The default mode network and salience network in schizophrenia

DMN dysconnectivity?

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Abstract

The default mode network (DMN) is a network in the brain associated with activity during the so-called resting state, also called a "task negative" network. This network has been shown to decrease in activity when engaged in a task (i.e. cognitive task), and increases when at rest. Recent studies have found that the DMN in patients with schizophrenia have shown tendency for a failure of deactivation of the DMN when engaging in various tasks in the scanner. We wanted to explore if the DMN in fact has a tendency for failure of deactivation. In addition to this, we wanted to investigate whether the salience network (SN) has a role in regulating the "switching" between the DMN and task positive networks. Here, data from n= 129 controls and n= 89 patients with DSM- IV schizophrenia which had undergone a working memory paradigm, were analysed with independent component analysis and dual regression approach.

We compared the two wm conditions in all three components across groups, followed by comparing components between the HC and SZ groups. We found no significant group differences in the wm conditions when comparing components across groups. However, an interesting pattern of correlation was found within groups between the ADMN and PDMN. We could not confirm a SN contribution to DMN dysfunction, but our findings did not dismiss this possibility.

Acknowledgements

This thesis has been collaboration between me, my supervisor post.doc Lars Tjelta Westlye and the Thematically Organized Psychosis (TOP) study, at Ullevål University Hospital. The TOP study is an ongoing research endeavour dedicated to gaining increased knowledge about the clinical, biological and environmental conditions that contributes to the development and onset of psychosis disorder, with a main focus on bipolar disorder, schizophrenia and related disorders.

The data used in this study, including behavioural data, SCID-I, PRIME-MD, MRI etc, have not been acquired by the author. The data has been collected at a previous occasion, and was available to the author through collaboration with TOP.

Post.doc Westlye have had a large part in helping me develop an idea for a thesis project, and introduced me to the methods and some of the concepts used in this paper. In addition, he has guided and helped with the data analysis process along the way and been extremely generous with his time. This thesis would not have been accomplished without his help.

In addition, others have been very helpful to me in this process. Christine Lycke Brandt I owe thanks for helping me with numerous questions about task paradigms, and Kristina Skåtun for help with FSL in the early stages of analysis.

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Table of content

Introduction

Schizophrenia (SZ) is a severe mental disorder that has been characterized as a disorder of connectivity (Fornito, Zalesky, Pantelis, & Bullmore, 2012). SZ has a range of clinical symptoms including characteristic distortions of thinking and perception, cognitive impairments, motor abnormalities, avolition and apathy, difficulties in communications and restricted affective expression (Rajiv Tandon, 2009; Tandon, Nasrallah, & Keshavan, 2009). These symptoms are categorized into positive and negative symptoms in addition to cognitive symptoms, disorganized thinking, mood and motor symptoms (Tandon et al., 2009).

Positive symptoms mainly present as reality distortions, which typically are in the form of delusions and hallucinations. Delusions are false beliefs that resist counterargument, typically sustained in spite of evidence that would suggest otherwise, and that under normal circumstances would alter or remove the beliefs altogether (Tandon et al., 2009). There are different categories of delusions divided into five branches, including delusions of grandeur, delusions of control, somatic delusions, persecutory delusions and ideas of reference. The latter two are the most common in patients with SZ (Tandon et al., 2009).

Hallucinations is another symptom that is typical for psychosis, and auditory hallucinations are the most frequent in SZ (Tandon et al., 2009), although hallucinations can occur in every sensory modality. Such hallucinations can for example take the form of voices speaking to the patient. Voices that threaten or accuse the patient can occur, or voices giving comments either to the patient or to other voices (Tandon et al., 2009). The onset of positive symptoms occurs generally in adolescence and early adulthood, although the physiological processes underlying the symptoms may have been active for some time before the actual symptoms emerge (Tandon et al., 2009).

Psychosis in SZ may differ from that of other psychotic disorders, in that they tend to be mood incongruent with their present feelings, and is often filled with bizarre content which may suggest a schizophrenic diagnosis (Junginger, Barker and Coe, 1992).

Negative symptoms involve affective flattening or blunting, loss of motivation, apathy and a range of other impairments in both the experience and expression of emotions. Other examples are lack of initiative, lack of social interest and an inability to experience pleasure (Andreasen, 1982; Carpenter, Heinrichs, & Wagman, 1988; Crow, 1980). There is however an important distinction between primary and secondary negative symptoms. Primary negative symptoms are fundamental or intrinsic to schizophrenic illness, whereas secondary

negative symptoms are caused by extrinsic factors linked to schizophrenia. Such factors can be for example certain types of treatment or environmental deprivation (Tandon et al., 2009).

Cognitive impairment is frequently found in SZ, albeit to a varying degree (Keefe, Eesley, & Poe, 2005; Saykin et al., 1991). Deficits are quite general, and persist through the course of the illness, although psychopathology varies across patients (Tandon et al, 2009). Cognitive domains found to be impaired to some extent in SZ includes processing speed (Dickinson, Ramsey, & Gold, 2007), episodic memory (Achim & Lepage, 2005; Aleman, Hijman, de Haan, & Kahn, 1999; Ranganath, Minzenberg, & Ragland, 2008), verbal fluency (Henry & Crawford, 2005), attention (Fioravanti, Carlone, Vitale, Cinti, & Clare, 2005; Orzack M, 1966) executive functions and working memory (Aleman et al., 1999; Barch & Smith, 2008; Laws, 1999; Reichenberg & Harvey, 2007; Tandon et al., 2009).

There are other symptoms that fall under different dimensions of mood symptoms, disorganized thought/behavior, motor symptoms, lack of insight and anxiety (Tandon et al., 2009). Patients may experience disorganized thought and speech (word salad), motor symptoms may express themselves as catatonic behavior among other symptoms, and mood can in addition to the negative symptoms be expressed as depression, mood swings and in conjunction with positive symptoms increase arousal in patients (Tandon et al., 2009).

Although the exact pathophysiological processes underlying the development of SZ are poorly understood (Fitzsimmons, Kubicki, & Shenton, 2013), there is evidence for both functional and structural connectivity brain abnormalities (Fitzimmons et al, 2013), and aberrant connectivity patterns may reflect a core mechanism.

Intrinsic activity and the default mode network

In the case of functional activation patterns and functional connectivity (FC), functional magnetic resonance imaging (fMRI) research has been at the forefront the last decade investigating the association between brain function and behavior, with important implications for disorders of the brain (Gur & Gur, 2010).

Studies on brain functioning using fMRI have often taken the path of measuring blood oxygenated level dependent (BOLD) signal response to environmental stimuli (Raichle & Zhang, 2010), typically in the form of psychological task paradigms designed to evoke a certain behavioral and neuronal response. Task based paradigms which have been used to study the activity of the brain in healthy and diagnosed individuals, but relative BOLD increases or decreases in response to experimental manipulations are typically only in the

range of 1-5%. Thus, task-based approaches have not been able to take into account the continuous intrinsic brain activity which is responsible for the main part of the energy consumption of the brain (Raichle & Zhang, 2010).

