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# Clarifying associations between cortical thickness, subcortical structures, and a comprehensive assessment of clinical insight in enduring schizophrenia

Sophie Béland [a], Carolina Makowski [a,b], Susanna Konsztowicz [c], Lisa Buchy [d], M. Mallar Chakravarty [a,e,f], Martin Lepage [a,c,e,*]

[a] Douglas Mental Health University Institute, McGill University, Montreal, Canada
[b] McGill Centre for Integrative Neuroscience, Montreal Neurological Institute, McGill University, Montreal, Canada
[c] Department of Psychology, McGill University, Montreal, Canada
[d] Department of Psychiatry, University of Calgary, Calgary, Canada
[e] Department of Psychiatry, McGill University, Montreal, Canada
[f] Department of Biological and Biomedical Engineering, McGill University, Montreal, Canada

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ABSTRACT

*Background:* The relationship between poor insight and less favorable outcomes in schizophrenia has promoted research efforts to understand its neurobiological basis. Thus far, research on neural correlates of insight has been constrained by small samples, incomplete insight assessments, and a focus on frontal lobes. The purpose of this study was to examine associations of cortical thickness and subcortical volumes, with a comprehensive assessment of clinical insight, in a large sample of enduring schizophrenia patients.
*Methods:* Two dimensions of clinical insight previously identified by a factor analysis of 4 insight assessments were used: Awareness of Illness and Need for Treatment (AINT) and Awareness of Symptoms and Consequences (ASC). T1-weighted structural images were acquired on a 3 T MRI scanner for 110 schizophrenia patients and 69 healthy controls. MR images were processed using CIVET (version 2.0) and MAGeT and quality controlled pre and post-processing. Whole-brain and region-of-interest, vertex-wise linear models were applied between cortical thickness, and levels of AINT and ASC. Partial correlations were conducted between volumes of the amygdala, thalamus, striatum, and hippocampus and insight levels.
*Results:* No significant associations between both insight factors and cortical thickness were observed. Moreover, no significant associations emerged between subcortical volumes and both insight factors.
*Conclusions:* These results do not replicate previous findings obtained with smaller samples using single-item measures of insight into illness, suggesting a limited role of neurobiological factors and a greater role of psychological processes in explaining levels of clinical insight.



## 1. Introduction

Poor clinical insight in schizophrenia is associated with an array of unfavorable clinical and functional outcomes (Drake et al., 2007; Erol et al., 2015). The potential neuroanatomical basis of poor clinical insight in schizophrenia has attracted considerable attention over the past decade and evidence suggests that clinical insight may be associated with various neuroanatomical markers such as total brain size (Flashman et al., 2000), grey matter (Cooke et al., 2008; Morgan et al., 2010) and white matter volumes (Palaniyappan et al., 2012). Nevertheless, to date, the literature on the structural neural correlates of clinical insight has revealed some discrepancies, with a subset of studies revealing no relationship with neuroanatomy, despite using similar neuroimaging techniques and focusing on similar neuroanatomical markers (Bassitt et al., 2007; Buchy et al., 2016; McFarland et al., 2013; Rossell et al., 2003). Moreover, to our knowledge, no study has yet examined whether clinical insight levels are associated with the anatomy of subcortical structures in *enduring* schizophrenia. These inconsistencies in the literature, as well as the lack of exploration of potential links to subcortical structures, have posed a challenge in drawing clear conclusions about the potential neuroanatomical basis of clinical insight.

A possible explanation for the inconsistencies found previously may largely stem from the existence of multiple tools to assess clinical insight, an issue that is exacerbated by the multi-dimensionality of the insight construct. Available assessments of clinical insight in schizophrenia often vary in the types and number of questions used to

* Corresponding author at: Douglas Mental Health University Institute, 6875 LaSalle Blvd., Verdun, Quebec H4H 1R3, Canada.
*E-mail address:* martin.lepage@mcgill.ca (M. Lepage).

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evaluate a single insight dimension. This makes it difficult to compare scores between scales and prevents inference that an association with insight found in one study would also be found when using different assessments. In addition, several studies have relied on single item (Gerretsen et al., 2013a; Palaniyappan et al., 2011; Shad et al., 2004), or global measures of clinical insight (Rossell et al., 2003), that do not necessarily capture specific dimensions of clinical insight, which themselves may have unique neural correlates (Xavier and Vorderstrasse, 2016).

