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Association between prefrontal *N*-acetylaspartate and insight in psychotic disorders

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ABSTRACT

Insight is impaired in most patients with psychosis and has been associated with poorer prognosis. The exact neural basis of impaired insight is still unknown, but it may involve disrupted prefrontal neural connectivity. Numerous studies have indeed found white matter (WM) abnormalities in psychosis. The association between prefrontal WM abnormalities and insight has not been studied yet by means of proton magnetic resonance spectroscopy (^{1}H-MRS). ^{1}H-MRS can be used to measure *N*-acetylaspartate (NAA), which is considered to be a marker of neuronal integrity. We measured insight with the Birchwood Insight Scale (BIS) as well as item G12 of the Positive and Negative Syndrome Scale (PANSS) in 88 patients with psychosis. Prefrontal WM concentrations of NAA and ratios of NAA to creatine (Cr) were assessed with ^{1}H-MRS. Nonparametric partial correlational analyses were conducted between NAA concentrations and insight controlling for illness duration, standardized antipsychotic dose, symptom scores, voxel grey matter content and voxel cerebrospinal fluid content. We found a significant correlation between reduced NAA/Cr ratios and poorer insight as measured with the BIS, which remained significant after additional correction for full width at half maximum, signal/noise and age. This is the first study reporting a relationship between lower prefrontal concentrations of a marker of neuronal integrity and impaired insight, providing further evidence that prefrontal pathology may play an important role in impaired insight in psychosis. This may be explained by the involvement of the prefrontal cortex in several executive and metacognitive functions, such as cognitive flexibility and perspective taking.

1. Introduction

Awareness of illness, also called insight, is impaired in approximately 50 to 80% of schizophrenia patients (Dam, 2006) and is one of the most common reasons for poor treatment adherence. Numerous studies have shown an association between impaired insight and poorer outcome of the disorder (Lincoln et al., 2007). Two types of insight can be distinguished, namely clinical and cognitive insight (Beck and Warman, 2004), separating a person's awareness of illness (clinical insight) from their ability to evaluate and reflect upon their own aberrant views and interpretations (cognitive insight). Of our particular interest is the construct of clinical insight, which includes three dimensions: (i) awareness of being ill, (ii) ascribing specific symptoms to the illness, and (iii) awareness of the need for treatment (David, 1990).

Several theories have been proposed to explain poor insight. Some authors have suggested that impaired insight may be caused by impaired cognitive functioning due to frontal pathology (Shad et al., 2006a). The distribution of impaired brain regions (Antonius et al., 2011; Davis et al., 2003) implies that impaired insight might be caused by disrupted neural connectivity instead of impairment of just one brain area. Numerous studies have indeed found white matter (WM) abnormalities in schizophrenia (Wheeler and Voineskos, 2014). Diffusion tensor imaging (DTI) studies, for example, found reduced fractional anisotropy (FA) in schizophrenia, suggesting reduced WM integrity. Yet, only a few studies have investigated the relation between WM integrity and insight so far. Antonius and colleagues found an association between awareness of symptoms and WM integrity in fronto-temporal regions and an association between the ability to relabel symptoms and reduced WM integrity in temporal and parietal areas (Antonius et al.,

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2011). A previous study from our group found an association between clinical insight and subtle differences in WM integrity in the left middle frontal gyrus (Ćurčić-Blake et al., 2015). In contrast, Orfei and colleagues did not find any significant correlation between cognitive insight and WM integrity (Orfei et al., 2013).

The relationship between insight and WM integrity in psychotic disorders has not been studied yet by means of proton magnetic resonance spectroscopy (^{1}H-MRS). ^{1}H-MRS is a non-invasive neuroimaging technique that offers information on brain chemistry, and can be used to assess concentrations of neurometabolites such as *N*-acetylaspartate (NAA), glutamate (Glu), glutamine (Gln), choline (Cho), creatine (Cr) and myo-Inositol (mI). Further information on the use of ^{1}H-MRS and functions of these neurometabolites can be found in Currie et al. (Currie et al., 2013). Of our main focus is NAA, which is considered to be a marker of neuronal integrity (both of the cell body and the axon) (Urenjak and Williams, 1993). A study in healthy individuals found that a high proportion of variability (23% for ages 28–50; 66% for ages 57–80 years) in FA could be explained by levels of WM NAA (Wijtenburg et al., 2013). A post-mortem study in multiple sclerosis (MS) patients also showed a correlation between axonal density and WM NAA levels (Bjartmar et al., 2000). ^{1}H-MRS studies found reduced NAA in frontal WM as well as grey matter (GM) in psychotic disorders, while other studies did not observe significant NAA abnormalities. ^{1}H-MRS studies on frontal glutamate and glutamine (Glx) concentrations found increased Glx in the lateral prefrontal cortex (PFC) (of recently ill patients) and the medial PFC, with decreasing Glx levels in patients with higher age and illness duration. No differences in prefrontal Cr, mI and Cho concentrations were found compared to healthy controls (see Kraguljac et al., 2012; Marsman et al., 2013; Schwerk et al., 2014; Steen et al., 2005 for meta-analyses and reviews). However, most ^{1}H-MRS studies have been underpowered and methodology differed between studies, causing inconsistent and often contradictory findings.