It has been demonstrated that specific and consistent parts of the brain shows deactivation during task performance, and increases activation during periods of rest (Raichle, 2001). The discovery of this task-negative brain network, or the so-called default mode network (DMN) (Raichle, 2001) have motivated a wave of research investigating the DMN and its implications for psychiatric disease. Among the areas in the brain involved in the DMN is the lateral and medial parietal cortex, medial prefrontal cortex and hippocampus (Öngür et al., 2010). The DMN in addition to increased activity during rest, have also shown a pattern of persistent intra-network synchrony (Raichle, 2010), in both early stages of sleep and under anesthesia in humans, monkeys and also rats (Raichle, 2010), indicating an organization of intrinsic brain activity.

The DMN in schizophrenia

The increased focus of intrinsic connectivity in fMRI data, which manifests as spatiotemporal correlations between distinct regions of the brain, has led to an increased number of studies investigating large-scale brain networks in psychiatric disorders (Calhoun & Adali, 2012).

Although the literature regarding connectivity in SZ has produced partly inconsistent results, two main trends of findings have emerged. The first is that patients with SZ show reduced connectivity within and between networks, manifested as both structural and functional abnormal connectivity patterns in patients compared to healthy controls (Petterson-Yeo, Allen, Benetti, McGuire, & Mechelli, 2011). Secondly, reduced connectivity in frontal brain regions in patients versus controls have been reported (Petterson-Yeo et al., 2011). This suggests that frontal brain regions are implicated in the pathophysiology. In line with this notion, previous studies have pointed to involvement of these regions in working memory and executive functions, both found to be impaired to some extent in SZ (Tan, Callicott, & Weinberger, 2009).

This should potentially have implications for the DMN. Indeed, several recent findings suggest abnormal DMN connectivity in SZ. Ongür et al. (2010) compared DMN activity in patients with SZ and bipolar disorder to healthy controls using both positron emission tomography (PET) and fMRI. The authors reported abnormal DMN activity in both patient groups, where patients with SZ showed higher activity of the frontopolar cortex and

basal ganglia, while bipolar subjects showed abnormal activity in the parietal cortex. In addition both patient groups showed higher frequency fluctuations than the healthy controls.

Garrity et al. (2007) found greater DMN activity in the posterior and anterior cingulate, parahippocampal gyrus, posterior cingulate and in the superior and medial frontal gyri, as well as left middle frontal and temporal gyri, in patients with SZ compared to healthy controls during an auditory oddball task (Garrity et al, 2007). In contrast, healthy controls showed greater DMN activation in right posterior cingulate and left and right precuneus (Garrity et al., 2007). Pineda, E. Fakra, McKenna, Clotet, and Blin (2010) reported DMN deactivation in patients compared to healthy controls during a matching task, particular in the cingulate gyrus, supporting DMN dysfunction in SZ (Pineda et al., 2010). The authors also reported reduced activation in the amygdala and putamen bilaterally, the inferior frontal gyrus, hypothalamus and right superior temporal cortex. In addition, during a labeling task the patients showed a relative failure to deactivate anterior and posterior parts of the cingulate (Pineda et al., 2010), indicating that DMN abnormalities in schizophrenia can manifest as failure of deactivation during cognitive load. Supporting this, Pomarol-Clotet and colleagues observed a failure to deactivate the DMN during a 2-back working memory (WM) task in patients with SZ compared to controls (Pomarol-Clotet et al., 2008). The authors also reported reduced activation in a network normally activated during working memory performance, including the right dorsolateral PFC (DLPFC), the frontal opercular region bilaterally and the supplementary motor area (SMA) bilaterally, the basal ganglia, the cerebellum and the right thalamus (Pomarol-Clotet et al., 2008).

Whitfield-Gabrieli et al. (2009) have further investigated DMN in combination with working memory tasks. They investigated hyperactivity and hyperconnectivity in the DMN of SZ patients and their first- degree relatives. Using a WM task consisting of 0-back and 2-back conditions, they reported that patients and relatives exhibited significantly reduced task related suppression of the DMN compared to controls. In addition, the authors found differences in neuronal recruitment during a WM task with greater activation in the right dorsolateral prefrontal cortex (DLPFC) in HZ relative to healthy controls. Importantly, the patients showed a trend of abnormally high FC in the DMN during both rest and task (Whitfield-Gabrieli et al., 2009).

Preacher (2002) also reported findings of DMN regions which supports these previous findings. In particular, the authors compared SZ patients with HC during a Sternberg item recognition paradigm (SIRP) and found abnormal recruitment in several DMN associated

regions in the patient group. Especially relevant for WM tasks, they found differences in the inferior parietal lobule, inferior frontal gyrus, medial frontal gyrus, superior frontal gyrus and cingulate gyrus.

In summary, the studies reviewed above converge on abnormal deactivation of the DMN in patients with SZ during cognitive load. However, findings from studies on SZ and the DMN have also produced diverging results (Williamson & Allman, 2012), and important questions remain. One issue is to whether connectivity abnormalities in SZ mainly reflect alterations in DMN *within-* or *between-network* connectivity, e.g. connectivity between DMN and other large-scale brain networks (Raichle & Zhang, 2010). This outstanding question is important because it would be of interest to resolve whether the tendency for failure of DMN deactivation depends on other brain networks.

Moreover, intrinsic connectivity networks (ICNs) that have largely been investigated during various task paradigms are increasingly also subject to investigation during resting-state studies (Laird et al., 2011). Indeed, resting-state networks show strong similarities to task-related networks (Smith et al., 2009), indicating that the fundamental functional organization of the brain persist across different psychological states.

The salience network: A DMN switch?

It has been proposed that a failure to deactivate the DMN during cognitive processing is an important contributing factor in psychosis disorders (Palaniyappan & Liddle, 2012). One hypothesis implicating insular cortex (FIC) have suggested that the salience network (SN), consisting mainly of the bilateral insula and anterior cingulate cortex, functions as a switch between DMN and task positive networks, although the neural mechanisms modulating the interactions between large-scale networks are unknown (Sridharan, Levitin, & Menon, 2008). Partly because of consistent structural alterations in SZ, the insula has been suggested to play a key role in the pathophysiology of the disorder (Palaniyappan & Liddle, 2012).

The insular cortex is a reciprocally connected region (Deen, Pitskel, & Pelphrey, 2011) (Augustine, 1996) and it has been found coactivation between the insula and ACC in several cognitive task (Taylor, Seminowicz, & Davis, 2009). In addition, there is evidence for both structural and functional connectivity between these two regions (Taylor et al., 2009; van den Heuvel, Mandl, Kahn, & Hulshoff Pol, 2009). Functional MRI studies of SZ have revealed abnormalities in the activation of the insula and ACC in a range of tasks, from WM paradigms to social processing (Wylie & Tregellas, 2010). Also, studies have reported

reduced connectivity involving both the insula and ACC (Palaniyappan & Liddle, 2012), but it is uncertain to what extent and under which circumstances the insula contributes to the pathology of SZ (Wylie & Tregellas, 2010).

Palaniyappan et al. (2012) proposes the concept of proximal salience, defined as a momentary state of neural activity as a result of a stimulus, which results in updating expectations, and which possibly contributes to the initiation or modification of action (Palaniyappan & Liddle, 2012). In other words, proximal salience, in order to have a potential effect of modifying or initiating action, should be tightly connected to task positive networks.

