Research clerkship

Exploring the neurobiological underpinnings of apathy: relationship between apathy and deactivation of the default mode network in schizophrenia patients

Floor Loonstra  
S211039  
Prof. dr. A. Aleman  
Dr. E. Liemburg  
Neuro Imaging Centre te Groningen  
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Summary

English
A critical component with regard to functional outcome in schizophrenia patients is apathy, characterized by lack of motivation and diminished goal-directed behavior. Since the default mode network (DMN) is involved in internally-directed cognitive function and attenuated during goal-directed activity, failure to suppress the DMN has been linked to several clinical features of schizophrenia. Here we suggest that apathy can be attributed to lack of DMN suppression. We hypothesized that schizophrenia patients with high apathy levels show less deactivation of the DMN during a task compared to patients scoring low on apathy. We investigated the association between apathy and DMN deactivation using arterial spin labeling in 46 patients with schizophrenia or psychotic spectrum disorder and 11 healthy controls, while performing the tower of London task during fMRI scanning. We used independent component analysis to identify DMN regions and to extract mean time courses from these corresponding components for both patients and controls. The time courses for the DMN components were plotted with apathy score as coloring and a scatterplot was used as a visual representation of the correlation. Our results demonstrated DMN deactivation during goal-directed activity. The DMN showed less activation during rest and less deactivation during the task in patients compared to controls during certain time points equally distributed between rest and task blocks. We were not able to detect a significant difference between patients and controls in modulating the DMN for most time points during the task, however. Moreover, we found no significant relationship between apathy and DMN deactivation. These results suggest that schizophrenia patients may show abnormalities in DMN operation compared to controls. However, research repeating our study needs to be performed considering our limitations (e.g., small sample size of control group and use of ASL instead of BOLD fMRI).

Nederlands
Een cruciaal component in schizofrenie patiënten met betrekking tot functioneel resultaat is apathie, wat gekenmerkt wordt door gebrek aan motivatie en verminderd doelgericht gedrag. Omdat het default mode network (DMN) betrokken is bij extern gericht cognitieve functies en verzwakt is tijdens doelgerichte activiteit, is een verstoring in het onderdrukken van het DMN gelinkt aan verschillende klinische kenmerken van schizofrenie. We suggereren dat apathie toegeschreven kan worden aan gebrek aan DMN suppressie. Onze hypothese luidt dat schizofrenie patiënten met hoge apathiescores minder deactivatie vertonen van het DMN tijdens een taak in vergelijking tot patiënten met lage apathiescores. Met arterial spin labeling onderzochten we de associatie tussen apathie en DMN deactivatie bij 46 patiënten met schizofrenie of met psychotisch spectrum stoornis en 11 controles, tijdens het uitvoeren van de tower of London taak in de fMRI scanner. Door middel van independent component analysis identificeerden we DMN gebieden en verkregen we gemiddelde tijdsreeksen voor de overeenkomstige componenten voor patiënten en controles. De tijdsreeksen van de DMN componenten werden geplott met de apathiescores als kleuring en met een scatterplot is deze correlatie visueel weergegeven. Onze resultaten lieten DMN deactivatie zien tijdens doelgerichte activiteit. Het DMN toonde minder activatie tijdens rust en minder deactivatie tijdens de taak bij patiënten vergeleken met controles tijdens bepaalde tijdpunten die gelijk verdeeld waren over rust- en taak blokken. We hebben geen significant verschil tussen patiënten en controles aan kunnen tonen in DMN modulatie tijdens de gehele tijdsreeks. Daarnaast hebben we geen significant verband gevonden tussen apathie en DMN deactivatie.
Deze resultaten suggereren dat schizofrenie patiënten afwijkingen laten zien in de werking van het DMN in vergelijking tot controles. Echter, onderzoek die onze studie herhaalt, is nodig met in acht name van onze beperkingen (zoals de kleine controlegroep en het gebruik van ASL data in plaats van BOLD fMRI).

1. Introduction

Schizophrenia is a severe psychiatric disorder with major impairments in functioning. Negative symptoms represent a distinct domain in the disease, with apathy as its core aspect (Foussias and Remington 2010). Apathy is characterized by lack of motivation and reduced levels of interest, clinically manifested by diminished goal-directed behavior, goal-directed cognition, and affective responsivity to events (Marin 1990; Marin 1991). Apathy is consistently considered as the key contributor in the relationship between negative symptoms and (psychosocial) functional impairment in schizophrenia (Foussias et al 2009; Foussias and Remington 2010; Konstantakopoulos et al 2011). In addition, recent studies report apathy as the most critical component in regard to functional outcome, unemployment and severity of disease in both chronic schizophrenia (Kiang et al 2003; Foussias et al 2009) and first episode psychosis (Faerden et al 2009). In this view, apathy is the most important factor in schizophrenia to examine, given its contribution to poor social functioning and economic impairment.

