Divergent relationship between brain structure and cognitive functioning in patients with prominent negative symptomatology

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ABSTRACT
Investigating commonalities in underlying pathology of cognitive dysfunction and negative symptoms in schizophrenia is important, as both are core features of the disorder and linked to brain structure abnormalities. We aimed to explore the relationship between cognition, negative symptoms and brain structure in schizophrenia. A total of 225 patients with Schizophrenia spectrum disorder and 283 healthy controls from the Norwegian Thematically Organized Psychosis (TOP) cohort were included in this study. Patients were categorized into four patient subgroups based on severity of negative symptoms: no-negative- (NNS), threshold-negative- (TNS), moderate-negative- (MNS), and prominent-negative (PNS) subgroups. MRI measures of brain volume, mean cortical thickness and surface area from pre-selected brain regions were tested for relationships with general cognitive ability and negative symptom subgroups. Positive associations were found between brain volume, thickness, surface area and cognition in the dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), fusiform gyrus (FG) and the left anterior cingulate cortex (ACC), but with no differences between subgroups. In the PNS subgroup, cognition was conversely negatively associated with brain volume in the left ACC. These results indicate that patients with prominent negative symptoms have different associations between cognition and brain structure in the left ACC, which may point to abnormal neurodevelopment.

1. Introduction
Cognitive dysfunction and negative symptoms are core features of schizophrenia (SZ) (Kahn and Keefe, 2013; Kirkpatrick et al., 2006; Sheffield et al., 2018) linked to higher levels of functional impairment and disability (Kahn and Keefe, 2013; Tandon et al., 2000). Both symptom domains are frequently observed in the SZ population (Galdersi et al., 2018; Habterwold et al., 2020), present early in the course of the illness, often before the first psychotic episode, and persist during and after treatment (Kahn and Keefe, 2013; Mucci et al., 2017). While cognitive functioning generally refers to the ability to perform mental operations or skills, the amotivation and reduced goal-directedness underlying negative symptoms can impact the likelihood of actually performing cognitive tasks. Negative symptoms include affective flattening, avolition/apathy and anhedonia (Kirkpatrick et al., 2006). Cognitive functioning encompasses both social and non-social cognitive processes. Social cognition refers to sub-processes such as emotion processing, social perception, attributional style, and mentalizing (Green et al., 2019) while non-social or neurocognitive processes, which is the prime focus of this study, refers to sub-processes such as verbal learning and memory, processing speed, working memory and executive functions (Heinrichs and Zakzanis, 1998).

Cognitive dysfunction and negative symptoms are interlinked. There are several reports of strong associations between negative symptom severity and cognitive impairments, where the patients with the highest negative symptom levels show poorer cognitive performance compared to patients with no or few negative symptoms (Engen et al., 2019; Hovington and Lepage, 2012; Ince and Ucok, 2018; Lewandowski et al., 2018).
Chain models of how negative symptoms and cognitive functioning are related to functional outcome in SZ have been proposed, for instance that processing deficits lead to negative symptoms which in turn lead to poor daily functioning. (Green et al., 2012; Ventura et al., 2014). It is however, not clear how mechanisms underlying cognitive and negative symptoms are related and whether they share the same underlying neuropathologies. It has here been suggested that the two symptom dimensions are separate, but with related underlying etiologies and some shared neuropathologies (Harvey et al., 2006).

Over the last decade considerable effort have been put into understanding and conceptualizing the negative symptom dimension (Galderisi et al., 2018; Mueller et al., 2017). The presence and severity of these symptoms (First et al., 1995; Ence and Ucok, 2018) has consistently been linked to both thinner prefrontal cortex (OFc, Bodnar et al., 2014; Morch-Johnsen et al., 2015; Walton et al., 2018), the anterior cingulate cortex (ACC, Cassella et al., 2010), and medial temporal regions such as the parahippocampus and fusiform gyrus (Bodnar et al., 2014; Nestor et al., 2007) Furthermore, negative symptoms have been linked to brain functional alterations in the dorsolateral prefrontal cortex (Chung and Barch, 2016), the fusiform gyrus (Shaffer et al., 2015) and abnormalities in white matter connections between orbitofrontal cortex and anterior cingulate cortex (Ohtani et al., 2014).

