Journal Pre-proof

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PII: S0149-7634(20)30449-8

DOI: https://doi.org/10.1016/j.neubiorev.2020.06.022

Reference: NBR 3819

To appear in: *Neuroscience and Biobehavioral Reviews*

Received Date: 13 November 2019

Revised Date: 4 March 2020

Accepted Date: 13 June 2020

Please cite this article as: Pijnenborg GHM, Larabi DI, Xu P, Hasson-Ohayon I, de Vos AE, Ćurčić-Blake B, Aleman A, der Meer LV, Brain areas associated with clinical and cognitive insight in psychotic disorders: a systematic review and meta-analysis, *Neuroscience and Biobehavioral Reviews* (2020), doi: https://doi.org/10.1016/j.neubiorev.2020.06.022

Brain areas associated with clinical and cognitive insight in psychotic disorders: a systematic review and meta-analysis

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Highlights

1	Clinical and cognitive insight are associated with different brain areas.
2	Clinical insight is associated with spatially diffuse global abnormalities, suggesting it relies on a broad range of (social) cognitive functions.
3	Cognitive insight is mainly associated with ventrolateral prefrontal cortex and hippocampal areas and appears to rely more on the retrieval and integration of self-related information.

Abstract

In the past years, ample interest in brain abnormalities related to clinical and cognitive insight in psychosis has contributed several neuroimaging studies to the literature. Published findings on the neural substrates of clinical and cognitive insight in psychosis are integrated by performing a systematic review and meta-analysis.

Coordinate-based meta-analyses were performed with the parametric coordinate-based meta-analysis approach, non-coordinate based meta-analyses were conducted with the *metafor* package in R. Papers that could not be included in the meta-analyses were systematically reviewed.

Thirty-seven studies were retrieved, of which 21 studies were included in meta-analyses. Poorer clinical insight was related to smaller whole brain gray and white matter volume and gray matter volume of the frontal gyri. Cognitive insight was predominantly positively associated with structure and function of the hippocampus and ventrolateral prefrontal cortex.

Impaired clinical insight is not associated with abnormalities of isolated brain regions, but with spatially diffuse global and frontal abnormalities and might rely on a range of cognitive and self-evaluative processes. Cognitive insight is associated with specific areas and appears to rely more on retrieving and integrating self-related information.

Keywords: awareness, neuroimaging, psychoses, schizophrenia, MRI

1. Introduction

Impaired clinical insight, defined as impaired awareness of illness, relabeling of symptoms and need for treatment (Amador et al., 1993; David, 1990), is highly prevalent in psychotic disorders and is associated with both favorable and unfavorable outcomes (Lincoln et al., 2007). While patients with poor insight often have more psychotic and negative symptoms and experience more problems in social functioning and treatment compliance, they may also show lower levels of depression and a better quality of life (Francis and Penn, 2001; Hasson-Ohayon et al., 2009, 2006; Kvrgic et al., 2013; Olfson et al., 2006; Yen et al., 2002). Recent studies questioned whether clinical insight really represents reflective awareness of the illness and implications as classical definitions (e.g. insight as a three-dimensional construct (David, 1990)) indicate and suggest that clinical insight might merely reflect compliance with the medical model, i.e. agreement with the DSM- or ICD-label, need for treatment and illness' implications (Hasson-Ohayon, 2018; Lysaker et al., 2018). According to this conceptualization, clinical insight might present an attitude toward the diagnosis, similar to self-stigma, and not a symptom of the illness or a neurobiological deficit (Hasson-Ohayon, 2018).

Several models have been suggested to explain the etiology of impaired insight, suggesting contributions of brain abnormalities, cognitive functions, stigma and defensive denial (Vohs et al., 2016). Evidence for the neurobiological model derives from the fact that numerous studies showed associations between brain abnormalities and impaired insight. Moreover, several cognitive processes have been associated with impaired clinical insight, ranging from basic processes such as memory (Nair et al., 2014) to more complex processes such as self-reflection and Theory of Mind (Pijnenborg et al., 2013). Given the complex nature of insight and studies supporting several models, a multi-causal integrated explanation of impaired insight appears most likely. Thus, a question remains whether and to what level neuropsychological deficits are related to poor clinical insight, as conceptualized by David (1999) and Amador et al. (1993) (Amador et al., 1993; David, 1999).