According to a review by van Reekum et al (2005), subcortical-frontal circuits are implicated in the pathophysiology of apathy, with a major role of the anterior cingulate and the dorsolateral prefrontal cortex. These disrupted neural circuits partially overlap with regions of the default mode network (DMN). Indeed, several studies have documented dysfunction in the DMN of schizophrenia patients (Buckner et al 2008; Broyd et al 2009; Bluhm 2007; Whitfield-Gabrieli et al 2009). The DMN consists of brain regions that are active during rest and attenuated during goal-directed activity, such as performing a task (Gusnard and Raichle 2001; Buckner et al 2008). Main regions of the DMN include the medial, lateral and inferior parietal cortex, medial prefrontal cortex (MPFC), anterior cingulate cortex (ACC), posterior cingulate cortex (PCC) and the precuneus (Gusnard and Raichle 2001), with the highest resting-state metabolism in the ACC and PCC (Gusnard and Raichle 2001).

The DMN is involved in different internally oriented mental processes, for example self-related cognitive activity (Buckner et al 2008; Raichel and Snyder 2007) and mind-wandering (Mason et al 2007). DMN deactivation appears to operate as a suppressor of internal activity and as enhancer of externally-directed cognitive function (Anticevic et al 2012). Indeed, failure to deactivate the DMN during cognitive demanding tasks is associated with neuropsychiatric disorders, like schizophrenia (Anticevic et al 2011; Pomarol-Clotet et al 2008; Schneider et al 2011; Whitfield-Gabrieli et al 2009).

The DMN is of interest to investigate neural substrates of the functional pathology of schizophrenia, since failure to suppress the DMN has been linked to several clinical features of schizophrenia (Buckner et al 2008; Broyd et al 2009). To illustrate this, reduced task-related suppression of DMN regions is correlated with impaired performance on a working memory task in schizophrenia patients (Whitfield-Gabrieli et al 2009). In addition, DMN dysfunction is involved in self-relevant internal information processing (Raichle and Snyder 2007), which possibly leads to blurring of the normal boundary between internal thoughts and external perceptions in patients diagnosed with schizophrenia (Whitfield-Gabrieli et al 2009).
In our search to assess the neurobiological basis of apathy in schizophrenia patients, we started from the definition of apathy: diminished goal-directed behavior, goal-directed cognition, and affective responsivity to events (Marin 1990; Marin 1991). Thus per definition, patients with apathy have difficulties to switch to goal-directed behavior, suggesting that apathy can be attributed to lack of DMN suppression (reduced task-related suppression). This idea is further supported by findings that DMN suppression is reduced in conditions associated with cognitive impairment in general, e.g. in mild cognitive impairment, cognitive ageing and Alzheimer disease (Lustig et al 2003; Celone et al 2006), with less deactivation as an early marker for subtle cognitive decline in ageing (Hansen et al 2014). Patients with memory disorders such as AD also suffer from early behavioral changes. Delrieu et al (2014) indicated that apathy belongs to the spectrum of prodromal AD symptoms. Likewise, dysfunction of the DMN may be related to apathy in schizophrenic patients.

DMN alteration as the basis for apathy is of interest for its potential clinical relevance. Modulation of DMN suppression could improve clinical outcome of schizophrenic patients. By investigating the change in resting state activity of patients with different apathy levels during a task, our fundamental knowledge on the neural biological underpinnings of apathy will be improved.

To our knowledge, research on apathy in patients with schizophrenia has not yet investigated a possible link with the DMN. In the present study we aim to investigate whether deactivation patterns of the DMN may be associated with apathy in schizophrenic patients. We expect patients with high apathy levels to show less deactivation of the DMN during a task compared to patients scoring low on apathy.

2. Methods

Participants
Data from the baseline fMRI measurement of two different trials were used for this study. The first trial investigated the effect of aripiprazole versus risperidone on negative symptoms (EUDRA-CT:2007-002748-79). The second trial consisted of patients included in a double-blind multicenter randomized controlled trial investigating the effect of rTMS on negative symptoms (Dutch Trial Registry: NTR1261). The baseline conditions for both studies were the same. The local ethical committee of the University Medical Center of Groningen approved all studies and the studies were executed in accordance to the declaration of Helsinki. All participants gave oral and written informed consent after they had been fully informed about the research procedures.