Another potential reason for the inconsistency in the literature is that studies on the neuroanatomy of clinical insight have often been limited by small sample sizes, with most studies including a sample size smaller than 57 schizophrenia patients (Antonius et al., 2011; Bassitt et al., 2007; Cooke et al., 2008; Flashman et al., 2001; Gerretsen et al., 2015; Laroi et al., 2000; Palaniyappan et al., 2012; Sapara et al., 2007; Shad et al., 2004). This relatively low statistical power may significantly weaken the reliability of available research (Button et al., 2013), especially in the face of contradictory findings with respect to this particular research question.

Finally, the available literature on insight is limited by the fact that many analyses have been restricted to the frontal lobes as regions of interest, due to the hypothesis that poor insight may reflect frontally-mediated neurocognitive deficits (Flashman et al., 2001; Sapara et al., 2007; Shad et al., 2006). However, this focus prevents us from identifying potential associations of clinical insight with other brain structures. This latter point is especially important given evidence that clinical insight is associated with factors such as social cognition (Vaskinn et al., 2013) and verbal memory (Nair et al., 2014), whose correlates may lie in regions other than the frontal lobes.

It is clear that additional studies of clinical insight are warranted, specifically improving upon the aforementioned limitations. These include i) using a large sample size, ii) a comprehensive, reliable assessment of insight, and iii) a more exhaustive exploration of the whole brain, including both whole-brain analyses, and complementary region of interest analyses that are not limited to the frontal lobe, in addition to subcortical volumes analyses that include the hippocampus, thalamus and basal ganglia structures.

Recently, we conducted a large cross-sectional study to address these limitations by recruiting a large number of schizophrenia patients and healthy controls, administering multiple assessments of clinical insight, and acquiring over 100 high quality structural MRI scans. Using this data, a factor analysis was performed using the performance of 141 patients with a diagnosis of non-affective psychotic disorder on four self-report and observer-rated scales of insight (Konsztowicz et al., 2018). Results of this study revealed that clinical insight is largely driven by two factors: Awareness of Illness and Need for Treatment (AINT) and Awareness of Symptoms and Consequences of the illness (ASC), with the ASC factor encompassing both the awareness and attribution of symptoms. These two statistically derived factors, obtained from a range of self-report and interviewer-rated assessments, yielded a more comprehensive and statistically reliable assessment of the dimensions of clinical insight, bridging information that one can obtain from most available clinical insight assessments.

The primary objective of this manuscript was therefore to examine the neuroanatomical correlates of clinical insight in schizophrenia, both at the level of the cortex and subcortex, using the two factors identified previously by our group: AINT and ASC (Konsztowicz et al., 2018). Of note, in (Konsztowicz et al., 2018), the ASC dimension represented a less stable factor than AINT, demonstrating low internal reliability ($\alpha = 0.57$), therefore its use in the current study was primarily exploratory.

To address this objective, we examined the relationship between whole-brain cortical thickness and AINT and ASC in a large sample of well-characterized enduring schizophrenia patients. As a means of comparison, we also included a healthy control group. In addition, to reduce the burden of multiple comparison correction while replicating previous findings from ROI analyses, we also conducted a-priori based region-of-interest analysis in 8 brain regions that have been the most associated with clinical insight and self-reflective processes. Cortical thickness, as opposed to grey matter volume, was used as a neuroanatomical marker, as it provides a robust index of grey matter morphology, proposed to reflect the laminar structure of the cortex (Lerch, 2001), and it has been associated with relevant clinical phenomena in schizophrenia (Oertel-Knochel et al., 2013; Rimol et al., 2010; Xiao et al., 2015).

Finally, in line with our objective to examine associations between clinical insight using a more comprehensive whole-brain approach, we also conducted exploratory analyses of associations between the two clinical insight dimensions and volumes of 4 subcortical structures: the hippocampus, whole striatum, thalamus, and amygdala. These exploratory analyses were conducted for several reasons. First, because of evidence that clinical insight is associated with factors whose correlates may lie in brain regions other than the cortex, such as verbal memory (Nair et al., 2014) which has been associated with hippocampal function (den Heijer et al., 2012; Phelps, 2004). Second, given that patients with schizophrenia present abnormalities in subcortical structures compared to healthy subjects (van Erp et al., 2016), it is reasonable to posit that a phenomenon such as clinical insight which is associated with indicators of illness severity in schizophrenia (Gerretsen et al., 2013b) may also be associated with subcortical structures. Finally, these cortical and subcortical structures do not function in isolation, as there is evidence for extensive connections between these structures (Kim et al., 2011; Stein et al., 2007). It follows that an abnormality that could be identified at the level of the frontal lobes may also be represented in the subcortex.

