamine in gebieden waar het PFC een controlerende werking over heeft, hetgeen leidt tot positieve symptomen.

De eerste antipsychotica, die vrij specifiek de dopaminereceptor blokkeerden, hadden een redelijk goed effect op positieve symptomen, maar geen bevredigend effect op negatieve symptomen en prefrontale functioneren (Bishara and Taylor 2008; Jarskog et al. 2007). Het lijkt er echter op, dat ook vele andere neurotransmitters betrokken zijn bij het ontstaan van schizofrenie (Grace 2000). Waarschijnlijk is er een verstoorde signaaloverdracht van verschillende neurotransmitters, die leidt tot een verstoorde stimulatie en remming van verschillende hersencircuits (Belsham 2001; Grace 2000; Jarskog et al. 2007; Laruelle et al. 2003). Om deze reden werden nieuwe types antipsychotica ontwikkeld, die ook aangrepen op receptoren van andere neurotransmitters, en mogelijk een beter effect op negatieve en cognitieve symptomen hebben (Arnt and Skarsfeldt 1998; Bishara and Taylor 2008; Jarskog et al. 2007).

Neuroimaging studies hebben onderzocht of er sprake is van een genormaliseerde hersenactiviteit na behandeling met verschillende antipsychotica, onder andere het effect op de PFC (Da Silva Alves et al. 2008; Davis et al. 2005; Röder et al. 2010; Vita and De Peri 2007). Een volledig overzicht van de effecten van antipsychotica op prefrontale functie was echter niet aanwezig. Dit overzicht wordt gegeven in hoofdstuk 8. Dit hoofdstuk laat zien dat een beperkte remming van dopamine, en daarnaast het aangrijpen op een andere neurotransmitter serotonine, prefrontale functie kan verbeteren. Er zijn ook verscheidene studies die een positief effect laten zien op cognitie of negatieve symptomen of prefrontaal functioneren door aan te grijpen op andere

neurotransmitters (Belsham 2001; Bishara and Taylor 2008; Gozzi et al. 2010; Jarskog et al. 2007; Laruelle et al. 2003; Meltzer et al. 2003; Nahas et al. 2003; Yurgelun-Todd et al. 2005). Kortom, toekomstig onderzoek zal ook zeker moeten kijken naar andere neurotransmitter systemen (Vita and De Peri 2007).

Veel studies richten zich op hersenactiviteit, terwijl klinische en gedragsmatige maten over het hoofd worden gezien of niet lijken te verbeteren. Dit zouden juist de primaire uitkomstmaten moeten zijn. Dit beeld was ook te zien in de studies die worden behandeld in hoofdstuk 8, zoals bij (Bishara and Taylor 2008; Honey et al. 1999). In te toekomst zouden zowel de effecten op symptomen als het functioneren van de hersenen breder in kaart moeten worden gebracht.

Een nieuwe methode om symptomen van schizofrenie te behandelen zijn zogenaamde partiële antagonisten. Zij blokkeren de dopaminereceptor niet, maar bootsen een stabiele activiteit van dopamine na (Jarskog et al. 2007; Lieberman 2004). Op deze manier zou dopamine-activiteit kunnen normaliseren in zowel de PFC als de ontremde gebieden, en zouden zowel positieve als negatieve symptomen verminderd kunnen worden (Bishara and Taylor 2008; Jarskog et al. 2007; Lieberman 2004). Hoofdstuk 9 laat zien dat bepaalde negatieve symptomen verbeteren na behandeling met een dergelijk antipsychoticum, voornamelijk op het gebied van gevoelsleven. Interessant om te zien is dat dus niet alle negatieve symptomen gelijktijdig veranderen.

Concluderend, aangezien verschillende neurotransmitter systemen betrokken zijn bij schizofrenie, en schizofrenie waarschijnlijk een multi-dimensionaal concept is, zou costum-made medicatie een grote sprong voorwaarts kunnen zijn in behandeling. Maar ook andere manieren van behandelen zouden een belangrijke rol kunnen spelen. Zo is er een onderzoek gaande in het Universitair Medisch Centrum Groningen naar het effect van het stimuleren van de prefrontale cortex (met Transcraniële Magnetische Stimulatie). Ook Behavioral Activation Therapy als een voorbeeld van psychologische behandelmethoden lijkt een interessant optie te zijn (Mairs et al. 2011). Het uiteindelijke doel zou een persoonlijke behandelaanpak kunnen zijn, waar symptoomprofielen een belangrijk uitgangspunt vormen.

14. Dankwoord

Ik zou willen beginnen met zeggen dat volgorde in dit dankwoord niet belangrijk is, en ook lengte van de alinea niet. Iedereen die heeft meegeholpen aan mijn proefschrift wil ik sowieso heel erg bedanken. Ik hoop ook dat personen die ik vergeten heb te noemen begrijpen dat een promotie een project met een groot aantal betrokkenen is, en dat iemand vergeten daarom snel gebeurt.

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Ik zou durven beweren dat een wetenschappelijke instelling niets is zonder secretaresse. Kijk maar eens wat er in een vakantie gebeurt. Door mijn promotie heb ik een boel toffe secretaresses leren kennen, maar Hedwig, jij staat op nummer 1! Bedankt voor je ongezouten mening over zaken in het NiC en daarbuiten, voor de gezamenlijke kopjes koffie (met/zonder sigaret), de gezamenlijke glaasjes rosé (na werktijd!) en ook voor het uitvoeren van de hele reeks stomme klusjes die ik je vroeg. Als er een prijs zou zijn voor nummer 1 secretaresse, zou ik hem aan jou toekennen.

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15. Curriculum vitae

Edith was born on 18th of July 1985 in Heerenveen, in the North of the Netherlands. In 1998 she started high school at the OSG Sevenwolden in Heerenveen, where she in 2003 received her Gymnasium diploma. In the last year of high school, she won the second prize in a quiz about natural sciences hosted by the University of Groningen. Always interested in nature and animals, she started studying biology in the Biological Center in Haren, near Groningen. There she discovered that despite the green surroundings and her love for animals, she would prefer to do research on human subjects. Therefore, she choose to specialize in medical biology and neurobiology. In 2005, she started - partly by chance - an internship on brain connectivity during resting state in patients with depression and anxiety, in the NeuroImaging Center. Her second internship concerned the effects of antipsychotic medication on brain function. This was in cooperation with the University Center Psychiatry of the UMCG. In 2008 Edith graduated as a medical biologist, and continued as a PhD student in the section of Cognitive Neuropsychiatry, supervised by André Aleman. Inclusion of patients in the medication trial of the project was challenging. She therefore used her experience acquired during her first internship to study brain connectivity in relation to different symptoms of schizophrenia. This resulted in this thesis on the role of prefrontal networks in schizophrenia.