A construct related to clinical insight is cognitive insight, which is conceptualized as a combination of self-reflection and the ability to question one's own conclusions (Beck et al., 2004). Cognitive insight refers to reflection about aspects that are beyond having a psychiatric disorder.

Initially, cognitive insight was believed to be a prerequisite for clinical insight. However, literature on the association between clinical and cognitive insight is inconsistent; with several studies not finding a significant association (e.g. (Greenberger and Serper, 2010)). Thus, the relationship between clinical and cognitive insight remains inconclusive.

Neuroimaging studies have attempted to shed light upon the neuropsychological processes underlying clinical and cognitive insight by investigating brain areas related to either construct. Regarding structural abnormalities, most studies focused on clinical insight and found abnormalities in frontal, temporal and parietal areas (e.g. (Cooke et al., 2008; Flashman et al., 2001; Sapara et al., 2007; Shad et al., 2006, 2004)), while other studies did not find significant relationships between brain volume and clinical insight (e.g. (Morgan et al., 2010; Raij et al., 2012)). The few studies addressing structural abnormalities in cognitive insight, mostly showed involvement of the prefrontal cortex and hippocampus, but also involvement of other frontal, parietal (i.e. inferior partial lobule, posterior cingulate cortex) and temporal regions (i.e. parahippocampal gyrus) (Buchy et al., 2016, 2010; Orfei et al., 2017, 2013). Functional neuroimaging studies showed that both cognitive and clinical insight are associated with functional abnormalities in (medial and lateral) frontal, temporal and parietal regions, that are involved in social-cognitive and metacognitive processes such as self-reflection (van der Meer et al., 2013), illness related self-reflection (Raij et al., 2012), and processing of feedback (de Vos et al., 2015).

In sum, although studies have shown that cognitive and clinical insight are associated with brain abnormalities, thus far, no study integrated this literature. Therefore, the aim of the present study is to provide a systematic review and meta-analysis of neuroimaging studies that examine the relationship between clinical and cognitive insight on the one hand, and brain structure and function on the other hand. By integrating literature on the two different forms of insight and different neuroimaging methods, we aim to achieve a better understanding of cognitive processes that underlie different aspects of impaired insight.

2. Methods

2.1 Literature search

A search was performed in the following databases: MEDLINE, PSYCINFO, and PUBMED. The following search terms were used: (insight OR awareness) AND (fMRI OR "functional magnetic resonance imaging)" OR “neuroimaging” OR “structural imaging” OR “magnetic resonance imaging” OR “MRI” OR “cortical thickness” OR “morphometry” OR “VBM”) AND (schizophren* OR psychos* OR psychot*). This search included papers published until May 8, 2018. Reference lists of selected papers and reviews were screened for relevant papers that were not picked up by our search.

2.2 Study selection

After removing duplicates, two assessors (MP and DL) independently identified studies eligible for inclusion in a 2-step procedure. First, a selection based on abstract and title was made. Studies were selected when the following inclusion criteria were met: (1) written in English language, (2) participants were diagnosed with a psychotic disorder, (3) insight was assessed with a validated measure, such as the Insight and Treatment Attitudes Questionnaire (ITAQ) (McEvoy et al., 1989), the Schedule for the Assessment of Insight (SAI) -Expanded (SAI-E) (David, 1990; Kemp and David, 1997), the Scale to Assess Unawareness of Mental Disorder (SUMD) (Amador et al., 1993), the Birchwood Insight Scale (BIS) (Birchwood et al., 1994), item G12 of the Positive and Negative Syndrome Scale (PANSS) interview (Kay et al., 1987), or the Beck Cognitive Insight Scale (BCIS) (Beck et al., 2004), (4) empirical results of neuroimaging methods (i.e. functional magnetic resonance imaging (fMRI), magnetic resonance imaging (MRI), voxel-based morphometry (VBM)) were reported, (5) a cross-sectional association was reported between a) insight and BOLD-response during a specific task or b) between insight and brain volume, and (6) it was published as a full-text original article in an international peer-reviewed journal. The correlations between the SUMD, SAI, SAI-E, PANSS G12 and ITAQ are significant and of large magnitude (r=.82-.97) (Sanz et al., 1998; Soriano-Barceló et al., 2016). This implies that these measures asses a highly similar latent construct and can be included together.