Our primary hypothesis was that greater ASC would be correlated with cortical thickness in previously associated regions such as the insula and temporal gyri, but that AINT would show little to no associations with cortical thickness given previous results from our group (Emami et al., 2016). For replication purposes, we also compared vertex-wise cortical thickness between healthy controls and patients, where we predicted that patients would exhibit reductions in cortical thickness in temporal, occipital, and cortical midline structures, as previously demonstrated (Rimol et al., 2010). As analyses of subcortical structures were exploratory in nature, no a priori hypotheses were formulated.

## 2. Methods

### 2.1. Subjects

One hundred forty-one subjects (73% male) meeting diagnostic criteria for schizophrenia or schizoaffective disorder for a duration of at least 3 years, and aged between 18 and 50 years old, were recruited from inpatient and outpatient units of the Douglas Mental Health University Institute and affiliated community centers. Participants were recruited as a part of a larger cross-sectional study investigating the determinants of insight in schizophrenia. Of this group, 114 patients accepted to participate in the neuroimaging portion of the study. Information on diagnosis, antipsychotic dosage (converted to chlorpromazine equivalent), and duration of illness were collected by medical chart review, or directly confirmed with patients' medical teams. An abbreviated version of the Structured Clinical Interview for DSM-IV Axis I Disorders was administered to all patients to confirm patients' illness history. Exclusion criteria included low neuropsychological performance, lifetime or familial history of neurological condition, head injury with loss of consciousness, diagnosis of substance dependence, and presence of metallic objects in the body.

Additionally, 71 healthy controls, without any personal or familial history of psychotic illness were recruited using a classified advertising website in Montreal. The Structured Clinical Interview for DSM-IV-TR Axis 1 Disorders, non-patient version (SCID-NP) was administered to all healthy controls during the first assessment to rule out the presence

of current mental illness. Healthy subjects were recruited based on their education level, age, and sex, to match the demographic characteristics of the patient group. All participants provided written informed consent, and the study procedures were approved by the Douglas Mental Health University Institute human ethics review board.

### 2.2. Clinical insight

Levels of clinical insight were obtained by computing sum scores on the items included in the two insight dimensions, AINT and ASC (details on the assessment can be found in Konsztowicz et al. (2018)). Items included in the AINT factor, which explained 15.2% of total variance, were derived from 3 of the 4 scales designed to assess clinical insight used in Konsztowicz et al. (2018) factor analysis: the Birchwood Insight Scale (BIS) (Birchwood et al., 1994), Scale for Unawareness of Mental Disorder (SUMD) (Amador et al., 1993), and Schedule for the Assessment of Insight – expanded (SAI-E) (David et al., 1992). Items included in the ASC factor were derived from items 4, 5, 7 and 8 of the SAI-E, and together these items explained 9.5% of variance in insight. Higher scores on AINT and ASC indicate higher levels of clinical insight into illness and need for treatment, and awareness/attribution of symptoms and their consequences, respectively. For each individual participant, the same rater was responsible for administering both interviewer-rated insight scales, the SAI-E and SUMD.

### 2.3. Clinical and neuropsychological assessment

Symptoms were assessed by summing global symptom scores from the Scale for Assessment of Negative symptoms (SANS) (Andreasen, 1984) and Scale for Assessment of Positive symptoms (SAPS) (Andreasen, 1983) for the assessment of negative and positive symptoms, respectively. The global score for the attention domain of the SANS was excluded from the latter calculations (Hovington et al., 2012). The Weschler Abbreviated Scale of Intelligence (WASI) was administered to both patient and control groups to estimate intellectual quotient (IQ).

### 2.4. Statistical analyses of demographic, clinical, and neuropsychological data

Descriptive statistics were computed to characterize the patient and control groups. Independent samples *t*-tests (two-tailed) were performed to compare demographic and psychological characteristics of the patient and control groups. Pearson correlations were conducted between the two insight factors, and demographic and clinical variables.