Sridharan et al. (2008) obtained components of the central executive network (CEN), SN and DMN in task performance using independent component analysis (ICA), and investigated the switching between activation and deactivation in the context of these three components (Sridharan et al., 2008). The authors found support for earlier onset of the right frontal insular cortex (rFIC) compared to activation in the CEN nodes and deactivation of the DMN nodes (Sridharan et al., 2008), supporting a sequential and thus possibly causal modulation of the CEN and DMN by the insula. These findings indicate a pivotal role of the insula in large scale brain network regulation that may be abnormal in patients with SZ.

White, Joseph, Francis, and Liddle (2010) have found results consistent with the latter findings, reporting that reduced activity of the SN was associated with poor deactivation of the DMN when attending external stimuli. Furthermore, the authors measured functional network connectivity (FNC) using constrained-lagged correlation analysis between networks identified using ICA, including insular regions, ACC, ventromedial frontal cortex, left CEN and pDMN (White et al., 2010). Supporting the hypothesis of SN dysfunction, the authors reported reduced connectivity in SZ patients compared to controls between the INS and ACC components, the INS and FDMN and LCEN and pDMN (White et al., 2010). It should be mentioned that insular dysfunction is not unique to SZ, as insula dysfunction have been reported in patients with bipolar disorder (BD) as well (Mamah, Barch, & Repovs, 2013)

Mamah et al. (2013) extracted resting-state fMRI time-series data from select ROIs, including the SN and computed average between and within network connectivity in a range of DMN related networks, demonstrating various degrees of dysconnectivity in patients with BD and SZ (Mamah et al., 2013). Notably the SN showed abnormal connectivity with cingulo opercular network (CO) and cerebellar networks (CER), although this was found to be significant in patients with BD only. Manouli et al, (2013) reported a relationship between impaired SN, DMN and CEN activity comparing healthy controls to patients with SZ during

psychosis, and reported aberrant insula, DMN and CEN activity in SZ. Furthermore, they linked SZ to impaired SN functioning during psychosis. With patients, they found a tendency for abnormal functional connectivity within SN, DMN and the CEN. They observed the SN in patients which showed decreased FC in bilateral anterior INS and increased FC in bilateral ACC, both of which are parts of the SN (Manoliu et al., 2013). In addition they found time-lagged correlation between the SN and DMN and CEN and also reported that dysconnectivity in the right anterior INS is associated with both DMN- CEN interaction, and psychosis severity in patients. Their findings indicate that the right anterior insula may be a key region in regulating the severity of psychosis (Manoliu et al., 2013).

Among the models proposed for SZ, findings regarding the SN are somewhat inconsistent (Williamson & Allman, 2012) and remains to be determined. For instance Woodward et al (2011) investigated functional resting state networks in SZ using seed-based ROI correlation analysis, identifying the DMN and SN among others. Patients with SZ showed greater connectivity between the posterior CC, and left inferior gyrus, left middle frontal gyrus and left middle temporal gyrus. Controls on the other hand showed stronger connectivity between these same regions and the CEN. Patients had less connectivity in the ECN and dorsal attention network, but no differences between the two groups were found in the SN (Woodward, Rogers, & Heckers, 2011). Unsurprisingly, it has been suggested that SN dysfunctions are alone not enough to explain all the characteristic symptoms of SZ, and that other networks are likely to be involved (Williamson & Allman, 2012).

The ambiguity of previous findings provides a rationale for further investigation of DMN-SN interactions during different task paradigms. Therefore, the main aim of the present study was to investigate a possible interaction between the DMN and SN in SZ patients. We hypothesized that there is abnormal deactivation of the DMN in patients with SZ relative to controls. We posed the question if a failure of deactivation of the DMN during a cognitive task is influenced by diagnosis, and secondly if a potential functional dysconnection between the SN and DMN contribute to such a deactivation failure. In SZ, working memory deficits are a consistently found, as has been proposed as a candidate neurocognitive marker (Preacher, 2002). Therefore we chose to investigate the impact of a WM paradigm to investigate these hypothesizes.

Materials and Methods

Participants

All subjects took part in the Thematically Organized Psychosis (TOP) study, a collaborative study involving the University of Oslo and Oslo University Hospital, funded by the University of Oslo, Regional Health Authorities and the Research Council of Norway. Healthy control subjects were randomly selected from the Norwegian citizen registration of people living in Oslo and the Oslo area, and invited by letter. Before participating, healthy control subjects were screened to exclude somatic and psychiatric illness, substance abuse, MRI- incompatibility or serious head trauma. All subjects gave written informed consent before participation and received an honorarium.

Participants with psychiatric diagnoses were recruited when attending to treatment from psychiatric units connected to the four University Hospitals in Oslo. Diagnoses were based on the Structural Clinical Interview for DSM- IV Axis I disorders (SCID-I) (*Diagnostic criteria from DSM-IV tm*, 1994; First, Spitzer, Gibbon Miriam, & B.W., 2002) administered by a physician or a clinical psychologist. Interviews covered diagnostics, symptomatology, neurocognition, drug use, and status of medication. Blood and urine tests were extracted to screen for psychopharmacological agents and substance use (St. Olavs Hospital). Diagnostic reliability was found satisfactory with and overall agreement for DSM-IV diagnosis categories of 82% and the overall kappa 0.77 (95% CI: 0.60-0.94). Exclusion criteria for all groups included hospitalized head injury, neurological disorder, IQ below 70 and age outside the range of 18-65 years.

The healthy control sample was screened with the Primary Care Evaluation of Mental Disorders (PRIME-MD) (Spitzer et al., 1994) and subjects were excluded if they or any of their close relatives had a life time history of a severe psychiatric disorder (SZ, bipolar disorder and major depression), if they had a medical condition known to interfere with brain function (including hypothyroidism, uncontrolled hypertension and diabetes), or substance abuse in the last three months. The current sample comprised 129 healthy controls and 89 patients with DSM-IV schizophrenia. Further demographics are shown in Table 1.

Table 1.

Diagnoses	Gender	N	Mean	Minimum	Maximum	Std. Deviation
KTR	M	76	34,21	18,15	54,18	7,7
	F	53	36,87	19,44	59,36	10,18

SZ	M	61	32,1	19,23	52,24	7,7
	F	28	33,36	20,26	61,55	9,94
Total	M	137	33,27	18,15	54,18	7,74
	F	81	35,66	19,44	61,55	10,17

Working memory paradigm

Data from the n-back paradigm containing 2 conditions (see below) collected during the scan session were included in the present analysis. E- prime software (version 1.0 Psychology Software Tools, Inc, Pittsburgh, PA, USA) was used to control the presentations of the stimuli using VisualSystem goggles (NordicNeuroLab, Bergen, Norway) and registering of responses through dedicated response grips.