In case the abstract did not provide sufficient information, the study was selected for full-text review. Full texts of papers within this selection were critically examined to see whether inclusion criteria for the study were met. In case the study reported both an association between insight and brain areas and a between-group comparison, only the association was included in the meta-analysis. If the paper provided insufficient information, the corresponding author was contacted. Studies using the same subject sample were included if other neural correlates were investigated or if other neuroimaging techniques were used. If samples overlapped, the most recent study with the largest sample size was included.

2.3 Data extraction

The following information was extracted from every included study by two independent reviewers (MP and DL) using a predetermined form: (1) first author and publication year, (2) size of patient sample, (3) direction of findings, (4) normalization template (MNI or Talairach), (5) whole brain or ROI, (6) smoothing kernel, (7) whether findings were significant or not, (8) brain region location information (x/y/z coordinates of the peak coordinates and the corresponding automated anatomical label (Tzourio-Mazoyer et al., 2002), (9) statistical values (p, r, T, F or Z), threshold and correction methods (uncorrected, FDR or FWE). If there were no significant findings, the fields for (8) and (9) were left empty. In addition, the following information was extracted: (1) participant characteristics (i.e. number of participants, mean age, sex, and for the patient samples: diagnosis and symptoms), (2) study characteristics (i.e. design and control condition), (3) neuroimaging characteristics (i.e. technique, scanner, field of view and outcome).

2.4 Statistical Analysis

For the meta-analyses, studies were divided into categories based on the following characteristics: 1) clinical vs cognitive insight and 2) neuroimaging technique. We conducted separate meta-analyses that pooled studies examining either total clinical insight, clinical insight sub-dimensions, total cognitive insight or cognitive insight sub-dimensions. Included neuroimaging

techniques were either (a) global brain volume (i.e., i) global gray matter volume (GMV) plus white matter volume (WMV), ii) global GMV, iii) global WMV, or iv) global cerebrospinal fluid (CSF) volume), (b) volume of certain regions of interest (ROIs), (c) voxel-based morphometry (VBM) or (d) functional activation as measured with fMRI. A meta-analysis was only carried out if the number of studies in a category was larger than two.

For the coordinate-based meta-analyses, the parametric coordinate-based meta-analysis (PCM) approach was used (Costafreda, 2012). With this approach, the effect sizes for each focus are convolved with a 25-mm kernel to create Z-value summary maps for each study. These summary maps are pooled to create an overall Z-value map, on which a two-tailed t-test can be conducted with the estimated Z mean value for each voxel to determine voxels that have a Z mean value significantly different from zero. Correction for multiple comparisons was done with a false discovery rate (FDR) threshold of 0.05 and extent threshold of 50 mm^3 (Sankar et al., 2018; Xu et al., 2018), which resulted in thresholded effect size summary maps.