### 2.5. MRI acquisition and processing

T1-weighted structural images were acquired on a Siemens 3 T Tim trio MRI at the Brain Imaging Centre of the Douglas Mental Health University Institute. The scans were MPRAGE (TR = 2300 ms, TE = 2.98 ms, FOV 256 mm, 1 mm × 1 mm × 1 mm voxels, flip angle = 9) and lasted 9 min. All raw T1-weighted scans were visually inspected by one rater (S.B.) to ensure that no artefacts were present due to motion, and that the grey/white matter delineation was sufficiently clear for extraction of cortical thickness. Any scan that did not pass this first step of quality control was not further processed nor analyzed. Quality-controlled scans were then submitted to the CIVET processing pipeline to extract cortical thickness (version 2.0, Montreal Neurological Institute at McGill University, Montreal, Quebec, Canada) (Ad-Dab'bagh et al., 2005; Kim et al., 2005). Processing steps included 1) registration of T1-weighted images to the ICBM152 nonlinear template and correction for uniformity (Collins et al., 1994; Sled et al., 1998); 2) tissue classification (Zijdenbos et al., 2002); 3) extraction of grey and white matter surfaces within 40,962 vertices from each hemisphere (MacDonald et al., 2000); 4) distance between white and grey surfaces was measured and smoothed using a 30-mm kernel (Lerch and Evans, 2005; Lerch et al., 2008). Detailed description of processing steps from our group can be found elsewhere (Emami et al., 2016; Makowski et al., 2016). Regions of interest were defined using the Automated Anatomical Labeling (AAL) atlas (Lyttelton et al., 2007; Tzourio-Mazoyer et al., 2002).

Quality-controlled scans were also submitted to the Multiple Automatically Generated Templates (MAGeT)-Brain algorithm to extract subcortical volumes (striatum, amygdala, hippocampus, thalamus) (Chakravarty et al., 2015; Pipitone et al., 2014). Previous studies have been conducted to validate the use of MAGeT (Chakravarty et al., 2013; Pipitone et al., 2014), including a study from our group showing its applicability in a first-episode psychosis sample (Makowski et al., 2017). The input atlases for these subcortical structures were based on previous work, which reconstructed and warped a histological data set to an MRI-based template. The histological data used in this method have been described previously (Chakravarty et al., 2006) (https://github.com/CobraLab/atlases). Labels from these atlases were then propagated to a subset of 21 subjects (templates) included in the current study, which comprised a representative sample of 11 patients and 10 controls, a number shown to be optimal based on previous work (Pipitone et al., 2014). This subset represented approximately equal female-to-male ratio and good quality scans. A description of the technique used in segmenting each scan based on these atlases has been detailed previously (Collins and Pruessner, 2010). All scans processed through CIVET and MAGeT were also finally visually inspected to ensure quality of grey/white matter surface extraction and the accuracy of segmentation of subcortical structures. MRI scans of 110 patients and 69 controls were retained for subsequent analyses.

### 2.6. Cortical thickness analyses

The RMINC statistical package was used to conduct cortical thickness analyses (https://github.com/Mouse-Imaging-Centre/RMINC). First, patients and controls were compared using whole-brain vertex-wise linear models, controlling for age, handedness and sex. Second, in the patient group, AINT and ASC factor scores were regressed against cortical thickness, additionally controlling for antipsychotic dosage. A second set of the same analyses was also conducted by adding SAPS total scores as covariate, due to evidence that illness severity is related to levels of clinical insight (Mintz et al., 2003; Zhou et al., 2015). Finally, vertex-wise bilateral a-priori region-of-interest regression analyses were conducted in 8 regions previously associated with insight, or processes related to insight such as self-reflectiveness (detailed in Table 1). We did not control for total intracranial volume in our analyses, because cortical thickness and brain volume have been shown to be poorly correlated (Sowell et al., 2007). All analyses were corrected for multiple

**Table 1**
List of regions of interest included in cortical thickness analyses accompanied by associated studies supporting their potential role in insight or self-reflective processes.

| Anatomical landmark; AAl number | Associated reference |
|---|---|
| Insula, 29–30 | (Morgan et al., 2010; Palaniyappan et al., 2011; van der Meer et al., 2010) |
| Dorsolateral prefrontal gyrus, 3–4 | (Buchy et al., 2012; Shad et al., 2007; Shad et al., 2004) |
| Medial superior frontal gyrus, 23–26 | (Flashman et al., 2001; Sapara et al., 2007) |
| Anterior cingulate cortex, 31–32 | (Bassitt et al., 2007; Emami et al., 2016; Flashman et al., 2001; Shad et al., 2007) |
| Precuneus, 67–68 | (Buchy et al., 2012; Cooke et al., 2008; Morgan et al., 2010) |
| Inferior parietal lobe, 61–64 | (Cooke et al., 2008; Morgan et al., 2010; Shad et al., 2007) |
| Angular gyrus, 65–66 | (Gerretsen et al., 2013a; Vostrikov et al., 2013) |
| Orbitofrontal gyrus, 5–6 | (Buchy et al., 2012; Sapara et al., 2007; Shad et al., 2007) |

comparisons using the False Discovery Rate procedure, with a threshold of q = 0.05 (Genovese et al., 2002).