The working memory paradigm was a visual n-back task that contained consecutive presentations of numbers between 1 and 9 (Haatveit et al., 2010; Hugdahl et al., 2004). The task consisted of two load conditions. In the 0-back condition, participants were instructed to press a response button when two numbers presented were identical. In the 2-back condition, the subjects were asked to press a response button when the two numbers presented were the same as the numbers shown two trials back in the sequence. The participants responded with their right index finger or thumb. Before scanning, all subjects underwent a short training procedure to ensure that they had understood the task instructions. Immediately before the start of the experiment, task instructions were shown. The task was presented with four ON-blocks (stimuli) and four OFF-blocks (no- stimuli). The blocks contained 18 stimulus presentations, with 3 presentations being pseudo randomized per block in the 0-back condition (12 in total), and 3-4 presentations pseudo-randomized per block in the 2-back condition (13 in total). Stimulus duration was 300 ms and the interstimulus interval was 2500 ms. ON blocks lasted for 52 s and OFF blocks lasted for 26 seconds were only a fixation cross was presented and no task performed.

MRI acquisition

MRI scans were acquired on a 1.5 T Siemens Magnetom Sonata scanner (Siemens Medical Solutions, Erlangen, Germany) supplied with a standard head coil. Volumes (n= 144 in the faces paradigm, n=156 in the n- back paradigm, n=160 in the go/no-go paradigm, 24 axial slices, 4mm thick with 1 mm gap) covering the whole brain were acquired in the axial plane, using a T2*-weighted BOLD echo-planar imaging (EPI) sequence (TR=2040 ms, TE= 50 ms, flip angle 90°, matrix 64x 64, FOV 192 x 192 mm). The first seven volumes were discarded.

Prior to the fMRI runs a sagittal T1-weighted 3D Magnetization Prepared Rapid Gradient Echo (MPRAGE) seuquence (TR= 2000ms, TE= 3.9 ms, flip angle =7°, matrix 128 x 128, FOV 256 x 256 mm) was collected and used for registration purposes in the present analysis. This sequence was run twice and combined during processing in order to increase signal-to-noise ratio (SNR).

MRI analysis

Preprocessing of the T-1weighted data was performed using FreeSurfer (http://surfer.nmr.mgh.harvard.edu) including averaging of the two MPRAGEs, motion correction and removal of non-brain tissue (Segonne et al, 2004). Preprocessing of functional data was performed using fMRI Expert Analysis Tool (FEAT) version 5.1 from FMRIB's software library (FSL, http://www.fmrib.ox.ac.uk/fsl). Conventional preprocessing was performed, including motion correction, spatial filtering by mean of SUSAN (Wolf et al., 2009) (FWHM=6.0mm), temporal filtering (sigma = 45.0s), and non-linear registration into standard space by means of FLIRT (Kim et al., 2009) and FNIRT (Whitfield-Gabrieli et al., 2009) using the T1-weighted data as interims. All preprocessed volumes were manually assessed for registration accuracy.

ICA and dual regression

ICA is a statistical method that in recent years has become a frequently used method in the analysis of resting state fMRI data and functional connectivity networks (FCN). ICA is a model free data-driven approach that extracts independent spatial components from fMRI time series maps. ICA may provide a favorable alternative to other methods because it eliminates the need of selecting a priori regions of interest as with seed based approaches or requirements of orthogonality as in principal component analysis, where components are forced to be uncorrelated (Poldrack, Mumford, & Nichols, 2011). A basic assumption of ICA is that the observed signal is actually a mix of signals from separate underlying sources. In the case of fMRI the underlying sources are assumed to reflect independent neural processes (Poldrack et al., 2011) ICA maximizes independence of the signal sources, and can also detect signal changes that are due to artifacts or subject motion (van de Ven, Formisano, Prvulovic, Roeder, & Linden, 2004).

The main interest of the current analysis was to compare large- scale brain networks between two working memory conditions, and investigate possible effects of diagnosis. We

used temporal concatenation group ICA which concatenates all datasets temporally and performs the decomposition on the full 2D space concatenated data matrix in order to identify common large scale networks across all input files without assuming common time courses.

We used multi-session group ICA with temporal concatenation using Multivariate Exploratory Linear Optimized Decomposition (MELODIC) (Beckmann, DeLuca, Devlin, & Smith, 2005; Harrison, Yucel, Pujol, & Pantelis, 2007)in FSL to compute spatial maps reflecting common components across subjects and paradigms. The decomposition was performed on a subset of 150 representative subjects due to computational (RAM) constraints. The subjects had all been through the paradigms described, making up a total of five input files per subject (GNG, 0-back, 2-back, faces negative, faces positive). Since the optimal number of components reflecting true dimensionality in the brain has not yet been established, we chose to extract 40 components based on previous studies (Beckmann et al., 2005).

Dual regression (DR) (Smith et al., 2009) was used to identify individual component spatial maps and associated time courses corresponding to the multi-subject ICA components. DR was run on all 40 components, of which three were chosen for further analysis using voxel-wise between subjects permutation testing. DR comprises several steps (Beckmann et al., 2005; Smith et al., 2009). Firstly, it uses spatial regression to obtain time-courses for each component and subject. This is done by applying a linear-model fit from the gICA components to the subject-specific data sets creating matrices of time courses for each component and subject. Secondly, time courses are normalized by their variance, and implemented in a temporal regression, were the associated fMRI data is used in a linear model fit with the time courses to create subject specific spatial maps. These maps reflect degree of synchronization, representing both amplitude and coherence across space (Roosendaal et al., 2010). Thirdly, the individual synchronization maps are collected across subjects into 4D files, were the fourth dimension is subject identification and submitted to statistical testing.

Statistical analysis

Sociodemographic variables including age and sex, behavioural response times (RTs) and accuracy in the cognitive paradigms were analysed using statistical package for the social sciences (SPSS) 21.0. Independent sample t tests were performed on the behavioral data in

both conditions of the n-back paradigm to investigate possible behavioral differences in RT accuracy between patients and controls.

For fMRI, cross-subject analysis was performed on three components: anterior default mode network (ADMN), posterior default mode network (PDMN) and the salience network (SN) using non-parametric permutation testing with randomise, part of FSL (Harrison et al., 2007). Contrasts were run with 2500 permutations.

We tested for main effects of condition (0-back > 2-back and 2-back > 0-back) across groups including age and gender as covariates. To preclude having to set cluster size thresholds and smoothing levels randomly, Threshold-Free Cluster Enhancement (TFCE) was used (McKiernan, Kaufman, Kucera-Thompson, & Binder, 2003), and significance threshold was set to $p < 0.05$ corrected for multiple comparisons across space. Next, in order to test for differences in WM modulation between groups, we extracted FC measures from voxels showing significant load modulation and performed additional tests in SPSS. Specifically, we calculated difference scores for each component (2-back minus 0-back) and performed analysis of covariance (ANCOVAs) in order to test for effects of diagnosis on WM modulation while covarying for age and sex.

Next, in order to evaluate whether degree of between-network co-activation differed between groups, we calculated the correlation coefficients between each of the component's co-activation values in each of the load conditions and compared between groups using Fischer's tests. Coefficients was further converted into a *z*-score using Fisher's *r*-to-*z* transformation on the r score of the same component from each group (Preacher, 2002)

ICA components

The main three ICA components chosen for permutation testing is shown in Figure 1, comprising the anterior (IC00) and posterior (IC05) portions of the DMN and the SN (IC01). IC00 (green) which makes up the anterior DMN (aMDN) consists mainly of the medial frontal cortices as well as a smaller portion of the medial parietal and lateral parietal cortex. IC01 (red), reflect the SN, comprising the insular cortex as well as the ACC. IC05, makes up the posterior DMN (pDMN), consists mainly of a larger part of the medial parietal cortex, the precuneus, and the posterior cingulate.