Fourty-six patients were recruited from mental health care centers in the Northern part of the Netherlands based on a diagnosis of schizophrenia or a related non-affective psychotic disorder according to the DSM-IV criteria. Diagnosis of schizophrenia and related non-affective psychotic disorder were confirmed using the Schedules for Clinical Assessment in Neuroscience (SCAN 2.1) diagnostic interview (Giel en Nienhuis 1996). Symptoms of schizophrenia were assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay et al 1987). Alcohol and drug abstinence was required 24 hours prior to testing.

To determine an apathy proxy measure, we selected items from the PANSS based on a factor analysis on negative symptoms (Liemburg et al 2013.) One factor includes the
following items of the PANSS: N2 Emotional withdrawal, N4 Apathetic social withdrawal and G16 Active social avoidance (Cronbach’s alfa = 0.75). These apathy-related items approximated to aspects of the ‘social amotivation’ domain of DSM-V (Liemburg et al 2013). Moreover, according to Liemburg et al. (2014), based on Faerden et al. (2008), there is a correlation between the PANSS proxy measure and the Apathy Evaluation Scale total score (AES) of 0.58.

Exclusion criteria for all subjects included: age < 18 or >60, MRI incompatible objects (for example medical pumps, prostheses, pacemakers, red tattoos), pregnancy, claustrophobia, history of any neurological disorder, history of severe head injury, brain infarction and inability to provide informed consent. A comorbid depression or history of substance abuse in the preceding 6 months was not considered as exclusion criterion.

Patients were matched on age, gender, education level and handedness to healthy participants (n=11), recruited by advertisements in newspapers and posters in local supermarkets. A total of 57 subjects were included in this study. Education level was ranked according to Verhage (1984), with ascending education levels starting from elementary school (ranked 1) to university (ranked 8) (Verhage 1984). The highest education level was noted.

Task
During the MRI session, an anatomy scan, a socio-emotional task, MR spectroscopy and a resting state scan were executed. In this paper we investigated a planning task that was the first scan in the MRI protocol.

While in the scanner participants completed the Tower of London task, based on the task from a previous study (Lazeron et al 2000). The purpose of the test is to move three colored beads (blue, red, green) on three rods from a starting configuration to the aimed configuration, in a minimum number of moves. The three rods differed in length and could accommodate 1, 2 or 3 beads, respectively. The participants were asked to count the minimum number of moves and respond by choosing the correct answer between two options, which were shown below in the task screen. Only a top bead could be moved and one at a time. The task consisted of easy trials (1-2 moves/balls) and complex trials that required more moves (3-5 moves/balls). A block design was used which contained the task condition (60 s), a control condition (60 s) and resting blocks. The control condition consisted of counting the blue and red beads. Throughout the resting blocks (30 s), subjects needed to fixate on a black cross in the centre of the screen. During the session, 5 blocks of both the task condition and control condition was presented, with self-paced stimuli within the blocks. After each stimulus, a fixation cross was shown for 250 ms. In between both task conditions, resting blocks were presented (Figure 1).

Oral instructions were given to the subjects and they practiced on a laptop prior to scanning. First five trials for the planning condition and two for the control condition were shown while oral feedback was given if subjects indicated the incorrect answer. The next practice session contained two planning blocks and one control block, one minute each, without feedback. While in the scanner, the task was presented through a projector to a computer screen using E-prime 1.2. Subjects were asked to respond by pressing their right index and middle finger on an MR-compatible button box. Log files of onset times and responses during the task were created by E-prime. Reaction times (s) and accuracy (percentage correct) were obtained to measure task performance.
Figure 1: Schematic illustration of the Tower of London task. Two alternating task conditions: count number of steps represents the planning condition, count blue and red beads represents the control conditions, interspersed with resting blocks.

Functional image acquisition
All data was collected on a Philips Achieva 3 Tesla MRI scanner (Best, the Netherlands). Foam pads were placed within the 8-channel SENSE head coil to position subjects’ head and to restrict head motion. In addition, earplugs were used to reduce scanner noise. We acquired a pseudo-continuous arterial spin labeling (PCASL) sequence (TR 4000 ms; TE 3.5 ms; flip angle 90°; 14 slices; field-of-view (ap, fh, rl) 224 x 98 x 224 mm; voxel size 1.75 x 1.75 x 7 mm). We obtained a series of 127 alternated control and labeling scans (labeling time 1650 ms; delay time 1525 ms; acquisition time 825 ms). Initially the two trials aimed to assess medication influence over time (not included in this paper), which therefore PCASL was the preferred technique. Measurements far apart in time can best be compared using ASL data instead of BOLD data. Moreover, PCASL allows to both assess relative signal changes and baseline activity. Based on the ASL measurements, pseudo-bold data was calculated.