In general, better cognitive performance is most commonly associated with thicker cortex, larger brain surface area and brain volumes both in healthy individuals and in SZ patients (Cobia et al., 2011; Hartberg et al., 2010; Waldovd et al., 2016; Zimmermann et al., 2006). In SZ, volumetric abnormalities underlying cognitive functioning has been found in frontal, parietal and temporal brain regions (Hartberg et al., 2010; Rodrigue et al., 2018; Aminoff et al., 2013; Ward et al., 2014). Furthermore, since brain structures are both anatomically and functionally connected, cognitive deficits are likely to reflect dysfunctional communication between large brain networks rather than localized functions (Menon, 2011). SZ has accordingly been implicated as a disorder of brain connectivity (van den Heuvel and Fornito, 2014). The DLPFC, a core hub of the fronto parietal brain network, has most consistently reported associations between increased severity of negative symptoms and brain structure abnormalities in frontal regions such as the orbitofrontal cortex (OFc, Bodnar et al., 2014; Morch-Johnsen et al., 2015; Walton et al., 2018), the anterior cingulate cortex (ACC, Cassella et al., 2010), and medial temporal regions such as the parahippocampus and fusiform gyrus (Bodnar et al., 2014; Nestor et al., 2007) Furthermore, negative symptoms have been linked to brain functional alterations in the dorsolateral prefrontal cortex (Chung and Barch, 2016), the fusiform gyrus (Shaffer et al., 2015) and abnormalities in white matter connections between orbitofrontal cortex and anterior cingulate cortex (Ohtani et al., 2014).

Clinical and cognitive assessments were performed by trained psychologists or physicians. Current positive and negative symptoms were assessed using the Positive and Negative Syndrome Scale. For positive symptoms, we used the original three-factor solutions including items P1-P6 (Kay et al., 1987). Current depressive symptoms were measured with the CGI-S scale (Guy, 1976). Global functioning was assessed using the Global Assessment of Functioning scale (GAF, Pedersen, 2007), which includes separate scores for symptoms (GAF-S), and functioning (GAF-F). Substance use was assessed using the Alcohol and Drug Use...
Disorder Identification Tests (AUDIT, DUDIT, Berman et al., 2005; Saunders et al., 1993). Defined daily doses (DDD, (http://www.whocc. no/)) of antipsychotic medication were calculated. Age at onset (AAO) was set as the age of the first SCID-verified psychotic episode, and duration of illness (DOI) was calculated subtracting the AAO from the current age. Duration of untreated psychosis (DUP) was calculated as the time in weeks from the onset of psychotic symptoms (the first week with a PANSS score of 4 or above on positive items 1, 3, 5 or 6, or general item 9) until the week of starting the first adequate treatment (defined in; Haatveit et al., 2016).

Current IQ was estimated using the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 2007). Executive functions were measured using the Verbal Fluency Test (Letter Fluency, Category Fluency and the Category Switching) and the Color-Word Interference Test (Inhibition and Inhibition Switching) both from the Delis Kaplan Executive Functioning System (D-KEEFS; Delis et al., 2006). Learning and memory were measured using two subtests from the California Verbal Learning Tests (verbal learning and recall; CVLT-II; Delis et al., 2000), and two subtests from the Wechsler Memory Scale (immediate and delayed recall; WMS; Wechsler, 1997). To measure processing speed we used the Digit Symbol Test (WAIS-III; Wechsler, 2003), and the Color Naming and Word Reading subtests from the Color-Word Interference Test (D-KEEFS; Delis et al., 2006). Lastly, working memory was measured using the Digit Span Test and Letter-Number Sequencing Test (Wechsler, 2003). Z scores were calculated for each test, using the entire sample mean, and divided into separate domain scores (supplementary, SF1). The separate domain scores were finally combined into a general cognitive ability score.

2.2.1. Subgrouping of negative symptoms

PANSS negative items; blunted affect (N1), emotional withdrawal (N2), poor rapport (N3), passive/apathetic social withdrawal (N4) and lack of spontaneity and flow in conversation (N6) were selected for subgrouping of participants based on the severity of negative symptoms (Engen et al., 2017; Marder and Galderisi, 2017; Rabinowitz et al., 2013).

1 No Negative Symptoms (NNS): Participants with negative symptom scores $\leq 2$ on all items, $n = 75$
2 Threshold Negative Symptoms (TNS): Participants with negative symptom scores $= 3$ on at least one item, $n = 68$
3 Moderate Negative Symptoms (MNS): Participants with a negative symptom score $\geq 4$ on one or two items, $n = 46$
4 Prominent Negative Symptom (PNS): Participants with negative symptom scores $\geq 4$ on at least three items or $\geq 5$ on at least two items, $n = 36$

The NNS and TNS group separate patients with no or threshold negative symptoms from those with moderate or prominent symptoms. The NNS group have low levels of negative symptoms considered to be within the normal range, while the TNS group have mild negative symptoms just below the PANSS threshold level ($< 4$) used in many studies focusing on negative symptoms (Engen et al., 2019; Mucci et al., 2017; Rabinowitz et al., 2013). Having a PANSS score of 3 or below is also in accordance with (Andreasen et al., 2005) criteria for remission. The MNS and PNS groups both have negative symptom values $\geq 4$, yet the PNS group differs from the MNS group in that this group reflects patients with more “pronounced and clinically relevant negative symptoms” (Correll and Schooler, 2020).