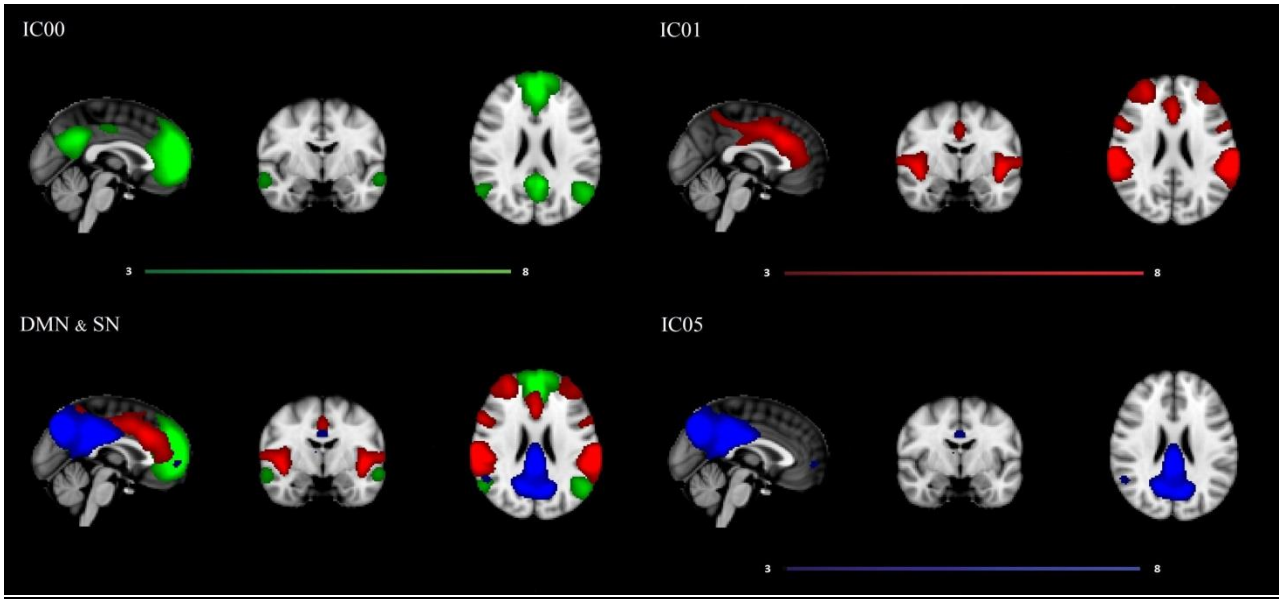

Figure 1. IC00 in green colour, consists of the ADMN, IC01 is the SN in red colour, and IC05 (blue) is the PDMN. The bottom picture shows ADMN and PDMN making up the entire DMN, together with the SN in red showing the component in context of the DMN.

Results

Behavioural data

We observed a significant (t_{198} = -2.24, p = .026, two tailed) between group difference in 0-back RT, indicating faster responses in healthy controls (M=524.2, SD = 80.77 ms) compared to the patients (M=556.6, SD= 123.7 ms). There was not significant (t_{198} = 1.52, p = .130) differences in accuracy scores in the 0-back condition between controls (M = .99, SD= .01) and patients (M = .98, SD = .10).

In the 2-back condition, we observed significant (t_{199} = -3.28, p = .001) differences in RT between controls (M = 606.4, SD = 148.8 ms) and patients (M=692.8, SD= 223.6 ms). There was also a significant (t_{199} = 3.49, p = .001) difference in accuracy in the 2-back condition between controls (M = .97, SD = .03 %) and patients (M = .94, SD = .10 %).

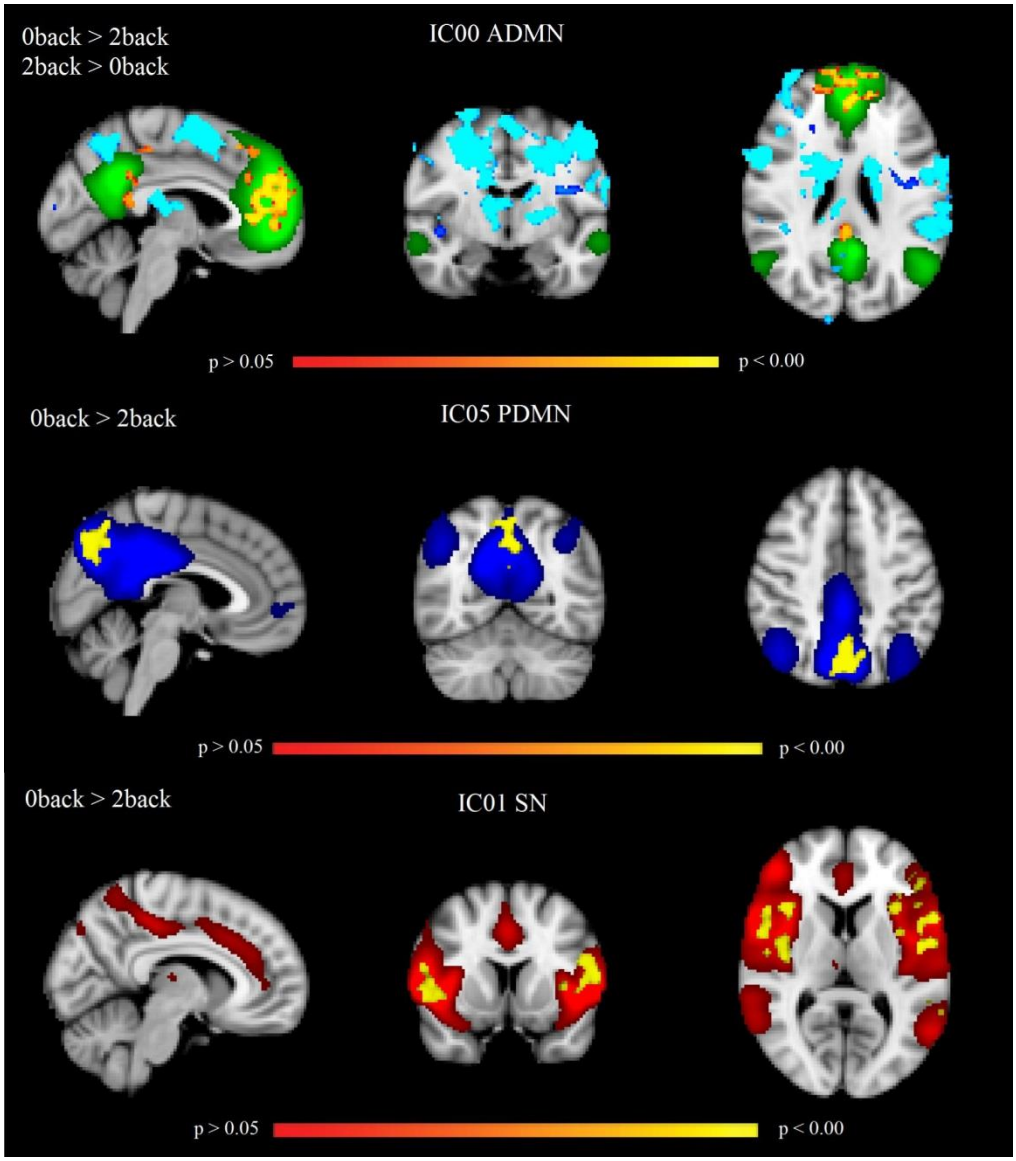

Figure 2. The picture shows significant effects after permutations testing ($p < 0.05$). The top picture shows the difference in the two wm conditions within the ADMN. The middle row shows the significant effects in the PDMN, and the bottom picture shows the significant effects in the SN.