Data analysis: preprocessing
The raw images were converted to NIFTI format and preprocessed using Statistical Parametric Mapping (SPM8; FIL Wellcome Department of Imaging Neuroscience, London, UK). Following this, images were realigned to correct for motion using a 6-paramter rigid body spatial transformation. Excessive movement was not considered as an exclusion criterion, because ASL images are subtracted and therefore relatively insensitive to head motion. Realignment was performed separately for labeled and control ASL images, since motion correction may be influenced by differences in image intensity induced by the labeling (Wang et al 2008). Therefore, mean images for both modalities were obtained. The mean labeled image created during realignment was co-registered to the mean control image, together with all labeled images. Thereafter, the images were spatially smoothed with an 8 mm full width at half-maximum Gaussian isotropic kernel.

The low signal to noise ratio (SNR) is a critical issue in ASL data. Therefore, denoising was performed by regression of the ASL images with nuisance factors, which included motion parameters, white matter (WM) signal and cerebrospinal fluid signal (CSF). This was separately done for both control and labeled images. The anatomical volume was co-registered with the mean control image and subsequently segmented, to generate (WM) and CSF masks. Components of the CSF and WM signal were removed from the ASL data using
the masks. The perfusion signal was calculated by pair-wise subtracting labeled images from control images using spline interpolation of labeled and unlabeled scans separately (Liemburg et al 2014; Wang et al 2008). PseudoBOLD images were calculated by summing subsequent labeled and control scans. Finally, images were spatially normalized to the T1 template in SPM.

**Independent component analysis**
A data-driven approach termed independent components analysis (ICA) was used: an analysis technique to separate fMRI signals in statistically independent spatial maps (independent components) and associated time courses. Individual components were calculated by the Group ICA fMRI toolbox (GIFT), which resulted into independent components per participant. For a detailed description of group ICA, we refer to the article of Calhoun et al (2001). The group ICA approach was performed on the pseudo-BOLD data, because ICA on ASL data failed to produce stable components. The number of components to be generated was set to 30, because the DMN was most apparent at this setting. The group ICA went through three stages: principal component analysis (PCA) for dimensionality reduction (data compression), independent component separation and back reconstruction. The resulting output, i.e. the spatial maps and the time courses were converted using Z-scores.

**Spatial sorting of components**
The selection of components reflecting the DMN was based on spatial sorting. Components with the highest spatial correlation were selected using spatial regression with the predefined ‘rDMN_ICA_REST 3x3x3’ template in GIFT. We visually inspected all components with a high spatial correlation for DMN areas, in order to select the components of interest.

**Temporal sorting of components**
Two components with high spatial correlation with the DMN were selected by spatial sorting in GIFT. Subsequently, temporal sorting of the task regressors with the time courses of the components was performed in GIFT to compare the model’s time course with the ICA time course. ‘Planning’ and ‘count’ were used in multiple regression to examine the correlation between the two selected components and the time course of the task.

Mean time courses for both patients and controls were calculated together with their standard deviations. The design matrix was used to indicate the onset and offset of the resting blocks. Thereafter, a permutation test was conducted to investigate the mean group differences in task (de)activation. In this permutation test, 1000 difference values were calculated based on groups constructed using random labeling. Here, groups remained the same size as the true group sizes. Consequently, the true group difference was compared with the distribution of the random differences and its position within this distribution yields a p-value.

Finally, the time courses were plotted with the apathy scores used as coloring. Spearman rank correlation was used to assess whether the apathy proxy measure correlated with the DMN (de)activation patterns.

**Group differences on behavioral data**
Behavioural data was analyzed by Statistical Package for Social Sciences (SPSS; version 22.0; Armonk, NY: IBM Corp). Differences in age and education level between patients and controls were assessed using Mann Whitney U tests; Chi-square tests were used to compare gender and handedness between groups. A Mann Whitney U test was performed to compare
task performance (reaction time and accuracy) between patients and controls, separately for easy and difficult trials during the planning condition. Task performance was correlated with the apathy proxy measure using Spearman’s correlation coefficient, since lack of motivation may influence the task output. In addition, the apathy proxy measures were correlated to age, gender, education, positive symptoms and anti-psychotica (Andreasen et al 2010) to test for possible associations.

3. Results

Demographics
One patient was excluded from the study due to a lack of interview data. As shown in Table 1, there were no significant differences between patients and controls in age, gender and handedness. The education level was significantly higher in the control group compared to the patient group (p = 0.033). Clinical characteristics are provided in Table 2. Within the patient group, 74% of the patients were diagnosed with schizophrenia. 21.7% of the patients were diagnosed with psychotic disorder, because their illness duration was too short to confirm a diagnosis of schizophrenia.