2.3. MRI acquisition

The participants were scanned on the same 1.5 T Siemens Magnetom Sonata scanner (Siemens Medical Solutions, Erlangen, Germany) equipped with a standard head coil. After a conventional 3-plane localizer sequence, two sagittal T1-weighted magnetization prepared rapid gradient echo (MPRAGE) volumes were acquired with the Siemens tfl3d1 ns pulse sequence (Echo Time = 3.93 ms, Repetition Time = 2730 ms, Inversion Time = 1000 ms, flip angle = 7°; Field of View = 24 cm, voxel size = $1.33 \times 0.94 \times 1\ mm^3$, number of partitions = 160) and subsequently averaged together, after rigid-body registration, to increase the signal-to-noise ratio. No major scanner upgrades were performed during the study period.

2.4. MRI post processing

Estimates of cortical thickness, surface area and volume were obtained automatically using the FreeSurfer software package version 5.3.0 (http://surfer.nmr.mgh.harvard.edu; Dale et al., 1999; Fischl et al., 2004). The main processing steps included motion correction (all scans were visually inspected for motion artefacts), removal of non-brain tissue, automatic Talairach transformation and intensity correction. A reconstruction of the grey/white matter boundary and pial surface was made based on the intensity and continuity information from three-dimensional (3D) T1- weighted MR images. Individual surfaces were mapped to a common template surface (fsaverage) using a non-rigid high-dimensional spherical co-registration method to align cortical folding patterns. The surface reconstructions were visually inspected by trained laboratory assistants, and manually edited according to FreeSurfer guidelines. Cortical thickness was measured as the shortest distance between the grey/white matter boundary and the pial surface at approximately 163 842 points (vertices) in each hemisphere. The Desikan atlas was used to parcellate the cortical surface into anatomical regions, allowing for regional calculations of ROI surface area, mean cortical thickness, and volume (Desikan et al., 2006).

2.5. Statistical analysis

Statistical analyses were performed with SPSS version 25.

2.5.1. Demographic and clinical data

Group differences in demographic and clinical data were assessed using t-test, analysis of variance (ANOVA) or analysis of co-variance (ANCOVA) for continuous, normally distributed variables. Chi-square statistics were applied for categorical data. The Kruskal-Wallis Test was used to analyze variables with a heavily skewed distribution (DDD, AAO, DOI, DUP, DUDIT, AUDIT), and pairwise comparisons are reported for significant effects. We used Pearson’s correlation analysis of selected PANSS negative-items total score (N1, N2, N3, N4 and N6 summarized) and the general cognitive ability score (composite z score) to explore potential collinearity between the investigated variables ($\alpha = 0.05/5$ tests, Bonferroni corrected).

2.5.2. Associations between cognitive functioning, negative symptoms and brain structure

Using two-way ANCOVAs we first investigated the associations between general cognitive ability (composite score) and negative symptom subgroup on brain structure, covarying for age, gender and estimated total intracranial volume (eTIV).

Secondly, we investigated if the association differed by exploring the interaction between negative symptom subgroup and general cognitive ability on brain structure. Outliers with residual scores over three standard deviations (SDs) on measures of brain structure were removed from the single analysis (see supplementary for details). As cortical volume and surface area is associated with individual head size, these analyses were performed with the eTIV as covariate. Additionally, all effects were corrected for multiple testing using the Bonferroni method (in five ROIs bilaterally, $\alpha = 0.05/10$ tests).

2.5.3. Post hoc comparisons

Post hoc analyses correcting for possible confounding effects were
performed if there was a significant effect of group or a significant interaction effect between negative symptom subgroup and general cognitive ability on brain structure. This was done using the parameter estimates function in the general linear model (GLM). A possible confounding effect was considered present if detected in the initial group analyses of clinical and demographic characteristics (Table 1). Also, to ensure generalizability of the study results, we conducted supplementary analyses within subsamples of patients (subgroup < 3 months' time to MRI; within first episode patients alone) and comparisons with healthy controls (supplementary section).