We hypothesize that if impaired insight is a consequence of disrupted prefrontal neural connectivity, NAA levels in the WM of the PFC should correlate positively with levels of clinical insight. To our knowledge, there are no published studies regarding the association between NAA concentrations and insight in psychosis. In patients with Alzheimer's disease, a negative correlation between unawareness of deficits and NAA/Cr in the anterior cingulate cortex (ACC), and a positive correlation between unawareness of deficits and NAA/Cr in the right orbitofrontal area was found after controlling for dementia severity (Yeh et al., 2014). As mentioned before, an earlier study of our group found an association between clinical insight and subtle differences in WM integrity (as measured with DTI) in the left middle frontal gyrus in schizophrenia (Ćurčić-Blake et al., 2015). In this study, we will examine NAA levels in a voxel at close proximity of the area studied by our group, namely in the dorsolateral prefrontal cortex (DLPFC), in a different and larger sample of patients diagnosed with a psychotic disorder.

2. Materials and methods

2.1. Participants

Data of 92 patients were included in this study. These patients were enrolled in one of the three clinical trials conducted at our centre in recent years. Data of 36 healthy controls (HC) were included for comparisons between patients and controls. Of these HC, 20 were matched to one of the earlier mentioned groups and 16 were part of an additional trial. Baseline ^{1}H-MRS and structural MRI scans of these clinical trials were combined for the purpose of this study. See Supplement 1 for more information about these clinical trials, as well as their inclusion and exclusion criteria.

As a criterion of reliability, ^{1}H-MRS data were excluded if the metabolites had an estimated standard deviation (Cramer-Rao lower bound; CRLB) higher than 20% of the estimated concentration as recommended by Provencher (Provencher, 2008). One patient (SZ) was excluded for this reason, and two additional patients (SZ) were excluded because their metabolite concentrations (one participant: NAA/Cr; other participant: NAA, Glx, mI, Cho) deviated more than three standard deviations from the group mean. In addition, one patient (SZ) and one HC were excluded because their signal-to-noise ratio (S/N) was more than three standard deviations lower than the group mean. This left data of 88 patients for analyses, who were diagnosed with schizophrenia ($n = 76$), schizophreniform disorder ($n = 1$), schizoaffective disorder ($n = 2$), delusional disorder ($n = 2$) or a psychotic disorder not otherwise specified ($n = 7$). Data of 35 HC were available for comparisons between patients and HC.

2.2. Insight measures

Clinical insight was measured with item 12 of the General Psychopathology subscale (item G12) of the Positive and Negative Syndrome Scale interview (PANSS) (Kay et al., 1987). The PANSS is a rating scale for assessing positive symptoms, negative symptoms and general psychopathology in schizophrenia. Item G12 measures lack of judgment and insight; its scores are given by a trained interviewer and range from 1 (no impairment) to 7 (severe impairment). Although the PANSS G12 item is a single-item measure, it incorporates the different dimensions of clinical insight. Examples of questions used to answer this item are 'Do you need treatment?' and 'Why are you in this mental institution?' The PANSS G12 item is one of the most-used measures of clinical insight (Shad et al., 2006a) and correlations with other measures of clinical insight, such as the Schedule of Assessment of Insight (SAI), expanded Schedule of Assessment of Insight (SAI-E; Kemp and David, 1997), Insight and Treatment Attitudes Questionnaire (ITAQ) and Birchwood Insight Scale (BIS) (Birchwood et al., 1994), have shown to be strong (Sanz et al., 1998).

Clinical insight was additionally assessed with the Birchwood Insight Scale (BIS) in 81 participants for whom this data were available. The BIS is an 8-item self-rating questionnaire with a total score ranging from 0 to 12. It consists of three subscales measuring three dimensions of clinical insight, namely awareness of illness, awareness of need for treatment and ability to relabel symptoms. Scores on all subscales range from 0 to 4. Total scores and scores on the subscales were calculated, with a higher score indicating better clinical insight.