Table 1
Demographical data of patients with schizophrenia and healthy participants

<table>
<thead>
<tr>
<th></th>
<th>Patients (SD)</th>
<th>Controls (SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>31.2 (11.8)</td>
<td>27.6 (11.5)</td>
<td>0.31</td>
</tr>
<tr>
<td>Sex (% Male)</td>
<td>78.3</td>
<td>90.9</td>
<td>0.67</td>
</tr>
<tr>
<td>Handedness (% right)</td>
<td>84.8</td>
<td>90.9</td>
<td>0.26</td>
</tr>
<tr>
<td>Education</td>
<td>5.0 (1.8)</td>
<td>6.1 (0.7)</td>
<td>0.033</td>
</tr>
</tbody>
</table>

Table 2
Clinical characteristics of patients (n = 54)

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD/%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol equivalents</td>
<td>3.1 (4.2)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>34 (74%)</td>
</tr>
<tr>
<td>Schizophreniform</td>
<td>2 (4.3%)</td>
</tr>
<tr>
<td>Psychotic disorder</td>
<td>10 (21.7%)</td>
</tr>
<tr>
<td>PANSS positive</td>
<td>13.9 (5.0)</td>
</tr>
<tr>
<td>Apathy proxy</td>
<td>12.4 (3.9)</td>
</tr>
</tbody>
</table>

Behavioral results
Scores on task performance (reaction time and accuracy) for easy and difficult trials of the control group and patients are presented in Table 3. A Mann Whitney U test showed that the patients and control group did not significantly differed on task performance, except for reaction time on easy trials during the planning condition and reaction time on difficult trials during the count condition. Patients showed significantly longer reaction times on easy trials (p = 0.003) with 7.2 (4.5) s, compared to 4.7 (0.71) s in the control group for the planning.
Likewise, a significant difference ($p = 0.014$) between patients and controls can be observed for the reaction time on difficult trials with 11.7 (4.5) s for the patients and 8.4 (1.8) for the controls. The reaction time during ‘count’ on difficult trials showed a similar effect ($p = 0.001$) with patients taking 2.7 (1.2) s to respond, compared to 1.9 (0.29) s for the healthy controls.

**Table 3**
Scores on task performance for easy and difficult trials for patients and controls

<table>
<thead>
<tr>
<th></th>
<th>Patients (SD)</th>
<th>Controls (SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Easy trials ‘planning’</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reaction time (s)</td>
<td>7.2 (4.5)</td>
<td>4.7 (0.71)</td>
<td>0.003</td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td>90.2 (13.2)</td>
<td>97.6 (4.19)</td>
<td>0.102</td>
</tr>
<tr>
<td><strong>Difficult trials ‘planning’</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reaction time (s)</td>
<td>11.7 (4.5)</td>
<td>8.4 (1.8)</td>
<td>0.014</td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td>74.1 (14.8)</td>
<td>79.8 (11.6)</td>
<td>0.240</td>
</tr>
<tr>
<td><strong>Easy trials ‘count’</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reaction time (s)</td>
<td>2.0 (0.86)</td>
<td>1.7 (0.39)</td>
<td>0.279</td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td>97.8 (5.7)</td>
<td>96.5 (4.3)</td>
<td>0.130</td>
</tr>
<tr>
<td><strong>Difficult trials ‘count’</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reaction time (s)</td>
<td>2.7 (1.2)</td>
<td>1.9 (0.29)</td>
<td>0.001</td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td>95.7 (4.7)</td>
<td>97.1 (1.5)</td>
<td>0.840</td>
</tr>
</tbody>
</table>

There was no significant correlation between the apathy proxy measure and age ($r = 0.032$, $p = 0.850$), gender ($r = -0.052$, $p = 0.759$), positive symptoms ($r = 0.087$, $p = 0.609$) and haloperidol equivalents ($r = 0.143$, $p = 0.477$). On the other hand, we found a strong correlation of the apathy proxy measure and education level ($r = -0.501$, $p = 0.003$).

Correlating apathy with task performance, only an association between apathy and reaction time on difficult trials during the planning condition was found ($r = 0.355$, $p = 0.034$). Besides, we detected a trend towards significance ($r = 0.311$, $p = 0.061$) in the association between apathy measures and reaction time on difficult trials during the count condition. When controlling for conditions that had a significant association with apathy (education), there was indeed a significant relation between apathy and reaction time on difficult trials during the count condition ($r = 0.389$, $p = 0.030$).