Independent Samples t- Test for 2back condition

		t-test for Equality of Means							
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference Lower	Upper
Response-time		8,634	,004	-3,284	199	,001	-86,33833	26,28826	-138,17763	-34,49903
				-2,975	113,478	,004	-86,33833	29,02001	-143,82959	-28,84707
Accuracy		11,594	,001	3,491	199	,001	,03306	,00947	,01439	,05174
				2,825	82,952	,006	,03306	,01170	,00979	,05634

Table 2. RT and accuracy was significantly different in the 2back condition between HC and SZ patients.

Components

We extracted mean values of clusters in each component. In the ADMN, there was found a statistically significant difference in co-activition in a cluster comprising the medial prefrontal lobe, frontal pole, superior frontal gyrus, paracingulate gyrus, between the 0-back (M = 22.93, SD = 6.96) and 2-back condition (M = 28.07, SD= 9.58), t (217) = -10.39, p < .01 (two tailed), indicating increased co-activation with increased load. Mean difference was -5.14, with a 95% CI ranging from -6.12 to -4.17. Within the SN component, we observed a cluster of voxel showing increased co-activation in the 0-back (M = 22.7, SD = 6.01) compared to the 2-back condition (M = 18.35, SD = 5.83), t (217) = 12.81, p < .01 (two tailed) in areas comprising the insular cortex, angular gyrus, middle temporal gyrus and inferior frontal gyrus. Mean difference was 4.35, with CI: 3.68 – 5.02.

In the PDMN, we observed a statistically significant difference in coactivity between the 0back (M=22.93, SD=6.96) and 2back condition (M=28.07, SD= 9.58), t (217) = -10.39,

p < .01 (two tailed) in areas comprising the precuneus cortex, cuneal cortex and supracalcarine cortex. Mean difference was 5.84, with a 95% with CI: 4.58- 7.09.

Figure 3. demonstrates the mean coactivation within components in the two different conditions. There is a slight tendency for patients to show a higher mean coactivity within both the ADMN and PDMN, although these differences between groups were found not to be significant.

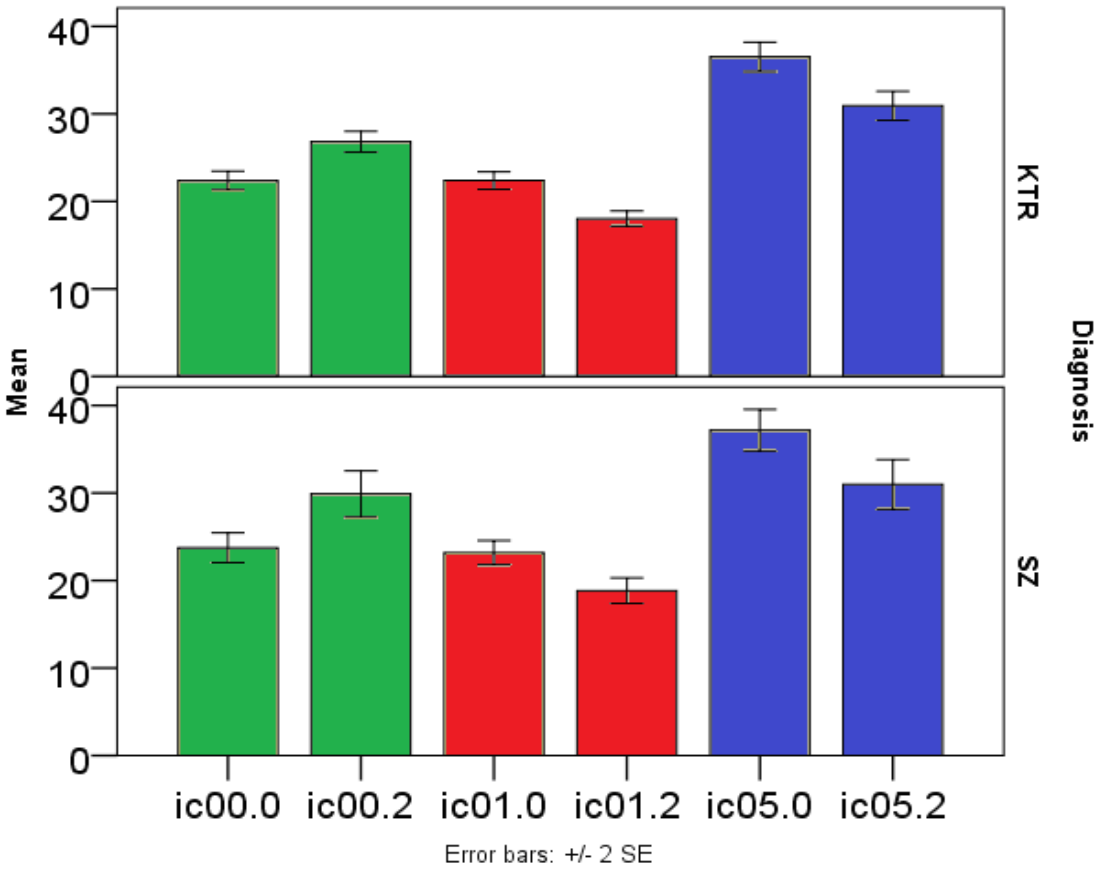

Figure 3. Mean co-activation within each component in 0-back and 2-back conditions. ADMN= green bar, SN=red, PDMN=blue.

Table 3.

Paired sample t-tests

		Paired Differences					t	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% CI Lower	95% CI Upper		
Pair 2	ic01.0 - ic01.2	4,35	5,01	,34	3,68	5,02	12,81	,000

Pair 3	ic05.0 - ic05.2	5,84	9,38	,63	4,58	7,09	9,19	,000
Pair 1	ic00.0 - ic00.2	-5,14	7,30	,49	-6,12	-4,17	-10,39	,000

Paired sampled t-tests performed within each component to obtain mean coactivity between conditions.

Univariate analysis of covariance (ANCOVAs) was performed to test the effects of the various difference scores (2back- 0back) with covariates being age and gender. Independent variable was the mean difference score between 0back and 2back within each component. In the ANCOVA for ADMN we did not observe a significant main effect of diagnosis F (1, 214) = 2,519, p =.114, or covariates gender F (1,214) = 3.206, p = .075 and age F (1,214) = .252, p= .616.

For SN we did not observe any significant main effects of diagnosis F (1,214) = .155, p= .694, or for the covariate age F (1,214) = .973, p=.325. We did however, obtain a significant covariant in gender within this component F (1,214) = 5.01, p=0.26. In the PDMN it was not found any significant main effects of diagnosis F (1,214) = .038, p=.846, or for covariates gender F (1,214) = .002, p=.964, and age F (1,214) =3.1, p= .08. Se table 4 below for details.