### 2.7. Subcortical volume analyses

Analysis of subcortical volumes was conducted in SPSS (version 20) and performed in two stages. First, two general linear models (GLM) were conducted to compare subcortical volumes between the two groups (healthy control vs patients). Included covariates were sex, age, and total brain volume. Second, partial correlations were conducted between scores on the AINT and ASC factors and bilateral hippocampus, striatum, thalamus, and amygdala volumes, including antipsychotic dosage, sex, age, and total brain volume as covariates. SAPS total scores were also added as covariates in a second round of these analyses. Significant correlations ($p < 0.05$) were corrected for the family-wise error rate using Bonferroni-Holmes correction.

## 3. Results

### 3.1. Demographic and clinical data

Descriptive statistics of demographic and clinical variables are listed in Table 2.

### 3.2. Associations with clinical insight

Correlations between clinical and demographic variables and clinical insight are listed in Table 3.

### 3.3. Whole-brain cortical thickness analyses

#### 3.3.1. Patients vs controls

Analyses revealed a significant difference in cortical thickness between schizophrenia patients and healthy controls in multiple regions of the left hemisphere ($p = 0.05$, FDR-corrected; Fig. 1). Specifically, the patient group displayed significantly thinner cortex in the left superior and middle temporal gyri, insula, precuneus, and cingulate cortex. No significant group differences between the two groups were observed for the right hemisphere.

**Table 3**
Pearson correlations between clinical and demographic characteristics and clinical insight, in the patient group only (n = 110). Positive correlations indicate that better insight is associated with greater scores on the associated variable.

| | AINT scores | | ASC scores | |
|---|---|---|---|---|
| | *R* | *p* | *r* | *p* |
| Age | 0.157 | 0.102 | −0.017 | 0.863 |
| Illness duration (years) | 0.190 | **0.049** | 0.104 | 0.306 |
| Education (years) | −0.39 | 0.686 | −0.006 | 0.950 |
| Antipsychotic dosage (mg) | 0.164 | 0.095 | 0.212 | **0.038** |
| WASI full-scale IQ | −0.078 | 0.418 | 0.188 | 0.060 |
| SAPS total score | 0.078 | 0.420 | −0.126 | 0.210 |
| SANS total score | −0.209 | **0.029** | −0.238 | **0.017** |
| CDS | 0.107 | 0.265 | 0.177 | 0.077 |
| HAS | 0.113 | 0.239 | 0.086 | 0.391 |

Bold values indicates significance at p < 0.05

#### 3.3.2. Associations with insight factors

No significant associations were observed between scores on both insight factors and cortical thickness in either the left or right hemisphere after FDR correction. The addition of positive symptom severity as a covariate had no effect on these results.

### 3.4. Region of interest cortical thickness analyses

#### 3.4.1. Associations with insight factors

No significant associations were observed when regressing AINT and ASC factors against mean cortical thickness in any region of interest, namely, the insula, medial superior frontal gyrus, orbitofrontal gyrus, dorsolateral prefrontal gyrus, anterior cingulate gyrus, inferior parietal lobe, angular gyrus, and precuneus ($p > 0.05$, FDR corrected).

### 3.5. Subcortical volume analyses

#### 3.5.1. Patients vs controls

Results of the GLM are presented in Table 4. Analyses revealed significantly larger left ($F(1,173) = 16.17$, $p < 0.001$) and right ($F(1, 173) = 15.44$, $p < 0.001$) striatum volumes in schizophrenia patients compared to controls (Table 4). These latter findings survived correction using the

**Table 2**
Descriptive statistics of demographic and clinical characteristics of the patient and healthy control groups. Sample sizes are $n = 110$ for the patient group, and $n = 69$ for healthy controls, unless otherwise specified.