**Spatial sorting results**
We found the DMN to be represented in two components: an anterior part and a posterior part (Figure 2). The anterior part of the DMN, consisting of the medial prefrontal cortex (MPFC), ACC, PCC, left and right inferior frontal gyrus, precuneus, posterior cingulate and superior frontal gyrus, showed the highest spatial regression value with the DMN template of all components (regression value = 0.257). Another component reflecting the posterior part of the DMN was selected after visually inspecting the top five components, and consisted of the inferior parietal cortex, middle temporal gyrus, precuneus, posterior PCC, post central gyrus and middle frontal gyrus (regression value = 0.033) (Figure 2).
Two selected components reflecting the DMN best. Component 1 (regression value = 0.257, red colored area’s) includes the medial prefrontal cortex (MPFC), ACC, PCC, left and right inferior frontal gyrus, precuneus and posterior cingulated. Component 7 (regression value = 0.033, blue colored area’s) includes the inferior parietal cortex, middle temporal gyrus, precuneus, post central gyrus and middle frontal gyrus.

Temporal sorting results
Temporal sorting showed peaks (activation) during the baseline and falls (deactivation) during the task conditions for the DMN components. Figure 3 depicts the mean time courses for both patients and healthy controls together with a graphically view of the resting blocks. Figure 3A represents the anterior part of the DMN, Figure 3B the posterior part of the DMN. The same pattern of on and offset can be observed for patients and controls. Patients and controls seem to differ in DMN deactivation, with less deactivation seen in the patient group.

When correcting for the hemodynamic response function (HRF), baseline blocks were shifted which is shown in Figure 4. The next figures shown are based on the baseline corrected for the HRF. However, there is a large variation in time courses, see Figure 5.

In order to determine differences in activation between patients and controls, Figure 6 illustrates a permutation test on the mean time courses. Patients significantly (p < 0.05) differed from healthy controls in activation and deactivation of the DMN on time points depicted in Figure 6. For the anterior part of the DMN, there was an almost equal distribution of significant different time points over resting blocks (52.1 %) and task blocks. For the posterior part of the DMN, a slight majority of significant different time points were part of resting blocks (60.7%).

We next assessed whether apathy scores of patients correlated with the degree of deactivation of the DMN. Figure 7 shows the time courses for the DMN components plotted with apathy proxy measure as coloring. A trend can be observed in which patients with the highest apathy measures show the most flattened pattern of activation and deactivation. A scatterplot was created to quantify these results, using the area under the curve (auc) as a measure for the degree deactivation, see Figure 8. A relation would be expected between the auc and apathy measures, in which auc decreases with higher apathy measures. However, there is no such correlation observable, with r = 0.005 (p = 0.972) for the anterior part of the DMN and r = -0.229 (p = 0.135) for the posterior part.
Figure 3: Mean time courses for both patients and healthy controls of the DMN. A. Anterior part of the DMN (component 1) B. Posterior part of the DMN (component 7)

Figure 4: Mean time courses for both patients and healthy controls of the DMN. The baseline is corrected for the hemodynamic response function (HRF)  A. Anterior part of the DMN (component 1) B. Posterior part of the DMN (component 7)

Figure 5: Mean time courses for both patients and healthy controls together with their standard deviations. A. Anterior part of the DMN (component 1) B. Posterior part of the DMN (component 7)
Figure 6: Time points showing a significant difference between the mean time courses of the patients and control group. The graph consists of 1000 differential lines calculated on groups determined by chance (dark gray color). The true differential variable between groups is represented as the red line; the baseline is depicted in light gray. * = p < 0.05 A. Anterior part of the DMN (component 1). Number of significant time points is 49. B. Posterior part of the DMN (component 7). Number of significant time points is 35.

Figure 7: Plotted time courses of the patients with apathy measures as coloring. Bright red = high apathy score, apathy ~ 0 = black. A. Anterior part of the DMN (component 1) B. Posterior part of the DMN (component 7)
4. Discussion

The present study aimed to investigate whether reduced deactivation of the DMN during a task may be associated with apathy in schizophrenia patients. By performing temporal sorting on two selected DMN components, we derived mean time courses for both patients and controls. Clear patterns of task-induced deactivation were found, with patients exhibiting more flattened (de)activation patterns suggesting that schizophrenia patients face difficulties in modulating their DMN. There was no significant relation between deactivation and apathy in schizophrenia patients.

Our results demonstrated patterns of DMN activation during rest and deactivation while performing tasks in patients and controls. These results corroborate the findings of previous research (Buckner et al 2008; Gusnard and Raichle 2001; Shulman et al 1997), indicating that the DMN is involved in goal-directed behavior. The spatial regions we extracted from the ICA are similar to DMN regions found in other studies: the PCC, bilateral inferior parietal cortex, left inferolateral temporal cortex, medial prefrontal cortex, and ventral anterior cingulate cortex are reported by Greicius et al (2004). Moreover, according to Franco et al (2010), the regions that have been most commonly reported in previous studies are the PCC, ACC, inferior and superior parietal lobes and superior frontal gyrus.