3. Results

3.1. Demographic, clinical and cognitive characteristics

Demographic, clinical and cognitive characteristics of the negative symptom subgroups are summarized in Table 1. There was a significant effect of age, with the NNS group being slightly older than the other groups, but no differences in gender distribution or IQ. Compared to the NNS and the TNS subgroups, the MNS and the PNS subgroups had higher negative symptom levels and worse psychosocial functioning (GAF-S and GAF-F), and more depressive symptoms (CDSS). Additionally, the NNS group had fewer positive symptoms (PANSS positive) than all other groups. There were no differences in reported alcohol use, medication dosages, AAO or DUP between subgroups, but the TNS group reported higher drug use (AUDIT/DUDIT) than all other groups.

3.2. Association between cognition and negative symptoms on brain structure

Results from the univariate ANCOVAs are summarized in Table 2. We found a statistically significant positive association between general cognitive ability and brain volume in the left OFC ($F_{(1,217)} = 14.7, p < 0.001, \eta^2 = 0.06$), with similar nominal (trend level) associations in the left and right DLPFC, left ACC and in the right OFC. There were no significant associations between negative symptom subgroups and brain volume in any of the inspected ROIs, except for a nominal (trend level) association in the right DLPFC.

For cortical thickness we also found trend level positive associations between general cognitive ability and cortical thickness in bilateral DLPFC and fusiform gyrus. There were no significant associations between cortical thickness and negative symptom subgroup in any of the inspected ROI’s.

Finally, we found a statistically significant positive association between general cognitive ability and surface area in the left OFC ($F_{(1,217)} = 9.0, p = 0.003, \eta^2 = 0.04$), and similar trend level associations with surface area in the right DLPFC and in the right OFC. There were no significant associations between negative symptom subgroups and surface area.

### Table 1

| Demographics       | NNS (gr1) | TNS (gr2) | MNS (gr3) | PNS (gr4) | F/K/$\chi^2$ | P | Post hoc |
|--------------------|-----------|-----------|-----------|-----------|--------------|---|---------|
| Age                | 33.5 (10.0) | 28.4 (7.6) | 30 (9.3)  | 28.4 (8.5) | 4.8          | 0.003 | 1>2,3,4 |
| Gender (% male)    | 51        | 56        | 59        | 61        | 1.4          | 0.714 |
| IQ                 | 106.8 (12.1) | 106.3 (11.7) | 102.4 (16.5) | 101.2 (15.5) | 2.2          | 0.093 |
| PANSS negative     | 34        | 27        | 34        | 24        |              |       |
| PANSS positive     | 10        | 6         | 2         | 5         |              |       |
| Schizophrenia      | 25        | 29        | 5         | 5         |              |       |
| % FEP patients     | 40        | 72        | 54        | 61        |              |       |
| PANSS negative     | 8.6 (1.7) | 13.4 (2.9) | 18.0 (3.2) | 25.1 (4.2) | 289.5        | <0.001 | 4>3,2,1>3,2,1>2>1 |
| PANSS positive     | 13.0 (5.6) | 15.4 (4.8) | 15.0 (5.6) | 16.0 (4.8) | 3.9          | 0.013 | 4,3>2,1>2 |
| CDSS               | 4.4 (3.8) | 5.4 (4.0) | 7.5 (4.7) | 7.4 (4.6) | 0.5          | 0.874 |
| GAF Symptom        | 47.1 (13.1) | 44.4 (11.5) | 39.7 (6.6) | 37.4 (9.2) | 8.5          | <0.001 | 1,2-3,4 |
| GAF Function       | 47.8 (11.9) | 47.2 (11.6) | 41.9 (8.0) | 37.3 (9.0) | 10.2         | <0.001 | 1,2-3,4 | 3>4* |
| DDD                | 1.0 (0.3-5.5) | 1.0 (0.1-4.5) | 1.0 (0.3-5.5) | 1.0 (0.3-5.5) | 0.7          | 0.874 |
| AAO                | 22.5 (7.51) | 23.8 (10-44) | 22.0 (15-47) | 21.0 (13-38) | 3.5          | 0.316 |
| DOI                | 6.5 (0-41) | 2.0 (0-25) | 5.0 (0-28) | 4.0 (0-22) | 9.7          | 0.021 | 2<1 |
| DUP                | 40 (0-780) | 52 (1-300) | 45 (1-468) | 75 (2-468) | 1.4          | 0.688 |
| AUDIT              | 5.0 (0-27) | 5.0 (0-24) | 3.5 (0-33) | 4.5 (0-33) | 0.8          | 0.851 |
| DUDIT              | 0.0 (0-22) | 1.5 (0-37) | 0.0 (0-37) | 0.0 (0-30) | 9.8          | 0.020 | 2>1 |

Note: Psychosis NOS: Psychosis not otherwise specified; CDSS: Calgary Depression Scale for Schizophrenia; GAF: Global Assessment of Functioning scale; DDD: Defined daily doses of antipsychotic; AAO: Age at onset; DOI: Duration of illness; DUP: Duration of untreated psychosis; AUDIT/DUDIT: Alcohol/Drug Use Disorder Identification Tests.