| | | Patients | | | Controls | | | *p* |
|---|---|---|---|---|---|---|---|---|
| | | Mean | Range | SD | Mean | Range | SD | |
| Male (%) | | 83 (76%) | – | – | 48 (70%) | | | |
| Age (years) | | 35.24 | 21–50 | 8.17 | 34.19 | 21–50 | 8.97 | 0.42 |
| Handedness[a] | Right | 85 (77%) | – | – | 54 (81%) | – | – | |
| | Left | 16 (15%) | – | – | 7 (10%) | – | – | |
| | Ambidextrous | 9 (8%) | | | 6 (9%) | | | |
| Education (years) | | 11.36 | 4–22 | 2.51 | 13.48 | 9–22 | 2.40 | <**0.001** |
| WASI full-scale IQ[b] | | 95.23 | 66–134 | 14.58 | 108.84 | 72–134 | 13.60 | <**0.001** |
| Age of onset (years)[c] | | 22.40 | 8–44 | 6.85 | – | – | – | – |
| Illness duration (years)[c] | | 12.66 | 3–37 | 7.58 | – | – | – | – |
| Antipsychotic dosage (mg)[d,f] | | 797.59 ($n = 105$) | 10.7–4835 | 820.48 | – | – | – | – |
| SAPS total score | | 6.56 | 0–16 | 4.35 | – | – | – | – |
| SANS total score | | 8.74 | 0–17 | 3.15 | – | – | – | – |
| AINT[g] | | 20.96 | 3–25 | 4.83 | – | – | – | – |
| ASC[e,g] | | 7.71 | 0.75-12 | 2.73 | – | – | – | – |

Bold values indicates significance at p < 0.05.
[a] Based on sample of $n = 67$ controls and $n = 110$ patients.
[b] Based on sample of $n = 68$ controls and $n = 110$ patients.
[c] Based on sample of $n = 108$ patients.
[d] Based on sample of $n = 105$ patients.
[e] Based on sample of $n = 101$ patients.
[f] Antipsychotic dosage reported as chlorpromazine equivalent in milligrams,
[g] Higher scores on the AINT and ASC factors indicate better performance.

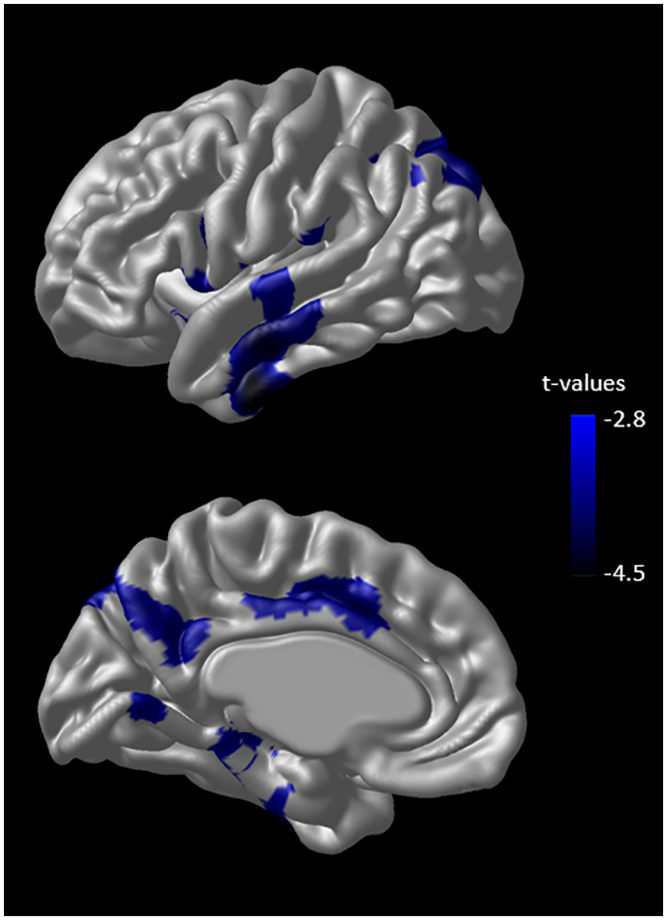


**Fig. 1.** Differences in left hemisphere whole-brain cortical thickness between 110 schizophrenia patients and 69 healthy controls ($p < 0.05$, FDR corrected).

Bonferroni-Holmes procedure. No other significant effect of group was observed on volume of the amygdala, hippocampus, or thalamus (all $p > 0.05$).

*3.5.2. Associations with insight factors*

Partial correlations revealed no significant association between bilateral subcortical volumes and both the AINT and ASC factor (all *ps* > 0.05). The addition of positive symptom severity as a covariate had no effect on these results.