Patients and controls significantly differed in DMN activity on time points almost equally distributed across resting blocks and task blocks: the DMN is less active in patients compared to controls during rest and hyperactive during task performance. This suggests that schizophrenic patients show abnormalities in DMN operation. It should be noted however, that these findings involve mean time courses of the patient and control group and that individual time courses appeared to be noisy with large variance amongst the subjects. Thus, caution is needed in interpreting the current findings. Therefore we report a tendency towards abnormal DMN operation in the patient group to avoid premature conclusions.
A possible explanation for the altered DMN modulation (lower deactivations during task and lower activations during rest) of patients compared to controls lies in the study of Schneider et al (2011). Schneider et al (2011) suggest that the capacity to reallocate cognitive resource to task-related regions exceeds at higher load and therefore result in lower task induced deactivations (TID). Lower DMN activation in schizophrenia patients than in healthy controls during resting blocks may thus be caused by a higher resource reallocation to attentional networks, resulting in attenuated activation (DMN suppression).

Another factor contributing to the altered DMN activity pattern of the patient group might be the use of antipsychotic medication. Sambataro et al (2009) studied the effect of olanzapine treatment in schizophrenia patients, which resulted in increases of DMN connectivity with ventromedial prefrontal cortex. In addition, another study concluded that the dopamine receptor agonist apomorphine modulates the DMN in patients with Parkinson’s disease (Nagano-Saito et al 2009). This implicates an effect of medication use on DMN function, but there is a gap in literature about the precise relation between antipsychotics and DMN modulation. Further research should investigate how anti-psychotic drugs influence the DMN, because anti-psychotic drugs might work by attenuating the effect of DMN (de)activations and therefore may have contributed to the flattened pattern of (de)activations of patients compared to controls.

However, there is no significant difference between patients and controls across the entire task, as we would have expected. The standard deviations may be too large to obtain an overall significant difference. Because the individual time courses contain considerable noise and have a large variance as we mentioned before, we suggest that a region of interest (ROI) approach based on the resting state scans would yield more accurate results. In this manner, a DMN mask can be created for each subject separately, reducing the noise effect when using a group mask.

We cannot rule out the possibility that the heterogeneity of the patient group may have contributed to the present findings. The present study is a combination of two trials assessing negative symptoms, including both young schizophrenic patients with a short disease duration and patients who have been diagnosed with schizophrenia for a longer period of time. Differences in overall negative and positive symptom severity further contribute to diversity amongst patients, and associated brain abnormalities. According to a review by Ananth et al (1991) negative symptoms may be linked to frontal system cognitive impairment. In addition, larger deactivation in the medial frontal gyrus, precuneus and middle temporal gyrus is associated with positive symptoms in schizophrenia (Garrity et al 2007). A patient group with more homogeneous symptom conditions, but with high variability of apathy scores would enable to adequately study the relation between apathy and DMN activity with less confounding factors. Therefore, findings should be replicated in a homogeneous sample addressing illness duration, disease severity and positive and negative symptoms.

Although a trend could be observed in which patients scoring high on apathy exhibited less activation and deactivation of the DMN, we found no significant relationship between apathy and DMN (de)activation. In this section we will follow two explanatory pathways that may account for the present findings. First, it is possible that apathy simply does not have any correlation with the DMN. However, this statement may be less plausible since apathy is manifested clinically by diminishment in goal-directed behavior, goal-directed cognition, and affective responsivity to events (Kiang et al 2003) and can be considered as an indifference to the external environment (Bleuler 1911). This is in line with the widely shared view that the
DMN is antithetical to goal-directed behavior (Anticevic 2012; Belleau et al 2014; Kelly et al 2008) and involved in internally directed processes (Buckner 2008; Gusnard et al 2001; Mason et al 2007).

Since we expected a clear relation between apathy and DMN deactivation, an overall effect of reduced task-related deactivation (hyper-activation) of the DMN combined with hypo-activation of brain areas related to apathy, may have contributed to less differences between patients with high or low apathy scores. According to a review by Van Reekum et al (2005), previous neuroimaging studies suggest abnormalities of frontal-subcortical brain circuits, in particular the ACC and dorsolateral prefrontal cortex, underlying the pathophysiology of apathy. For example, results of Migneco et al (2001) showed that the ACC was the common hypoactive structure in their apathetic patients. Also, the parietal cortex has been implicated by previous research. Low activation in the middle frontal cortex and inferior parietal cortex was reported in deficit schizophrenia (Lahti et al 2001), a syndrome in which apathy constitutes an important symptom. Taken on the whole, these areas show overlapping regions with the DMN. Hypo-activation of brain areas related to apathy that overlap with DMN areas may have caused different activation levels than we expected and therefore no detectable relation between apathy and DMN deactivation. When engaged in a task, schizophrenia patients with high apathy scores are expected to exhibit reduced deactivations, and therefore more activation compared to patients scoring low on apathy. For example, a patient scoring high on apathy may have shown strong reduced deactivations, which may be eliminated by the effect of hypo-activity in brain areas related to apathy.