60.4% of participants had impaired insight as defined by a score of at least 3 on the PANSS G12 item and 44.4% had impaired insight as defined by a score lower than 9 on the BIS. A Pearson's correlation between the PANSS item G12 score and the BIS total score revealed a strong significant negative correlation in the expected direction ($r = -0.596$, $p < 0.001$, $n = 81$). The demographic and clinical characteristics of all 123 participants can be seen in Table 1.

2.3. Spectral acquisition

Scans were acquired in the Neuroimaging Center of the University Medical Center Groningen (UMCG) in Groningen, using a 3T Philips Intera Quaser (Best, the Netherlands) equipped with a synergy SENSE eight-channel head coil. A T1-weighted 3D fast field echo (FFE) anatomical image (voxel size $1 \times 1 \times 1$ mm) containing 170 slices (TR = 9 ms; TE = 3.60 ms; slice thickness = 1 mm; 256×256 matrix; FOV 232, 170, 256) was acquired parallel to the bicommisural plane.

Proton metabolites in the WM of the left (dorsolateral) PFC were assessed with ^{1}H-MRS single voxel spectroscopy using an 8-cm^3 voxel. Trained operators placed the voxel using the T1-anatomical scan as a guide. The voxel was placed in line with the genu of the corpus callosum on the anterior side and oriented in the same line as the corpus callosum and the falx cerebri, inclusion of WM was maximized (see Fig. 1). Examination was carried out using a Point Resolved Spectroscopy (PRESS) sequence with one 90° and two 180° pulses to create a spin echo, and water suppression with an excitation pulse followed by a frequency-modulated pulse. Automated shimming of the field in the examined

Table 1
Demographic and clinical characteristics of participants.

Variable	Mean (SD) patients (n = 88)	Mean (SD) HC (n = 35)
Gender (percentage male)	78%	68%
Age (years)	32.95 (10.77)	26.63 (9.86)
Level of education[a]	5.25 (1.22)	5.71 (0.87)
Handedness (percentage right-handed)	81.8%	86%
Use of antipsychotic medication (percentage[b])		
None	16 (18%)	
Aripiprazole	15 (17%)	
Clozapine	17 (19%)	
Flupentixol	2 (2%)	
Haloperidol	3 (3%)	
Olanzapine	27 (31%)	
Quetiapine	5 (6%)	
Risperidone	9 (10%)	
Zuclopenthixol	2 (2%)	
Pimozide	1 (1%)	
Paliperidone	2 (2%)	
Illness duration (years)	8.19 (8.61)	
PANSS[c]		
Subscale negative symptoms	16.28 (5.31)	
Subscale positive symptoms	14.30 (4.49)	
Subscale general psychopathology	31.35 (6.63)	
Item G12	3.03 (1.50)	
BIS total score[d]	8.07 (3.15)	

Abbreviations: SD = standard deviation; HC = healthy controls; PANSS = Positive and Negative Syndrome Scale; item G12 = item 12 of the General Psychopathology subscale of the Positive and Negative Syndrome Scale; BIS = Birchwood Insight Scale.
[a] Based on Verhage (1964). Education data was missing for one HC.
[b] Some participants were using multiple antipsychotic medications.
[c] $n = 88$.
[d] $n = 81$.

region of interest (pencil beam auto first order option) was done. Spectra were recorded within the following parameters: TE = 144 ms, TR = 2000 ms, VOI = 20 × 20 × 20 mm, signal averages (NSA) = 128, data points = 1024; spectral bandwidth = 2000 Hz.

2.4. Post-processing

Version 6.2-2b of LCModel software (Provencher, 1993) was used to determine absolute metabolite concentrations of total NAA (*N*-acetylaspartate (NAA) + *N*-acetylaspartylglutamate (NAAG); tNAA) by using the unsuppressed water reference signal (Water-Scaling option in LCModel). Furthermore, tNAA ratios to total creatine (creatine + phosphocreatine (CrPCr); tCr) were determined. In addition, concentrations of other neurometabolites such as glutamate and glutamine (Glu + Gln; Glx), total choline (glycerophosphocholine (GPC) + phosphocholine (PCh); tCho), tCr, and myo-inositol (mI) were determined in order to conduct exploratory analyses of the relationship between insight and levels of these neurometabolites. These metabolites were also measured both as absolute concentrations and as ratios to total creatine (tCr). Spectral quality measures such as signal/noise (S/N), full width at half maximum (FWHM) and CRLB's for each metabolite can be found in Table 2.