For non-coordinate based meta-analyses, the data was analyzed using the *metafor* package (version 1.9-9) (Viechtbauer, 2010), implemented in the statistical software R (version 3.2.3) (R Core team, 2018). For meta-analyses focused on studies examining gray matter volume of certain ROIs, overall ROIs for the meta-analyses were selected based on the ROIs that were most often studied (and defined a priori) within these studies given that overlapping ROIs are necessary in order to perform meta-analyses. Therefore, two ROI meta-analyses on clinical insight studies included either the left or right frontal gyrus, while the cognitive insight ROI meta-analysis focused on the hippocampus. The correlation values and sample sizes were used to calculate the pooled correlation. Correlation coefficients were transformed with Fisher's r-to-z-transform. The resulted z-values were pooled and transformed back to a correlation coefficient. These values were then entered into the random effects meta-analytic model. The I^2 statistic was calculated to examine whether the percentage of total variation across studies represents realistic heterogeneity rather than chance. An I^2 value of 0-50% indicates low heterogeneity, an I^2 of 50-75% indicates moderate and an I^2 of 75-100% indicates high heterogeneity. The funnel plot asymmetry was investigated and Egger's regression test was performed to assess potential publication bias.

3. Results

3.1 Study selection

A total of 1938 publications were identified in databases. Three additional papers were retrieved from cross-references checks. 37 studies were selected for this review, of which some presented data of more than one imaging method. Twenty-one of these studies could be included in a total of seven meta-analyses (see Fig. 1).

Insert Figure 1

A total of 1088 patients was included in the meta-analyses, of which 798 were male (73%). Participants had a DSM-IV or ICD-10 diagnosis of schizophrenia (n=721; 66%), schizoaffective disorder (n=34), schizophreniform disorder (n=69), psychotic disorder not otherwise specified (NOS; n=1), or first-episode psychosis (n=263). Mean age was 32.3 years (range: 23.86-41.7), mean illness duration was 8.64 years (range: 0.01-18.9) and mean total PANSS scores were 67.05 (range: 43-84.43).

Findings of the 16 additional studies will be described in the main text but were not included in meta-analyses for various reasons (see details below). Methodological and clinical details of other neuroimaging studies conducted on insight that were not included in either the meta-analyses or the review (e.g. studies using positron emission tomography (PET) or examining connectivity), can be seen in Supplementary Tables S1-S8. A list of all abbreviations used in tables and their meaning can be found in Supplementary Materials.

3.2 Clinical insight

3.2.1 Global brain volume

We performed three meta-analyses regarding the association of clinical insight and global brain volume, including eight out of twelve studies that examined this association (Bassitt et al., 2007; Flashman et al., 2000; Gerretsen et al., 2013; Larøi et al., 2000; McEvoy et al., 2006; Morgan et al., 2010; Palaniyappan et al., 2011; Sapara et al., 2007) (Tables 1-2). More specifically, meta-analyses

concerned the relationship between clinical insight (i.e., total score) and (1) global gray matter volume (k=5) (Bassitt et al., 2007; Gerretsen et al., 2013; Larøi et al., 2000; McEvoy et al., 2006; Morgan et al., 2010), (2) global white matter volume (k=4) (Bassitt et al., 2007; Gerretsen et al., 2013; McEvoy et al., 2006; Palaniyappan et al., 2011) or (3) the sum of global gray matter volume and white matter volume (k=3) (Flashman et al., 2000; McEvoy et al., 2006; Sapara et al., 2007). In one of these studies, two associations between volume and two distinct measures of insight (SAI-E and BIS) were described in the same sample (Sapara et al., 2007). Only the association with the SAI-E measure was included in this meta-analysis.

Significant relationships were found between lower clinical insight and (1) smaller global gray matter volume (effect size=0.19, CI=0.09-0.29, p<0.0001, I_2= 0.02%; Figure 2), (2) smaller global white matter volume (effect size=0.20, CI=0.10-0.30, p<0.0001, I_2= 0.03%; Figure 3) and (3) smaller sum of global gray matter volume and white matter volume (effect size=0.21, CI=0.02-0.41, p=0.03, I_2=35%; Figure 4). Funnel plots can be seen in supplementary materials (Fig. S1-S3). No meta-analysis was performed on clinical insight and global CSF since only two (Flashman et al., 2000; McEvoy et al., 2006) out of three studies (Flashman et al., 2000; McEvoy et al., 2006; Rossell et al., 2003) reported effect sizes.