Presented are means, standard deviations (median, range for skewed variables) and results from negative subgroup comparisons.
3.2.1. Interactions between negative symptom group and cognition on brain structure

With regard to cortical volume, we found a statistically significant interaction between negative symptom subgroups and general cognitive ability in the left ACC ($F_{(3,213)} = 4.8, p = .003, \eta^2 = 0.06$). Subgroup comparisons showed that patients with PNS had a different function-structure relationship compared to patients with MNS ($t = 3.3, p = .001, \eta^2 = 0.05$) or TNS ($t = 3.1, p = .002, \eta^2 = 0.04$, Fig. 2). In the PNS group, poorer performance was associated with larger, not smaller volume as in the other groups. Similar trend level associations were found in the left fusiform gyrus. This was also found in the right parahippocampal gyrus for both cortical volume and thickness, and in the left ACC for cortical surface area, where the PNS group also tended to have different structure-function relationship compared to the other groups (Table 2).

Lastly, trend level interactions between negative symptom subgroups and general cognitive ability were seen for cortical thickness in right fusiform gyrus and for cortical surface area in the right OFC where the no negative symptoms group had a different function-structure relationship compared to the other groups (Table 2). However, one should be very careful interpreting these findings as they do not survive correction for multiple testing.

3.3. Post hoc analyses

In post hoc analyses, the interaction effect on brain volume in the left ACC remained significant after controlling for potential confounding variables, including positive symptoms ($F_{(3213)} = 4.9, p = .003, \eta^2 = 0.065$), depressive symptoms ($F_{(3213)} = 4.7, p = .003, \eta^2 = 0.081$), GAF-S ($F_{(3213)} = 4.7, p = .003, \eta^2 = 0.063$), GAF-F ($F_{(3213)} = 4.7, p = .003, \eta^2 = 0.062$), drug usage ($F_{(3213)} = 4.9, p = .003, \eta^2 = 0.092$), DOI ($F_{(3213)} = 4.8, p = .003, \eta^2 = 0.067$), and antipsychotic use measured in