Tissue segmentation was performed to determine contents of GM, WM and CSF of the voxel for each participant. This was performed on the T1-anatomical scan using the Statistical Parametric Mapping software package (SPM8) (www.fil.ion.ucl.ac.uk/spm) run in Matlab7. GM content and CSF content were added as covariates in all (partial) correlational analyses to avoid partial volume effects. Mean percentages of GM, WM and CSF in the voxel can also be seen in Table 2.

2.5. Differences between subgroups

To ensure that results of our correlational analyses were not confounded by any differences among the three different studies, we compared data quality among these studies. See Supplement 2 for further details on these examinations. No differences in spectral quality were found between subgroups. Based on literature, illness duration, standardized antipsychotic dose and PANSS symptom scores (PANSS subscale scores minus G12) were entered as covariates in partial correlational analyses. The standardized antipsychotic dose was based on equivalence to chlorpromazine (Gardner et al., 2010).

2.6. Comparison between patients and healthy controls

In order to check for regional abnormalities, several parameters were compared between patients ($n = 88$) and HC ($n = 35$). We compared GM, WM and CSF content of the voxel, as well as data quality (CRLB of tNAA, FWHM and S/N), tNAA and tNAA/tCr concentrations, and demographic variables (age, gender, education and handedness) between groups. Groups were matched on education, gender and handedness. A significant difference in S/N was found between patients (M = 20.92, SD = 3.19) and HC (M = 22.83, SD = 2.75); $t(121) = 3.106$, $p = 0.002$. We also found significant differences in FWHM ($\chi^2(2) = 9.359$, $p = 0.009$) and age ($\chi^2(2) = 14.423$, $p = 0.001$) between patients and HC, examined with non-parametric Kruskal Wallis tests since these variables were not normally distributed. No significant differences were found between groups in gender, handedness, education, GM, WM and CSF content of the voxel, tNAA CRLB's, tNAA and tNAA/tCr concentrations.

2.7. Statistical analyses

IBM SPSS Statistics 20 (SPSS Inc., Chicago, IL) was used for all analyses. A threshold of $p < 0.05$, two-tailed, was used as the standard for statistical significance. Correlational analyses between confounding variables (illness duration, standardized antipsychotic dose, PANSS negative symptom scores, PANSS positive symptom scores, PANSS general

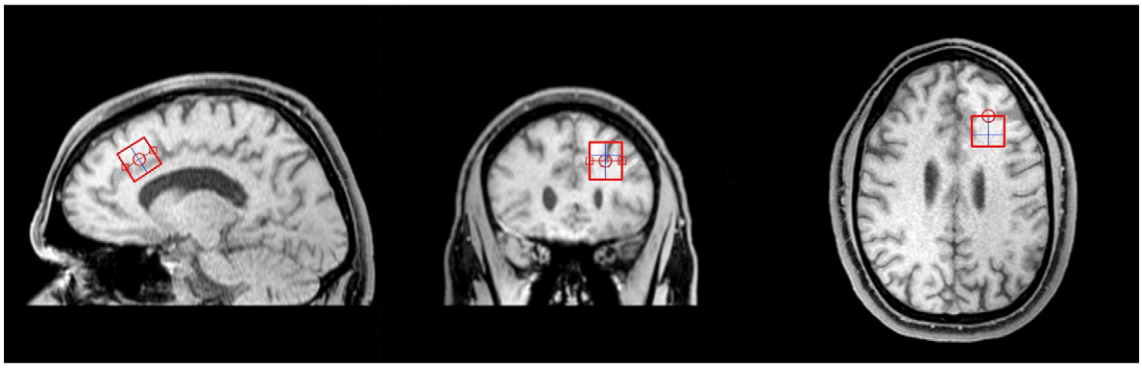

Fig. 1. T1-weighted magnetic resonance imaging of voxel in the white matter of the (dorsolateral) prefrontal cortex.

Table 2
Spectral quality measures and content of the voxel.

Metabolites (IU)	Mean (SD) and CRLB patients (n = 88)	Mean (SD) and CRLB HC (n = 35)
tNAA	24.06 (2.33)	24.73 (1.82)
	2.34 (0.48)	2.20 (0.41)
Glx	10.45 (1.47)	10.97 (1.11)
	11.36 (1.74)	10.57 (1.29)
tCho	4.01 (0.58)	3.85 (0.44)
	4.08 (0.35)	4.17 (0.38)
tCr	13.01 (1.28)	13.25 (0.73)
	3.28 (0.48)	3.11 (0.32)
mI	16.53 (2.56)	17.20 (1.96)
	9.10 (2.49)	8.43 (1.31)
tNAA/tCr	1.86 (0.16)	1.87 (0.12)
Glx/tCr	0.81 (0.10)	0.83 (0.08)
tCho/tCr	0.31 (0.04)	0.29 (0.03)
mI/tCr	1.28 (0.17)	1.30 (0.13)
Spectral quality measures		
S/N	20.92 (3.19)	22.83 (2.75)
FWHM	0.04 (0.008)	0.04 (0.009)
Voxel (percentages)		
WM	60.49 (10.66)	59.31 (12.59)
GM	35.23 (8.48)	36.43 (9.30)
CSF	4.37 (3.18)	4.26 (4.97)