IC00 ADMN

Parameter	B	Std. Error	t	Sig.	Partial Eta Squared
Intercept	3,958	2,202	1,798	,074	,015
Gender=M	1,841	1,028	1,791	,075	,015
Gender=F	0[a]	.	.	.	.
Diagnosis=HC	-1,611	1,015	-1,587	,114	,012
Diagnosis=SZ	0[a]	.	.	.	.
Age	,029	,057	,502	,616	,001

IC01 SN

Parameter	B	Std. Error	t	Sig.	Partial Eta Squared
Intercept	-4,516	1,510	-2,991	,003	,040
Gender=M	-1,578	,705	-2,238	,026	,023
Gender=F	0[a]	.	.	.	.
Diagnosis=HC	-,274	,696	-,393	,694	,001
Diagnosis=SZ	0[a]	.	.	.	.

Age	,039	,039	,986	,325	,005

IC05 PDMN

Parameter	B	Std. Error	t	Sig.	Partial Eta Squared
Intercept	-10,465	2,845	-3,679	,000	,059
Gender=Male	,060	1,329	,045	,964	,000
Gender=Female	0[a]	.	.	.	.
Diagnosis=HC	,254	1,311	,194	,846	,000
Diagnosis=SZ	0[a]	.	.	.	.
Age	,130	,074	1,761	,080	,014

Table 4. ANCOVAs testing effects of group on the difference scores, with covariates being age and gender.

Correlation between component scores

In HC we found a positive correlation between co-activation in the two load conditions in the DMN cluster (r = .480, n= 129, p < .001), in the SN cluster (r=.586, n= 129, p < .001), and in the PDMN cluster (r =.677, n=129, p< .001, all two tailed). In the SZ group, we found a strong positive correlation between the two load conditions within the ADMN cluster (r = .762, n=89, p<.001), in the SN component (r=.698, n=89, p<.001) and in the PDMN (r = .580, n=89, p<.001, two tailed).

Fishers test revealed that the correlation between the two load conditions in the ADMN component was significantly stronger (z = 3.417, p<.0006, two tailed) in the SZ group compared to healthy controls. No statistically significant differences were found for neither the SN (z= 1.372, p<0.17) nor the PDMN (z= -1.152, p<0.249).

Correlations

		ic00.0	ic00.2	ic01.0	ic01.2	ic05.0	ic05.2
ic00.0	Pearson Correlation	1	,480**	,307**	,243**	,225*	,259**
	Sig. (2-tailed)		,000	,000	,005	,010	,003
	N	129	129	129	129	129	129
ic00.2	Pearson Correlation	,480**	1	,208*	,230**	,119	,204*
	Sig. (2-tailed)	,000		,018	,009	,179	,020
	N	129	129	129	129	129	129
ic01.0	Pearson Correlation	,307**	,208*	1	,586**	,423**	,352**
	Sig. (2-tailed)	,000	,018		,000	,000	,000

	N	129	129	129	129	129	129
	Pearson Correlation	,243**	,230**	,586**	1	,309**	,492**
ic01.2	Sig. (2-tailed)	,005	,009	,000		,000	,000
	N	129	129	129	129	129	129
	Pearson Correlation	,225*	,119	,423**	,309**	1	,677**
ic05.0	Sig. (2-tailed)	,010	,179	,000	,000		,000
	N	129	129	129	129	129	129
	Pearson Correlation	,259**	,204*	,352**	,492**	,677**	1
ic05.2	Sig. (2-tailed)	,003	,020	,000	,000	,000	
	N	129	129	129	129	129	129

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

a. Diagnoses = HC

Correlations

		ic00.0	ic00.2	ic01.0	ic01.2	ic05.0	ic05.2
	Pearson Correlation	1	,762**	,644**	,701**	,577**	,619**
ic00.0	Sig. (2-tailed)		,000	,000	,000	,000	,000
	N	89	89	89	89	89	89
	Pearson Correlation	,762**	1	,540**	,685**	,374**	,717**
ic00.2	Sig. (2-tailed)	,000		,000	,000	,000	,000
	N	89	89	89	89	89	89
	Pearson Correlation	,644**	,540**	1	,698**	,572**	,441**
ic01.0	Sig. (2-tailed)	,000	,000		,000	,000	,000
	N	89	89	89	89	89	89
	Pearson Correlation	,701**	,685**	,698**	1	,438**	,708**
ic01.2	Sig. (2-tailed)	,000	,000	,000		,000	,000
	N	89	89	89	89	89	89
	Pearson Correlation	,577**	,374**	,572**	,438**	1	,580**
ic05.0	Sig. (2-tailed)	,000	,000	,000	,000		,000
	N	89	89	89	89	89	89
	Pearson Correlation	,619**	,717**	,441**	,708**	,580**	1
ic05.2	Sig. (2-tailed)	,000	,000	,000	,000	,000	
	N	89	89	89	89	89	89

**. Correlation is significant at the 0.01 level (2-tailed).

a. Diagnoses = SZ

Table 5 & 6. Results from the correlation analysis, showing correlations for each component within groups.

Discussion

In the present study, we have found several interesting results. The ADMN showed interesting effect of coactivity during the 2back over the 0back condition, indicating a failure of deactivation in this component. In the SN and PDMN, we observed the opposite trend, with coactivity mainly in the 0back condition. We also found significant coactivity within components, although we did not find any significant differences between groups in mean coactivity. Further no significant effects of diagnosis were found. We did however obtain fairly strong correlations of which differed quite a bit depending on group and condition within the components. In addition we also obtained significantly different RT and accuracy in the behavioural data.

We hypothesized that there would be abnormal deactivation within the DMN of SZ patients during tasks in the scanner. Several patterns of interest emerged from or results. Firstly, the main trend in the coactivity of the ADMN was an increase in activity from 0back to 2back condition, while both the SN and PDMN showed the opposite trend with increased coactivity from 2back to 0back, as illustrated in figure 3.

Within the ADMN increased coactivity was high during the 2back condition, most notably in the paracingulate gyrus, medial frontal lobe and superior frontal gyrus. Areas like the paracingulate gyrus and frontal medial lobe are of interest since these regions shows clear effects during 2back over 0back contrast which may imply a failure of deactivation of the ADMN. These regions are considered parts of the DMN, and in addition to this, both the posterior cingulate and medial frontal cortices of the brain, are regions associated with deficits in schizophrenia (Petterson-Yeo et al., 2011). Decreased coactivity was evident outside of the component during the 0back condition, indicating the involvement of task positive networks.

The 2back over 0back contrast shows clusters in the temporal fusiform cortex, posterior division, inferior, temporal gyrus, post div. inferior temporal gyrus (tempooccipital part) and to a lesser extent the temporal fusiform cortex. These contrasts gives an indication of DMN activity differences between a relatively easy task (0-back) and the more challenging (albeit not very difficult) 2back task. If this difference in activity is because of stronger DMN activity during rest blocks, or failure to deactivate the DMN during task blocks is a question for further discussion. However, it seems unlikely based both on previous reviewed literature, and the behavioral data from the 2back condition, that the main difference in DMN activity is

caused by rest blocks, but rather more possibly induced by the task conditions. The only differences between the two conditions were the load in the ON blocks, which in the 2back condition required more cognitive effort. As such we would expect to find similar pattern of coactivity in the 0back condition if change in coactivity was induced by rest blocks, which we did not.