Table 2

| Cortical region | Negative subgroup | Cognitive composite score | Interaction | Post hoc |
|-----------------|-------------------|---------------------------|-------------|---------|
|                 | F     | p    | $\eta^2$ | F     | p    | $\eta^2$ | F     | p    | $\eta^2$ |
| Volume          |       |      |          |       |      |          |       |      |          |
| left DLPFC      | 1.6   | 0.195| 0.02     | 6.5   | 2.5  | 0.012    | 0.03  |       |          |
| right DLPFC     | 3.1   | 0.029| 0.04     | 6.5   | 2.5  | 0.012    | 0.03  | 1.4   | > 2     |
| left OFC        | 0.7   | 0.584| 0.01     | 14.7  | 3.8  | <0.001*  | 0.06  |       |          |
| right OFC       | 1.8   | 0.153| 0.02     | 4.9   | 2.2  | 0.028    | 0.02  |       |          |
| left ACC        | 2.3   | 0.081| 0.03     | 5.0   | 2.2  | 0.026    | 0.02  |       |          |
| right ACC       | 0.5   | 0.675| 0.01     | 1.7   | 1.3  | 0.199    | 0.01  |       |          |
| left FG         | 0.4   | 0.388| 0.01     | 3.0   | 1.7  | 0.083    | 0.01  | 2.7   | > 4-1,3 |
| right FG        | 0.6   | 0.603| 0.01     | 1.5   | 1.2  | 0.220    | 0.01  |       |          |
| left PHC        | 1.8   | 0.145| 0.03     | 1.0   | 1.0  | 0.308    | 0.01  |       |          |
| right PHC       | 0.4   | 0.750| 0.01     | 0.3   | 0.5  | 0.601    | 0.00  | 2.8   | > 4-1,3 |
| Thickness       |       |      |          |       |      |          |       |      |          |
| left DLPFC      | 1.1   | 0.340| 0.02     | 7.2   | 2.68 | 0.008    | 0.03  |       |          |
| right DLPFC     | 2.2   | 0.090| 0.03     | 5.2   | 2.28 | 0.023    | 0.02  |       |          |
| left OFC        | 0.1   | 0.970| 0.00     | 2.2   | 1.49 | 0.137    | 0.01  |       |          |
| right OFC       | 0.5   | 0.697| 0.01     | 0.2   | 0.44 | 0.663    | 0.00  |       |          |
| left ACC        | 1.3   | 0.265| 0.02     | 2.2   | 1.49 | 0.137    | 0.01  |       |          |
| right ACC       | 0     | 0.996| 0.00     | 0     | 0.11 | 0.917    | 0.00  |       |          |
| left FG         | 1.2   | 0.332| 0.02     | 6.2   | 2.49 | 0.014    | 0.03  |       |          |
| right FG        | 0.8   | 0.479| 0.01     | 4.6   | 2.1  | 0.034    | 0.02  | 3.3   | > 1-2,4 |
| left PHC        | 0.4   | 0.738| 0.01     | 1.3   | 1.13 | 0.258    | 0.01  |       |          |
| right PHC       | 1.2   | 0.312| 0.02     | 0.8   | 0.9  | 0.385    | 0.00  | 3.3   | > 4-1,2,3 |
| Area            |       |      |          |       |      |          |       |      |          |
| left DLPFC      | 1.5   | 0.219| 0.02     | 3     | 1.74 | 0.083    | 0.01  |       |          |
| right DLPFC     | 2.2   | 0.093| 0.03     | 6.3   | 2.51 | 0.013    | 0.03  |       |          |
| left OFC        | 0.5   | 0.667| 0.01     | 9     | 2.99 | 0.005*   | 0.04  |       |          |
| right OFC       | 1.4   | 0.254| 0.02     | 3.8   | 2    | 0.051    | 0.02  | 3.8   | > 1-2,3 |
| left ACC        | 1.5   | 0.221| 0.02     | 2.3   | 1.5  | 0.129    | 0.01  | 3.4   | > 1,4-2,3 |
| right ACC       | 0.5   | 0.717| 0.01     | 1.1   | 1.06 | 0.288    | 0.01  |       |          |
| left FG         | 0.4   | 0.785| 0.01     | 0.5   | 0.68 | 0.495    | 0.00  |       |          |
| right FG        | 0.8   | 0.475| 0.01     | 0     | 0.11 | 0.909    | 0.00  |       |          |
| left PHC        | 1.2   | 0.295| 0.02     | 0.2   | 0.47 | 0.639    | 0.00  |       |          |
| right PHC       | 0.4   | 0.787| 0.01     | 0.5   | 0.71 | 0.477    | 0.00  |       |          |

Univariate ANCOVAS tested for brain structure relationship with cognition and negative subgroup, and the interaction between the two. $p < .005$ were considered statistical significant (in five ROIs bilaterally, $\alpha = 0.05/10$). * indicates significant (corrected) p-values. Nominal significant p-values are in bold. Note, all analyses included age and gender as covariate. The cortical volume and surface area analyses also included intracranial-volume (ICV) as covariate.

3.3. Post hoc analyses

In post hoc analyses, the interaction effect on brain volume in the left ACC remained significant after controlling for potential confounding variables, including positive symptoms ($F_{(3213)} = 4.9, p = .003, \eta^2 = 0.065$), depressive symptoms ($F_{(3213)} = 4.7, p = .003, \eta^2 = 0.081$), GAF-S ($F_{(3213)} = 4.7, p = .003, \eta^2 = 0.063$), GAF-F ($F_{(3213)} = 4.7, p = .003, \eta^2 = 0.062$), drug usage ($F_{(3213)} = 4.9, p = .003, \eta^2 = 0.092$), DOI ($F_{(3213)} = 4.8, p = .003, \eta^2 = 0.067$), and antipsychotic use measured in
that the observed interaction effect was mainly driven by working memory performance (Working memory: $F_{3, 213} = 4.8, p = .003, \eta^2_p = 0.064$; Logical memory: $F_{3, 213} = 2.2, p = .093, \eta^2_p = 0.030$; Processing speed: $F_{3, 213} = 2.4, p = .071, \eta^2_p = 0.033$; Executive function: $F_{3, 213} = 3.5, p = .017, \eta^2_p = 0.047$). Also, partial correlation analyses revealed significant positive correlations between brain volume and working memory (controlling for age, gender and eTIV) in patients with TNS ($r(63) = 0.260, p = .037$) and in patients with MNS ($r(41) = 0.379, p = .012$), in contrast to a negative correlation between volume and cognitive function in patients with NNS ($r(30) = -0.391, p = .027$). In patients with NNS there were no significant correlations ($r(60) = -0.053, p = .660$).

4. Discussion

In the present study we investigated the relationship between cognition, negative symptoms and brain structure in SZ. Our main finding was that patients with prominent negative symptomatology had a different structure-function relationship in the left ACC, compared to patients with moderate or threshold negative symptomatology.