Abbreviations: IU = Institutional Units; SD = standard deviation; CRLB = Cramér-Rao lower bounds; HC = healthy controls; tNAA = total NAA = *N*-acetylaspartate (NAA) + *N*-acetylaspartylglutamate (NAAG); Glx = glutamate (Glu) + glutamine (Gln); tCho = total choline = glycerophosphocholine (GPC) + phosphocholine (PCh); tCr = total creatine = creatine + phosphocreatine (CrPCr); mI = myo-inositol; S/N = signal-to-noise ratio; FWHM = full width at half maximum; WM = white matter; GM = grey matter; CSF = cerebrospinal fluid.

psychopathology scores minus G12 scores, GM content and CSF content) were conducted to evaluate possible collinearity. Results were evaluated at an FDR-corrected level (corrected for 21 tests). (Partial) correlational analyses were also conducted between confounding variables and insight scores (evaluated at an FDR-corrected level; corrected for 14 tests), and between confounding variables and neurometabolite concentrations (evaluated at an FDR-corrected level; corrected for 63 tests). We also checked whether gender and education influenced insight or NAA concentrations.

Since a scatterplot showed a non-linear relationship between insight and tNAA, Spearman partial correlational analyses were conducted between insight scores and *N*-acetylaspartate concentrations. Next, these analyses were repeated while controlling for confounding variables. In addition, because of the significant differences in S/N, FWHM and age between patients and HC, we computed partial correlational analyses between insight and NAA concentrations with these variables as additional covariates. A value of $p < 0.05$ was used as the standard for statistical significance and all partial correlational analyses were evaluated at an FDR-corrected level (corrected for 4 tests). Follow-up partial correlational analyses between three BIS subscales and tNAA/tCr concentrations were also evaluated at an FDR-corrected level (corrected for 3 tests). In addition, exploratory partial correlational analyses were conducted between insight and other neurometabolite concentrations.

3. Results

3.1. Correlations with demographic and clinical variables

Significant correlations between confounding variables (illness duration, standardized antipsychotic dose, PANSS symptom scores, GM content and CSF content) were found after FDR correction for 21 tests: PANSS positive symptom scores and PANSS general symptom scores minus G12 ($r = 0.587$, $p_{FDR} < 0.001$), GM and CSF content ($r = 0.609$, $p_{FDR} < 0.001$), PANSS negative symptom scores and PANSS general symptom scores minus G12 ($r = 0.369$, $p_{FDR} < 0.001$), and illness duration and CSF content ($r = 0.325$, $p_{un} = 0.002$, $p_{FDR} = 0.011$).

No significant correlations between confounding variables and insight (BIS and G12) were found. Several significant correlations between confounding variables and neurometabolite concentrations (tNAA, tNAA/tCr, Glx, Glx/tCr, Cho, Cho/tCr, tCr, mI, mI/tCr) were found after FDR correction for 63 tests. No significant correlations between gender or education and insight or NAA concentrations were found. All significant correlations between neurometabolite concentrations and confounding variables can be seen in Table 3.

3.2. Neurometabolite concentrations and insight

Partial correlational analyses between tNAA concentrations and insight scores were evaluated at an FDR-corrected level (corrected for 4 tests). A significant correlation was found between tNAA/tCr and BIS scores corrected for GM content, CSF content, standardized antipsychotic dose, illness duration, symptom scores, S/N, FWHM and age ($r_s = 0.332$, $p_{un} = 0.005$, $p_{FDR} = 0.02$, $n = 81$). This partial correlation was also significant without correction for S/N, FWHM and age ($r_s = 0.341$, $p_{un} = 0.003$, $p_{FDR} = 0.012$, $n = 81$), and with correction for GM and CSF content of the voxel only ($r_s = 0.280$, $p_{un} = 0.012$, $p_{FDR} = 0.048$, $n = 81$). Thus, reduced tNAA concentrations were associated with poorer insight.