## 4. Discussion

The aim of this project was to clarify the relationship between clinical insight and neuroanatomy, i.e. cortical thickness and subcortical volumes. In doing so, we also aimed to address limitations of previous studies conducted in this field. The findings of this study highlight the complexity of identifying structural neural correlates of clinical insight. At the level of the cortex, no relationship between two comprehensive measures of clinical insight and cortical thickness was observed, both at the whole-brain and ROI level. Although these results are in line with the negative findings of studies such as by Bassitt et al. (2007) and Rossell et al. (2003), they contrast with numerous studies finding a link between neuroanatomy and clinical insight levels (Emami et al., 2016; Gerretsen et al., 2015; Ouzir and Azorin, 2014; Palaniyappan et al., 2011; Shad et al., 2004). The current results shed light on the possibility that previous findings of a link between insight and the cortex may have been inflated by small sample sizes, liberal statistical thresholds, and inadequate assessment of clinical insight.

**Table 4**
Differences in mean raw subcortical volumes comparing patient and control groups.

| Structure | Patients | Controls | *p* |
|---|---|---|---|
| | Mean volume in $mm^3$ (SD) | Mean volume in $mm^3$ (SD) | |
| L hippocampus | 3209.2 (300.9) | 3265.7 (349.5) | 0.906 |
| L amygdala | 1786.9 (144.5) | 1809.1 (146.6) | 0.850 |
| L striatum | 12,928.3 (1057.2) | 12,581.6 (1052.3) | **<0.001** |
| L thalamus | 7657.6 (585.4) | 7943.9 (683.1) | 0.902 |
| R hippocampus | 3211.8 (297.3) | 3299.0 (313.5) | 0.566 |
| R amygdala | 1778.1 (145.9) | 1784.2(143.8) | 0.349 |
| R striatum | 12,968.3 (1065.8) | 12,651.8 (992.8) | **<0.001** |
| R thalamus | 8252.9 (622.6) | 8582.0 (716.3) | 0.850 |

Bold values indicates significance at $p < 0.05$.

Our findings of reduced left hemisphere cortical thickness in patients compared to controls replicate others demonstrating cortical atrophy and grey matter volume deficits in temporal and cortical midline regions in schizophrenia patients compared to healthy subjects (Palaniyappan et al., 2012; Rimol et al., 2010; Torres et al., 2016). As such it suggests that our cortical thickness metric was sensitive enough to detect group differences, but failed to reveal a significant link between insight and cortical thickness.

Our findings also show that cortical thinning was observed only in the left hemisphere in schizophrenia patients. Although previous research has revealed bilateral cortical thinning in schizophrenia (Rimol et al., 2010), one potential explanation for the present finding may be related to reduced hemispheric asymmetry in schizophrenia (Crow et al., 1989; Pearlson et al., 1997). Hemispheric asymmetry has been documented in healthy controls, but not schizophrenia, in favor of the left hemisphere (Wada et al., 1975). The hemispheric specificity of our results could thus reflect this lack of asymmetry in patients compared to controls. Further, previous studies have also demonstrated larger effect sizes of left hemisphere cortical thinning in schizophrenia compared to controls (Rimol et al., 2010).

It is interesting to note that in this study, there was a trend towards higher antipsychotic dosage intake in individuals with greater levels of ASC and AINT, an association which has been documented previously (Bianchini et al., 2014; Pijnenborg et al., 2015). This highlights the importance of including medication as a covariate in analyses investigating links between structural brain measures and clinical insight. Moreover, evidence for a link between antipsychotic intake and neuroanatomy (Ho et al., 2011; van Haren et al., 2011) provides further justification for treating antipsychotic dosage as a potential confound. Nevertheless, future studies should be conducted to confirm this link and whether the relationship between antipsychotic medication and clinical insight is also represented at the level of the brain.

In the same vein, the potential relationship between insight, neuroanatomy, and antipsychotic dosage may also explain why we failed to replicate findings from a previous study published by our group, which examined the relationship between awareness of symptoms and cortical thickness (Emami et al., 2016). Emami et al. (2016) reported thinner right insular cortex in individuals with low insight into symptoms, compared to those with higher insight. Numerous differences between our two studies could explain this discrepancy, such as differences in covariates included in analyses, sample size differences, and the assessment method (categorical vs continuous) of the clinical insight dimension under study. In addition, the convoluted cortex present within the insular region renders this region difficult to automatically segment – making its exploration less reliable when using cortical thickness metrics. The difference between the findings of the two studies further emphasize the impact of slight variations across assessments of insight on exploration of this phenomenon's etiology.