Initial sample characteristics showed that patients with more prominent negative symptoms had poorer general cognitive ability compared to patients with fewer or no negative symptoms in accordance with our hypothesis. This is also in accordance with reviews showing associations between the severity of negative and cognitive symptoms (Dominguez Mde et al., 2009; Hovington and Lepeg, 2012; Ince and Ucok, 2018), and with recent findings from an overlapping sample of the present showing negative associations between PANSS negative-items and composite and sub-domain cognitive scores (Engen et al., 2019).

In the main analyses we found that better cognition was associated with larger volumes, surface areas and a thicker cortex. More specifically, we found a positive effect of cognition on brain volume bilaterally in the OFC, DLPFC and in the left ACC. Similar positive effects were found on cortical thickness bilaterally in the DLPFC and fusiform gyrus, and on surface area bilaterally in the OFC and in the right DLPFC. Although some previous studies have found that cortical thickness and surface area relate somewhat differently to cognitive sub-functions (Hartberg et al., 2011; Rodrigue et al., 2018), we found only positive associations with the investigated cognitive composite score, in accordance with most previous findings (Antonova et al., 2004; Gutierrez-Galve et al., 2010; Hartberg et al., 2010; Rodrigue et al., 2018).

Furthermore, contrary to our prediction and previous findings (Bodnar et al., 2014; Cascella et al., 2010; Morch-Johnsen et al., 2015), we did not find any significant differences in cortical thickness, volume, or surface area in any of the inspected ROIs between the negative symptom subgroups, except for a trend level difference in the DLPFC that was unrelated to prominent negative symptomatology. There could be several reasons for the negative finding. These include differences in patient stratification (reflecting the severity or persistence of negative symptoms), lack of longitudinal data on the persistence of symptoms, confounding by secondary negative symptoms, use of medications putatively affecting both brain structure and functioning, and different scanning parameters.

To our knowledge no previous study has investigated the association and potential interactions between both cognition and brain structure in patient subgroups defined by their severity of negative symptoms. Our main finding was that cognition was negatively associated with brain volume in the left ACC in patients with prominent negative symptoms, whereas in the other subgroups, cognition was either positively associated (MNS, TNS) or not associated at all (NNS). Posthoc analyses indicated that this was mainly driven by the working memory subdomain. Additionally, there were similar trend level interactions between negative symptoms subgroups and cognition for cortical volume in the left parahippocampus, and for cortical thickness in the right parahippocampus.

These results indicate that the structure-function relationship in patients with prominent negative symptoms is different than in patients with lower negative symptom levels in accordance with our hypothesis. The interaction for the ACC remained significant after controlling for potential confounding variables including potential sources of secondary negative symptoms. Furthermore, follow-up analyses indicated positive associations between brain structure and working memory in the TNS and MNS subgroups, but no significant associations between brain structure and working memory in the NNS group in parallel to the findings in our healthy control sample (supplementary, ST2). Brain heterogeneity is in general increased in SZ (Alnaes et al., 2019; Brugger and Howes, 2017), but with reduced heterogeneity for the ACC in FEP (Brugger and Howes, 2017). Since our sample was a mixture of FEP and multi-episode patients, this could potentially increase within-sample-variability and be the basis for differences in structure-function relationships. However, reanalyzing the FEP group alone we found the same results, indicating that this might be present from an early stage.

Negative symptoms reflect motivational problems, lack of interest in activities and social interactions and difficulties expressing emotions. Working memory dysfunction has previously been linked to prominent negative symptoms (Chan et al., 2015) and ACC involvement in the cingulo-opercular network activity (Repovs and Barch, 2012), suggesting that these patients are unable to keep goals in mind to motivate and guide behavior for future gains (Cella et al., 2017; Gold et al., 2008). ACC is part of the ventromedial brain circuit, connecting the brain’s limbic system with the prefrontal cortex, and consequently plays a key role in linking emotional and higher order cognitive processes that are found to be disrupted in SZ (Barch and Dowd, 2016; Benes, 2010). In the present study we see that patients with PNS have more severe cognitive deficits compared to the other subgroups, making them putatively more vulnerable to atypical structure-function relationships.