We also examined these partial correlations in schizophrenia patients only, to see whether exclusion of patients with other diagnoses changed the results. The correlation between tNAA/tCr and BIS scores corrected for GM content, CSF content, standardized antipsychotic dose, illness duration, symptom scores, FWHM, S/N and age was also significant after FDR-correction when only including schizophrenia patients ($r_s = 0.365$, $p_{un} = 0.004$, $p_{FDR} = 0.016$, $n = 76$), as well as without correction for FWHM, S/N and age ($r_s = 0.364$, $p_{un} = 0.003$, $p_{FDR} = 0.001$, $n = 76$). The correlation between tNAA/tCr and BIS scores was also significant after correction for GM and CSF content only ($r_s = 0.311$, $p_{un} = 0.009$, $p_{FDR} = 0.036$, $n = 76$) when only including schizophrenia patients.

Additional partial correlational analyses were conducted to further explore the relation between scores on separate subscales of the BIS and tNAA/tCr ratios controlled for GM content, CSF content, standardized antipsychotic dose, illness duration and symptoms. These analyses were evaluated at an FDR-corrected level (corrected for 3 tests), and revealed a significant correlation between the BIS subscale Awareness of illness and tNAA/tCr ratios ($r_s = 0.349$, $p_{un} = 0.002$, $p_{FDR} = 0.006$, $n = 81$). The correlations between the BIS subscale Ability to relabel symptoms and tNAA/tCr ratios ($r_s = 0.210$), and BIS subscale Need for treatment and tNAA/tCr ratios ($r_s = 0.194$) were not significant. The correlation between BIS subscale Awareness of illness and tNAA/tCr was also significant with additional correction for FWHM, S/N and age ($r_s = 0.337$, $p_{un} = 0.004$, $p_{FDR} = 0.016$, $n = 81$). In addition, the correlation between BIS subscale Awareness of illness and tNAA/tCr was also significant with correction for GM content, CSF content, standardized antipsychotic dose, illness duration and symptoms when only including schizophrenia patients ($r_s = 0.391$, $p_{un} = 0.001$, $p_{FDR} = 0.003$, $n = 76$), also with additional correction for FWHM, S/N and age ($r_s = 0.389$, $p_{un} = 0.002$, $p_{FDR} = 0.008$, $n = 76$).

We did not find significant correlations between the PANSS G12 item and NAA concentrations, nor between BIS scores and absolute NAA concentrations. In addition, no significant correlations were found between the other neurometabolite concentrations (absolute or ratios) and insight scores.

4. Discussion

The aim of this study was to investigate the relationship between insight and neurometabolite concentrations in the WM of the left PFC in patients with psychotic disorders. We hypothesized that if impaired insight were a consequence of prefrontal pathology, poorer insight would be associated with decreased NAA levels. We indeed found a medium

Table 3
Correlations between neurometabolite concentrations and confounding variables in patients (n = 88).

	Illness duration	Standardized antipsychotic dose	CSF content	GM content
tNAA		$r = -0.300$ ($p_{un} = 0.005$; $p_{FDR} = 0.039$)	$r = -0.464$ ($p_{FDR} < 0.001$)	$r = -0.361$ ($p_{un} = 0.001$; $p_{FDR} = 0.021$)
Glx	$r = -0.337$ ($p_{un} = 0.001$; $p_{FDR} = 0.021$)		$r = -0.323$ ($p_{un} = 0.002$; $p_{FDR} = 0.023$)	
tCho			$r = -0.305$ ($p_{un} = 0.004$; $p_{FDR} = 0.036$)	$r = -0.314$ ($p_{un} = 0.003$; $p_{FDR} = 0.032$)
tCr			$r = -0.418$ ($p_{FDR} < 0.001$)	
Glx/tCr	$r = -0.286$ ($p_{un} = 0.007$; $p_{FDR} = 0.049$)			

Abbreviations: tNAA = total NAA (*N*-acetylaspartate (NAA) + *N*-acetylaspartylglutamate (NAAG); Glx = glutamate (Glu) + glutamine (Gln); tCho = total choline (glycerophosphocholine (GPC) + phosphocholine (PCh); tCr = total creatine (CrPCr); CSF = cerebrospinal fluid; GM = grey matter; p_{un} = uncorrected for multiple testing; pFDR = FDR-corrected for multiple testing.

sized correlation (Cohen, 1988) between poorer insight (as measured with BIS) and reduced NAA concentrations, providing further evidence for the involvement of the PFC in impaired insight. No significant correlations between PANSS G12 scores and NAA concentrations were found, nor between other neurometabolite concentrations and insight.