A second objective of this study was to explore the relationship between clinical insight levels and subcortical volumes. The present findings do not suggest any significant association between levels of AINT, nor ASC, and bilateral subcortical volumes. Paired with the lack of association between clinical insight and cortical thickness, this further

indicates that clinical insight may be largely influenced by psychological variables that may not have isolated structural neural correlates. This also furthers the idea that poor clinical insight represents one's difficulty in engaging in dynamic thought processes rather than being a specific deficit in a specific modality. Nevertheless, it is possible that further research that assesses the relationship between insight and subcomponents of subcortical structures may reveal a different picture, given emerging interest in dissecting individual subcortical structures, and more specifically, in the distinct roles of hippocampal subfields. Therefore, one alternative to the current research could be to explore whether associations with levels of clinical insight may be specific to certain components of relevant subcortical structures. On the other hand, clinical insight has been shown to be related to higher-order cognitive processes such as working memory, executive function, and metacognition, which are mainly associated with cortical structures, suggesting that the role of subcortical structures in determining levels of clinical insight may be minimal.

Results of the comparison of subcortical volumes between patients and controls are not as extensive as previously shown and were restricted to the striatum. A recent paper investigating a sample of over 2000 schizophrenia patients demonstrated that individuals with schizophrenia have smaller hippocampus, thalamus and amygdala volumes (van Erp et al., 2016). Some potential explanations for the discrepancies with our findings include a difference in the tools used to process MRI scans. More specifically, the tool used to extract subcortical volumes in this paper, MAGeT, has been found to be more conservative in estimating measures of subcortical volumes compared to other automated segmentation tools such as Freesurfer (Bodnar et al., 2016; Makowski et al., 2017). Moreover, the healthy controls included in the present study were recruited to match the demographics of the patient group. It is possible that the similarity of the demographics of the patient and control groups might also be represented at the level of the brain, thus masking some potential brain differences between a more general population and schizophrenia patients. Finally, our sample was restricted to individuals from the same community and included a much smaller sample, compared to a more global representation in the study by van Erp et al. (2016).

### 4.1. Conclusions

Clinical insight is determined by a range of psychological, clinical and cognitive factors (Vohs et al., 2016). Therefore, one potential explanation for the lack of a relationship between clinical insight and neuroanatomy is that it may not be possible to isolate precise neuroanatomical determinants of clinical insight that are generalizable to all schizophrenia patients. The variance in clinical insight levels that is explained by neuroanatomical features, such as cortical thickness, versus psychological/social factors may vary depending on the specific set of symptoms of an individual, even within the same clinical population.

It is also likely that potential correlates of insight may be better isolated using network analyses. This latter proposition is supported by two factors. First, insight represents a dynamic thought process that requires the interplay of different factors (e.g. social cognition, working memory, etc.), rather than representing a specific deficit in one modality. Second, mounting evidence is pointing towards understanding schizophrenia as a disorder of dysconnectivity, as opposed to a disorder characterized by localized alterations of neuroanatomy (Fornito and Harrison, 2012; Friston et al., 2016). Consequently, it may not be possible to isolate clear structural neuroanatomical markers of poor or good clinical insight.

In sum, results of this study suggest that linking static brain structure to insight in a heterogeneous sample of enduring schizophrenia patients may not be the most fruitful endeavor. Future studies should instead aim to determine whether clinical insight has different predictors according to illness profiles, and thus determine whether neuroanatomy represents a predictor of clinical insight for specific subsets of schizophrenia patients. For example, in patients with neurocognitive deficits, neurobiology might explain more variance in insight levels than individuals with schizophrenia who only experience psychotic symptoms. Understanding the different routes towards achieving good or poor clinical insight will better equip the field to further probe its neuroanatomical correlates in a more directed and profitable manner.

### 4.2. Limitations

Although this may be the result of the tools used to analyze subcortical structures, or sample characteristics, a first limitation of the study is the lack of replication of previous evidence for reductions in hippocampal volume in schizophrenia patients compared to a healthy population. Second, it should also be noted that the current study was restricted to structural neural correlates. Because poor clinical insight likely represents a dynamic phenomenon as opposed to a stable and specific dysfunction, functional brain imaging or models of brain connectivity may offer a more appropriate method to understand the neural roots of clinical insight. Finally, this is the first study to investigate the correlates of the insight factors AINT and ASC. Additional studies using these factors should be carried out with different samples to confirm the validity of these findings.

**Conflict of interest**

ML reports having received financial assistance/compensation for research and educational events from Janssen-Ortho, Eli Lilly, Roche, and Otsuka/Lundbeck Alliance. SB, CM, SK, LB & MC declare that they have no conflicts of interest.

**Contributors**

ML, SK & SB contributed to the study design. SB, CM, LB & MC contributed to data processing and statistical analyses. SB wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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