The underlying mechanisms of the reverse structure-function relationship in patients with prominent negative symptoms can only be speculated on, and warrants replications and further investigations in independent samples. Although most studies report smaller volumes and thinner cortex of the ACC in psychotic disorders (Baião et al., 2007; Bersani et al., 2014) some prior studies have reported increases in ACC gray matter in SZ, however this was unrelated to negative symptomatology and cognitive functioning was not considered (Honea et al., 2008; Ren et al., 2013). In healthy individuals, cognitive development is said to follow maturation of the cerebral cortex (Lebel and Beaulieu, 2011; Walhovd et al., 2016) with somewhat different trajectories for cortical surface area, volume and thickness. Cortical volume increases as the cortical surface area expands into adolescence (Amlien et al., 2016) followed by volumetric decrease driven by thinning of the cortex (Storsve et al., 2014). Recent evidence suggests a positive relationship between general cognitive abilities and cortical surface area throughout life (Walhovd et al., 2016), whereas cortical thickness shows the opposite association during development and aging (Fjell and Walhovd, 2010; Tammes et al., 2011). During development, rapid levels of cortical thinning is related to increases in general abilities, and vice versa during aging (Smith et al., 2006; Tammes et al., 2011). Underlying observations of changes in cortical metrics during neurodevelopment are complex and include processes such as neurogenesis, neuronal migration and pruning of synapses to create efficient neuronal networks for cognitive processing. Previous studies have shown that negative and cognitive symptoms are linked to abnormal brain structure in the ACC even before the onset of psychosis (Brent et al., 2013; Fornito et al., 2008; Koutsoulis et al., 2012). Thus, one might speculate that in PNS patients, the inverse structure-function relationship we observe are caused by abruptons in normal development, creating less efficient neuronal networks for cognitive processing, leading to “bigger not always being better”. However, as we do not have longitudinal data, we cannot rule out that these results could also be caused by a more progressive illness course in the PNS group. This includes illness related factors such as...
having more psychotic and cognitive symptoms over longer time periods and a higher lifetime consumption of medication. Some studies have shown more progressive brain volume changes in relation to long term use of antipsychotics (Ho et al., 2011; Smieskova et al., 2009; van Haren et al., 2011) which potentially could interfere with the structure-function relationship.

4.1. Limitations

There are some limitations that warrant mentioning. The time range between the MRI scanning and the clinical assessment varied, with risk of symptom fluctuations. Negative symptoms however tend to be stable, as indicated by a recent study showing that high baseline negative symptoms predicted persistency at two year follow-up (Austin et al., 2018). A follow-up analysis for the group with < 3 months from start of evaluations to MRI scanning did not alter the results. The high levels of depressive symptoms within the MNS and PNS subgroups could potentially also confound the results. However, the observed interaction was retained after adjusting for depressive symptoms. Finally, using a cognitive composite score rather than single tests or domain specific scores may warrant concern, as the latter are potentially more sensitive to brain-specific processes. However, reduced test sensitivity within single tests could potentially cause false negative findings as most cognitive tests are multifactorial with respect to task demand and often tap into several cognitive functions.

4.2. Conclusions

The current study shows that patients with prominent negative symptomatology have poorer cognitive abilities and different brain structure-function relationship in the left anterior cingulate cortex, compared to patients with fewer or no negative symptoms, which may indicate abnormal neurodevelopment. There were however no differences in cortical volume, thickness or surface area between the negative subgroups indicating similar brain structural patterns across the patient groups. Future research should focus on investigating this in larger samples as well as in longitudinal designs. Furthermore, applying structural equation modeling (SEM) approach could help investigate the mediating relationships between these variables, which eventually could help understand the causality in this relationship. Whether the proposed dimensions of cognitive and negative symptoms represent different or unitary underlying psychopathologies remains an open question.

Contributors

BH, LMJ, IA, TU and IM took part in designing the study. Author BH undertook the statistical analyses and consulted with LMJ, DA and IM along the process. Authors BH and LMJ managed the literature search and author BH wrote the first draft of the manuscript. All authors have contributed to and approved the manuscript.

Declaration of Competing Interest

The authors declare no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2020.111233.

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With the development of more sensitive methods for detecting brain abnormalities, there is an increasing emphasis on understanding the underlying biological markers that contribute to cognitive function in schizophrenia. The importance of these findings is underscored by recent studies that have demonstrated significant relationships between brain structure and function in individuals with schizophrenia. These findings suggest that investigating the structural and functional connectivity of the brain may provide valuable insights into the mechanisms underlying cognitive impairment in schizophrenia. Future research in this area will likely involve the integration of advanced neuroimaging techniques, including diffusion tensor imaging (DTI) and functional magnetic resonance imaging (fMRI), to better characterize the brain circuits involved in cognitive processing in schizophrenia. The development of targeted interventions aimed at restoring these disrupted circuits may ultimately lead to improved cognitive outcomes for individuals with schizophrenia. Therefore, the understanding of the biological markers and their relationship to outcome is crucial for advancing the field of schizophrenia research.