The functional significance of decreased NAA concentrations in the WM of the PFC is still under debate. NAA is found almost solely in neurons and is seen as a marker for neuronal density or integrity (both cell body and axons). The reduced NAA concentration in the WM of the PFC might indicate impaired functioning of axons, for example because of reduced myelination, causing abnormal neural connectivity (Chang et al., 2007; Du et al., 2013). Several post-mortem studies have suggested evidence for abnormalities of myelin (Du et al., 2013), oligodendrocytes (Vostrikov et al., 2007), and axons (Uranova et al., 2007) in the prefrontal cortex in schizophrenia. The finding that patients with poorer illness awareness had reduced NAA concentrations in the WM of the left PFC, suggesting abnormal brain connectivity, is in line with previous findings from our group that changes in white matter in this area are subtly associated with insight (Ćurčić-Blake et al., 2015). In addition, while the specific relationship between signs of neuronal impairment in the PFC and insight has not been previously examined using ^{1}H-MRS, several studies demonstrated a relationship between volumetric abnormalities of the PFC and insight impairment in schizophrenia (Shad et al., 2006b, 2004). Resting state fMRI studies found lower connectivity of the anterior cingulate cortex (ACC) within the anterior default mode network (DMN) in patients with poorer clinical insight (Liemburg et al., 2012), as well as an association between cognitive insight and increased connectivity in the dorsal attention network with the right lateral PFC (Gerretsen et al., 2014). A previous study of our group also demonstrated a negative correlation between clinical insight and effective connectivity from the inferior parietal lobule (IPL), posterior cingulate cortex (PCC) and dorsomedial PFC (DMPFC) towards the ventromedial PFC (VMPFC), as well as from the IPL to the dmPFC and PCC. The same study found a positive correlation between clinical insight and effective connectivity from the VMPFC to the IPL (Ćurčić-Blake et al., 2015), indicating an important role of the PFC in insight.

It has been suggested that the relationship between PFC abnormalities and impaired insight may be explained by the role of the PFC in executive functions such as the ability to monitor and evaluate one's own behaviour and the ability to adjust one's own thoughts and beliefs to changing situations (Shad et al., 2007, 2006b). The neuropsychological model, which has been proposed to explain the aetiology of insight, suggests that impaired insight is a consequence of cognitive dysfunction (Amador et al., 1991). According to this model, this could be a generalized cognitive deficit (Keshavan et al., 2004) that is similar in magnitude across different cognitive functions, or it could be a more specific impairment, for example of executive functions. Several studies have reported a relation between abnormalities of the DLPFC and impaired executive functioning (Bertolino et al., 2003, 2000; Delamillieure et al., 2004; Galińska et al., 2007; Rüsch et al., 2008; Shirayama et al., 2010; Tanaka et al., 2006; Zong et al., 2015), as well as between impaired executive functioning and impaired insight (Shad et al., 2006a, 2004). The relation between impaired insight and prefrontal dysfunction is based predominantly on impaired performance on the Wisconsin Card Sorting Test (WCST). The WCST is one of the most widely used tests of prefrontal functioning, even though other areas outside the prefrontal cortex have also been shown to be activated during this task. In addition, significant correlations have also been found between frontal NAA concentrations and other cognitive functions such as verbal learning and memory (Ohrmann et al., 2007), attention/vigilance, verbal learning and social cognition (Jarskog et al., 2013), and verbal fluency (Shirayama et al., 2010), although other studies did not find significant relationships between frontal NAA concentrations and neuropsychological tests results (Buckley et al., 1994; Szulc et al., 2012). Evidence from meta-analyses also shows that impaired insight cannot be explained exclusively by abnormal executive functioning. Other cognitive deficits, such as impairments in verbal learning, memory and attention, may be associated with poor insight as well (Nair et al., 2014). Furthermore, other functions of the prefrontal cortex, such as metacognitive functioning, may also help explain lack of insight. The abilities to make complex representations of the self (and others), to reflect upon one's own behaviour, and to take the perspective of others may all play a role in the aetiology of impaired insight (Koren et al., 2004; Langdon and Ward, 2009). To our knowledge, only one study examined metacognitive insight, which was defined as self-monitoring ability, in schizophrenia thus far. This study found that impaired metacognitive insight was associated with reduced GM volumes in the right DLPFC, left ventrolateral PFC, right insula, bilateral premotor area and bilateral putamen (Spalletta et al., 2014). Such metacognitive functions have yet been insufficiently studied in relationship to poor clinical insight, although the initial findings do imply a role of these processes (De Vos et al., manuscript in preparation). Metacognition has also been associated with brain areas outside the prefrontal cortex, however (Fleming and Dolan, 2012).