Although mean coactivity was found to be significant within components in each group, we did not find significant differences between the component across groups. In addition, we did not find any significant effect of diagnosis on the difference scores between groups. However, our correlation analyses showed for instance that within component correlation was much stronger for the SZ patient group than for controls in ADMN, as shown in table 4 and 5. This may imply that there in fact is a tendency for deactivation failure in the medial frontal lobe and the posterior and anterior cingulate in patients. The bar chart in figure 3 also shows a slight tendency for patients to have a larger mean difference in coactivity in the different components than the HC, which seems most evident in the ADMN and to a lesser extent in the PDMN. Although we on the basis of our results cannot infer from this a failure of DMN activity in patients, we certainly cannot rule that possibility out.

The results in the ADMN show several regions with coactivity which is consistent with previous research investigating the DMN in schizophrenia during task paradigms. However, our findings do not necessarily reflect deficits in DMN deactivation.

Pomarol-Clotet et al. (2008) investigated the DMN in SZ patients using an n-back paradigm, and found reduced recruitment of the DLPFC, the frontal opercular region bilaterally, among other regions (Pomarol-Clotet et al., 2008). Our results showed effects in the frontal pole and to some extent the superior frontal gyrus, which is consistent with the latter findings.
Other studies comparing SZ patients and HC have consistently found abnormal connectivity patterns when comparing SZ patients to controls using various paradigms (Fitzsimmons et al., 2013). Kim et al. (2009) suggests the DMN possibly exists across multiple sub networks, and not simply one consistent task negative network, a notion that certainly fits with our findings. The apparent change in activity between both of the DMN components depending on the task at hand, may possibly be the result of conjunctions between the DMN and other task related networks (Kim et al., 2009). The medial PFC as well as the ACC may be a part of such a network conjunction, having been found to demonstrate aberrant connectivity consistently in

SZ patients across a range of cognitive tasks (Arbabshirani, Havlicek, Kiehl, Pearlson, & Calhoun, 2012; Garrity et al., 2007).

The behavioural data revealed significant differences between groups in both RT and accuracy in the 2back condition, and also revealed similarly significant result for RT but not accuracy in 0back, of which should be taken into account when interpreting these results. In addition, our study comprised a large dataset, contrary to earlier studies which have yielded inconsistent results when investigating the DMN in schizophrenia (Pineda et al., 2010). Garrity et al (2007) found increases in the DMN in SZ patients in the right ACC, parahippocampal gyrus, posterior cingulate and in the superior and medial frontal gyri. Compared to our study, these results are consistent in that we found abnormal activity in SZ patients in some regions overlapping with the ones found in Garrity et al`s (2007) study. Further, Kim et al. (2009) points out that degree of DMN deactivation is influenced by a range of factors, as task type (Tomasi, Ernst, Caparelli, & Chang, 2006), task load (McKiernan et al., 2003) and schizophrenia diagnosis (Harrison et al., 2007). This has implications for our findings as well. The DMN in schizophrenia has been associated with more frequent fluctuations between the DMN and task positive networks, where we expect to see a decrease in DMN activity in parallel to gradually increasing cognitive load (Garrity et al, 2007). As such we may have obtained different results with a more demanding cognitive task.

In both the PDMN and SN we observed higher coactivation in the 0back condition, indicating change in coactivity depending on cognitive effort. The PDMN showed activity mainly in the cuneal cortex and precuneus. Regarding our SN hypothesis, we wanted to explore whether the SN contributes to a failure of DMN deactivation in SZ patients.

The PDMN did show effects in the 0back condition within the precuneus among other regions (Figure 2), which indicates the posterior part of the DMN is co-active with task positive networks in this condition. In addition, the patient group showed a slight tendency for higher mean coactivity in the PDMN than in controls during 0back. Our findings suggest a high functional connectivity between the SN and PDMN components, while the ADMN indicates the opposite pattern, were the ACC is a crucial region. White et al. (2010) reported of significantly reduced connectivity within the INS and ACC, giving support to the idea that there is a dysconnectivity between these two regions, with further implications for the ADMN.

Interestingly, this finding may be consistent with Sridahan et al (2008) who have reported that the SN may both predict and precede DMN activity in certain regions, for instance the precuneus, in which the effect is evident in the 0back over 2back condition in our results.

The cuneal cortex is associated with more active during introspection which is not unlikely during an easy task like the 0back, although this does not explain the activity observed in the ADMN in the same condition, which was outside of the canonical ADMN component. Another possibility is the involvement of the CEN and its relationship with the SN.

Sridharan et al. (2008) found evidence for the right fronto insular cortex, a key part of the SN is involved in the switching between the CEN and DMN. They located the CEN using ICA, as the right DLPFC and right posterior parietal cortex (rPPC), which we did not include in our analysis. Although our findings alone cannot confirm this, other evidence presented here supports that the SN component does have a regulating effect within the DMN, and quite possibly networks outside the DMN as well. This is an intriguing possibility that should be explored with further research. It is possible we have tapped into such a regulation dynamic as seen between the ADMN and PDMN components, possibly with the SN having a crucial role in conjunction with other networks.

Limitations

There are several limitations to this study. Firstly, the groups here were SZ patients and healthy controls. However, as schizophrenia is a psychosis disorder, there are many facets of SZ that also are expressed in other disorders like for instance bipolar disorder. Including other patient groups could potentially give a more coherent picture when investigating functional connectivity in psychiatric disease. We have also focused on three main components, namely the anterior and posterior parts of the DMN, and the SN. This however, can possibly have been too restricted, in which other critical networks essential for the DMN and SN may have been overlooked. When it comes to cognitive task, the N-back paradigm may not be sufficient to induce enough cognitive effort, which might have reflected larger differences between groups. Also, we could possibly have found a more coherent picture of SN activity we had included the CEN in our analysis. As previous research mentioned here

supports, these networks works in conjunctions with each other. We have not tested for the differences across groups directly during the two conditions of the working memory paradigm. We focused on within group differences in wm conditions, so as to compare components across groups.

Conclusion

In our study, we have not been able to confirm that there is a significant difference in the deactivation of DMN during a cognitive task, compared to healthy controls. However, we did obtain an interesting correlation pattern. The ADMN seems to have quite different pattern of coactivity during tasks than the PDMN, although these component seemingly belong to the same network. The SN follows much of the same pattern as the PDMN, which should be further investigated. This intriguing pattern of coactivity demonstrates a divide within DMN which seems to be context dependent, giving support to the idea of the DMN as a network deeply in conjunction with other task related networks and subnetworks. Still open for debate are whether connectivity abnormalities in SZ mainly reflect alterations in DMN *within*- or *between-network* connectivity. From our findings we can only speculate that there is a degree of both in schizophrenia. Given that all three components in both groups demonstrated significant coactivity within both conditions, yet differences were found in behavioral data and correlational pattern within groups, it might be possible that within networks connectivity contributes more to these phenomena than between networks. This is a question for further research and exploration.

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