There were not enough studies to do a meta-analysis on any of the sub-dimensions of insight and global brain volume, nor volume of regions of interest, voxel-based morphometry or functional MRI.

Insert Tables 1-2

Insert Figures 2-4

Four studies were not included in meta-analyses for different reasons: not reporting effect sizes (David et al., 1995; Rossell et al., 2003), full-text unavailable (Takai et al., 1992) and not reporting associations with total clinical insight but only with sub-dimensions (Cooke et al., 2008) (Tables 3-4). Of these studies, one study (David et al., 1995) found no association between ventricular

enlargement and insight, while another study (Rossell et al., 2003) did not find significant associations between brain volumes and insight. The last study (Cooke et al., 2008) examined sub-dimensions of insight and did not report an association between global volume and total insight score.

Insert Tables 3-4

3.2.2 Volume regions of interest (ROIs)

A total of nine studies on clinical insight and volume of certain (a priori defined) ROIs were found. All of these studies took a region of interest approach. Two meta-analyses were performed, both including three studies that focused on volumes of the left and right frontal gyri separately (Gerretsen et al., 2013; Sapara et al., 2007; Shad et al., 2004) (see details in Tables 5-6). In these meta-analyses, only studies with overlapping ROIs were included; these ROIs were the only ROIs reported in more than two separate studies.

The meta-analysis on total insight and volume of the left frontal gyrus (k=3) (Gerretsen et al., 2013; Sapara et al., 2007; Shad et al., 2004) showed a significant positive correlation between clinical insight and left prefrontal volume (effect size=0.23, CI=0.04-0.42, p=0.02, I_2=0%; Figure 5). The meta-analysis on total insight and right frontal gyrus volume (k=3) (Gerretsen et al., 2013; Sapara et al., 2007; Shad et al., 2004) also yielded a significant positive correlation (effect size=0.37, CI=0.04-0.70, p=0.03, I_2=65.30%; Figure 6). Funnel plots can be seen in supplementary materials (Fig. S4 and S5).

Insert Tables 5-6

Insert Figures 5-6

Six studies were not included in meta-analyses for different reasons (see details in Tables 7-8).

Three studies did not report associations with total clinical insight, but only with sub-dimensions

(Asmal et al., 2018; Flashman et al., 2001; Shad et al., 2006). Asmal et al. (2018) found that poorer symptom attribution was related to lower cortical thickness of the left rostral middle frontal region and left caudal anterior cingulate, right superior frontal, and left and right pars triangularis (Asmal et al., 2018). The second study found significant positive correlations between awareness of illness and bilateral middle frontal gyri volume, and between attribution of symptoms and superior frontal gyrus volume (Flashman et al., 2001). The third study found that awareness of symptoms was positively associated with right dorsolateral prefrontal cortex volume, while symptom attribution was positively associated with right medial orbitofrontal cortex volume (Shad et al., 2006). Two other studies focused on specific ROIs that were not reported in more than two studies (Buchy et al., 2010; Palaniyappan et al., 2011). The first study focused on hippocampal volume and did not find any significant associations with clinical insight (Buchy et al., 2010). The second study focused on the posterior insula volume and found a significant positive relationship between right posterior insula structure and insight (Palaniyappan et al., 2011). An additional study was excluded from meta-analyses because of its longitudinal design (Parellada et al., 2011). They reported a significant correlation between reduced frontal and parietal gray matter volume at baseline and worse insight two years after baseline.

Insert Tables 7-8

3.2.3 Voxel-based morphometry (VBM) and cortical thickness

Fifteen studies reported an association between voxel-based morphometry or cortical thickness and clinical insight, of which 11 were included in a meta-analysis (Bassitt et al., 2007; Bergé et al., 2011; Buchy et al., 2017; Emami et al., 2016; Gerretsen et al., 2014, 2013; Ha et al., 2004; McFarland et al., 2013; Morgan et al., 2010; Raij and Riekki, 2012; Sapara et al., 2016) (see Tables 9-10 for details). This meta-analysis did not show significant results.