With regard to the association between NAA concentrations and clinical insight as measured with the BIS, we found that this relationship could mainly be explained by the correlation between the subscale Awareness of illness and tNAA/tCr ratios. Insight is regarded as a multidimensional construct and, indeed, our results suggest that prefrontal NAA concentrations are more strongly related to some than to other dimensions of insight. This is in line with previous studies that suggested involvement of different areas in separate dimensions of insight (Antonius et al., 2011; Shad et al., 2006b). Shad and colleagues, for instance, suggested that DLPFC abnormalities may underlie lack of awareness of illness by interfering with self-monitoring, while abnormalities of the orbitofrontal cortex (OFC) may underlie problems with attribution of symptoms (Shad et al., 2006b). This is in line with a study that found a relationship between cortical thickness of the OFC and delusion attribution in patients with a psychotic disorder (Buchy et al., 2012). Another study examined the effect of a 3-week course of bilateral rTMS of the DLPFC in schizophrenia patients with negative symptoms (Dlabac-de Lange et al., 2015), and the authors found improvement of

clinical insight, which was mainly the result of a higher score on the BIS subscale measuring awareness of need for treatment. All these studies suggest an association between DLPFC abnormalities and one or more dimensions of clinical insight. However, the construct of insight is rather complex and it may be associated with several (partially overlapping) cognitive functions coordinated by different brain regions (and interactions between them). For example, dorsomedial frontal areas and the anterior cingulate cortex could play an important role in conflict monitoring and switching from self to other perspective in order to enhance relabelling of symptoms, which may thus be less dependent on DLPFC function.

The correlation between NAA concentrations and insight as measured with the PANSS G12 item also showed a relationship between lower NAA concentrations and poorer insight, but this correlation did not reach statistical significance. No relationship was found between clinical insight and other neurometabolite concentrations (Glx, tCr, tCho and ml). This is in line with expectations, since most previous studies did not find abnormalities of creatine, choline and myo-inositol levels in schizophrenia (Kraguljac et al., 2012; Marsman et al., 2013; Poels et al., 2014). Some studies found abnormalities of glutamate but the relation between glutamate levels and insight has not been examined before. Furthermore, insight did not correlate with illness duration, standardized antipsychotic dose or symptom scores suggesting that insight may be independent of these variables. Earlier studies found a relationship between insight and negative or positive symptoms, while other studies failed to replicate this (see Joseph et al., 2015). We also did not find a correlation between NAA concentrations and positive or negative symptoms. Results of earlier studies examining these correlations were also mixed: one earlier study found an association between dorsolateral prefrontal NAA/Cr ratios (which were a mean of right and left hemispheres) and negative symptoms (Callicott et al., 2000), while another study did not find an association between NAA concentrations in the left DLPFC and negative or positive symptoms (Sigmundsson et al., 2003).

4.1. Limitations

First, our study is cross-sectional in design. Longitudinal studies are necessary in the future, to examine whether impaired insight could be the consequence of abnormal neurodevelopment or other neuropathological processes. Second, clinical insight was measured with both a one-dimensional (PANSS item G12) and a multidimensional measure (BIS). It is recommended to use multidimensional measures, since earlier studies have suggested that different dimensions of clinical insight are of differing complexities and rely on different brain areas (Shad et al., 2006b). Nevertheless, using both the PANSS G12 item and the BIS allowed us to assess clinical insight with a single item interview-based clinician/researcher-reported measure as well as a multi-item self-report measure. Other studies have shown that interview-based ratings may measure different aspects of insight compared to self-reported ratings (Young et al., 2003). In addition, even though the PANSS G12 item is a single-item measure, it incorporates the different dimensions of clinical insight. Future studies could benefit, however, from measuring insight with more elaborate measures, such as the Scale to Asses Unawareness of Mental Disorder (SUMD) (Amador et al., 1993), as these measures can give additional information on different aspects of insight.

4.2. Conclusion

Future studies are needed to further examine whether problems with impaired insight arise from DLPFC abnormalities or because of abnormal input to the DLPFC resulting from pathology in other areas. Future research should focus on the role of different cognitive abilities in different dimensions of insight and should consider neurocognitive, metacognitive and social cognitive factors in attempts to explain the aetiology of impaired insight. In addition, similarities between neurological patients with unawareness of deficits after right hemisphere damage and unawareness of illness in schizophrenia have been suggested based on results of structural and neurocognitive studies (Shad et al., 2007). Thus, besides focusing on the left DLPFC, neurometabolite abnormalities in the right DLPFC might be worth studying as well.

Conflict of interest

AA received speaker fees from Lundbeck; all other authors declare that they have no conflicts of interest.

Contributors

AA, BCB, DIL and RK designed the study. RK was also involved in the recruitment of patients. AEV, EJL and LB acquired the data, which DIL analysed. BCB, EJL and ASK were involved in the analyses. DIL wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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Appendix A. Supplementary data

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