Secondly, the possibility exists that our methods were insufficient to generate reliable results. Using ASL has some limitations, in that ASL images intrinsically contain more noise compared to BOLD images. In addition, ASL is especially suitable for exploring slow changes in brain activity over periods greater than a few minutes (Aguirre 2002; Detre 2002), have less imaging coverage and the magnitude of signal change for activation is smaller (<1%) (Detre 2002). In the present study we used resting blocks of 30 s, which is probably too short to accurately detect small differences in activation. Future studies could use BOLD instead of pseudo-BOLD as a more sufficient method.

In addition, we should address the question whether the AUC is a representative measure for the degree of activation and deactivation to investigate the relation with apathy. Because the individual time courses are noisy and involve large variances, the AUC possibly is not a good representation of the true degree of activation. Reducing sources of noise in future studies will enhance the suitability of AUC analyses.

The view that the PANSS had an extensive coverage for apathy in the present study may be questioned. The totality of information used for PANSS ratings is based on both the clinical interview as the notion of for example family members or nursing staff. In this study, for some patients we primarily focused on the information obtained from the patients during the clinical interview, instead of both clinical evaluation and family reports. Reports on daily functioning are an essential source of information for determining social and behavioral abnormalities (Kay et al 1986). These circumstances, plus the fact that the interviewers were not instructed to pay particular attention to apathy, probably contributed to little variation in apathy ratings.

Although the PANSS is a well-defined, standardized technique for the evaluation of the two symptom classes (negative and positive symptoms) in schizophrenic patients, the
Apathy Evaluation Scale (AES) (Marin 1991 et al) could be a more accurate instrument to evaluate apathy as this instrument is specifically designed to measure this. Faerden et al (2008) indicate that the AES has the potential to be used as an additional scale for the refinement of negative symptoms, functioning as a good supplement of boundaries of negative symptoms.

As in other studies, we found a strong correlation of the apathy proxy measure and education level. Although there are no studies that found an explanatory cause for this relation, we suggest that apathy early on in the course of the illness will compromise the level of education, thus the relationship between the two cannot be disentangled. Elaborating on the behavioral results, we reported a significant association between reaction times on difficult trials and apathy during the planning condition. Thus, it takes longer for patients scoring high on apathy to respond during the aforementioned condition, compared to patients with low apathy. When controlling for education, there was a significant association between apathy and reaction time on difficult trials during the count condition. While Kostantakopoulos et al (2011) and Faerden et al (2009) reported poor performance on tasks in patients with high apathy measures, a review by van Reekum et al (2005) showed mixed results in studies assessing the association between performance on executive tasks and apathy. In line with Liemburg et al (2014) examining an overlapping patient cohort, we suggest that high apathy scores generate longer response times during high cognitive demanding tasks, with increased performance on accuracy due to longer response times.

The task used in this study, the Tower of London, mainly focuses on working memory and goal-directed behavior (specifically planning), but doesn’t measure aspects in the field of social behavior, emotion and affect. The issue has been raised whether DMN suppression is equally functionally relevant across different domains (Anticevic et al 2012). Furthermore, Anticevic et al (2012) noted that performance-relevant DMN suppression could be different for patients and controls, depending on the task. Future studies with tasks on different cognitive aspects need to be performed to further explore these questions.

To illustrate the importance of these questions, the research of Schneider et al (2011) showed strong significant task-unspecific deactivations of the DMN in the control group, but not in the schizophrenia group. They found differences between patients and controls in different DMN regions depending on which task they performed. As mentioned earlier, Schneider et al (2011) suggested that the reallocation of cognitive resources is altered in schizophrenia patients. Taken altogether, these findings indicate that DMN activity is modulated differently in schizophrenia patients, depending on the brain regions activated by the task itself (Schneider et al 2011).

5. Conclusion

In conclusion, our results demonstrated patterns of DMN deactivation during goal-directed activity. The DMN showed less activation in patients compared to controls during certain time points equally distributed over rest and task blocks, which suggests that schizophrenic patients show abnormalities in DMN operation and are less able to switch networks. However, we were not able to detect an overall significant difference between patients and controls in modulating the DMN across the entire task (all time points together). Moreover, we found no significant relationship between apathy and DMN (de)activation. By investigating the relationship between apathy and the DMN, fundamental knowledge on the neural biological underpinnings of apathy will be enhanced. Therefore, research repeating our
study needs to be performed, with a larger control group and including different fMRI measures.

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