Insert Tables 9-10

Four studies could not be included in the meta-analysis for several reasons (see Tables 11-12): sample overlap with a more recent sample (Buchy et al., 2017, 2011), not reporting associations with total clinical insight but only with sub-dimensions (Buchy et al., 2012; Cooke et al., 2008) and reporting on *metacognitive* insight (Spalletta et al., 2014). Of these studies, Buchy et al. (2011) reported no significant correlations for VBM-data, but significant positive correlations between awareness of illness and *cortical thickness* in left middle frontal and inferior temporal gyri, and between need for treatment and cortical thickness of the left medial frontal gyrus, precuneus and temporal gyri (Buchy et al., 2011). Buchy et al. (2012) reported a significant association between attribution of delusions and orbitofrontal cortical thickness in first episode patients (Buchy et al., 2012), while another study found several significant positive associations between sub-dimensions and gray matter volume, namely between (i) the ability to recognize abnormal experiences and total and right superior temporal gyrus volume, (ii) awareness of problems and left precuneus grey matter volume, and (iii) awareness of symptoms and attributing them to the illness and left superior–middle temporal gyrus and right inferior temporal and lateral parietal gyri volume (Cooke et al., 2008).

A visualization of all areas that showed an association between brain structure and clinical insight can be seen in Figure 7. If samples overlapped, the results of the most recent study with the largest sample size were included in this visualization.

Insert Tables 11-12
Insert Figure 7

3.2.4 Functional MRI (fMRI)

Eight studies on clinical insight and fMRI were retrieved, of which five were included in a meta-analysis (Bedford et al., 2012; Gerretsen et al., 2015; Sapara et al., 2015, 2014; van der Meer et al., 2013) (Tables 13-14) . Results of the meta-analysis showed no significant associations.

These five studies used different fMRI-tasks. The first study used a self-evaluation task in which subjects were presented with adjectives and had to indicate whether these applied to themselves,

former British prime minister Tony Blair or contained the letter ‘a’. The adjectives were categorized as positive, negative, mental illness-related and physical illness-related (Bedford et al., 2012). Another study used an insight task based on the SAI-E. Patients were instructed to respond either “yes”/agree, or “no”/disagree to the brief statements derived from four categories: illness awareness, symptom awareness, awareness of need for treatment, and illness independent/neutral that derived from the participant's own experiences identified during the standardized assessment of his or her illness awareness with the SAI-E (Gerretsen et al., 2015). A third study used an n-back task in which subjects were instructed to monitor the position of dots, based on information provided either in the current, previous or previous but one stimulus (Sapara et al., 2014). Insight was also studied with a verbal self-monitoring task in which subjects were instructed to read words aloud. These words were transformed in real time. Patients were presented with either their own voice, their own voice lowered in pitch, the voice of another person from the same sex and the voice of another person from the same sex lowered in pitch and indicated subsequently whether they heard their own voice, that of another person of were unsure of the origin of the voice (Sapara et al., 2015). The last study that was included in the meta-analysis used a self-reflection task: subjects were presented with sentences subdivided in three categories: self (presented in combination with I or me), other (presented in combination with the name of a close other) and semantic (true or false statements). Subjects indicated for each statement whether it was true or false (van der Meer et al., 2013).

Insert Tables 13-14

Three studies that were not included in the meta-analyses (see Tables 15-16) either used a repeated-measurements design (Lee et al., 2006), did not assess insight with a validated measure (Raij et al., 2012) or only reported associations with a subdimension (Shad and Keshavan, 2015). Lee et al. (2006) found that increased medial prefrontal cortex activation during a social cognition fMRI-task was associated with improvement in insight scores after recovery from an acute episode (Lee et al., 2006). During this task, subjects required to judge brief scenarios requiring reflection on empathy or foregiveness. Each scenario was followed by a forced choice between two possible outcomes. Raij et

al. (2012) reported associations between insight and activation of cortical midline structures and the frontopolar cortex during an insight fMRI-task (Raij et al., 2012). During that task subjects were presented with statements based on scales that assess clinical insight and were instructed to rate these statements on a scale ranging from total disagreement to total agreement. A last study reported associations between awareness of symptoms and activation of prefrontal, and parietal areas, and associations between symptom attribution and activation in the prefrontal cortex and basal ganglia (Shad and Keshavan, 2015) during a self-awareness task. In this task, subjects were presented with verbal statements and had to indicate whether the speaker was talking about them or about another person.

A visualization of all areas that showed an association between brain activation and clinical insight can be seen in Figure 8. If samples overlapped, the most recent study with the largest sample size was included in this visualization.

Insert Tables 15-16
Insert Figure 8

3.3 Cognitive insight

3.3.1 Global brain volume

No meta-analyses were performed as no studies were retrieved.

3.3.2 Volume regions of interest (ROIs)

Three studies were found that reported on the relationship between cognitive insight and volume of certain ROIs (Buchy et al., 2016, 2010; Orfei et al., 2017) (see Tables 17-18). No meta-analyses were performed since ROIs did not overlap.

One study focused on hippocampal volume and did not find significant associations between self-reflectiveness nor self-certainty and total hippocampal or sub-field volume (Buchy et al., 2016). Another study also focused on hippocampal (subfield) volume and found a significant correlation

between left hippocampal volume and BCIS composite index scores (Buchy et al., 2010). Self-certainty scores also correlated with hippocampal volume (Buchy et al., 2010). The last study found that higher self-certainty scores were related to reduced volume of the left presubiculum, while there were no significant correlations with self-reflectiveness nor BCIS composite index scores (Orfei et al., 2017).

Insert Tables 17-18

3.3.3 Voxel-based morphometry (VBM)

No meta-analyses were performed, because only three studies were retrieved of which two had overlapping samples (see Tables 19-20). Of these studies, Buchy et al. (2016) found significant associations between both self-reflectiveness and self-certainty and cortical thickness in the ventrolateral prefrontal cortex, and other frontal, parietal and temporal areas (Buchy et al., 2016). Orfei et al. (2013) found that lower self-reflectiveness was related to lower volume of the right ventrolateral prefrontal cortex, while no significant relations were found for self-certainty nor BCIS composite index scores (Orfei et al., 2013). Buchy et al. (2018) reported a significant correlation between higher self-reflectiveness and cortical thickness in the right occipital cortex in first-episode patients but their sample overlapped with a previous study of their group (Buchy et al., 2018, 2016).

A visualization of all areas that showed an association between brain structure and cognitive insight can be seen in Figure 9. If samples overlapped, the most recent study with the largest sample size was included in this visualization.

Insert Tables 19-20

Insert Figure 9

3.3.4 Functional MRI (fMRI)

Five fMRI-studies were conducted on cognitive insight (See Tables 21-22). One of these studies only included healthy individuals, however (Buchy et al., 2014). No meta-analyses were performed since the other four studies examined different sub-dimensions of insight or ROIs did not overlap. Two of these studies reported significant correlations between self-reflectiveness and activation in the bilateral ventromedial prefrontal cortex (van der Meer et al., 2013) and bilateral ventrolateral prefrontal cortex (Buchy et al., 2015). They did not report significant correlations with self-certainty (Buchy et al., 2015; van der Meer et al., 2013) nor BCIS composite index scores (van der Meer et al., 2013). Two other studies found significant associations between self-reflectiveness or the BCIS composite index score and widespread areas across the brain (Lee et al., 2015; Pu et al., 2013).

A visualization of all areas that showed an association between brain activation and cognitive insight can be seen in Figure 10. If samples overlapped, the most recent study with the largest sample size was included in this visualization.

Insert Tables 21-22
Insert Figure 10

4. Discussion

The present study aimed to integrate the literature on neuroimaging studies that examine the relationship between clinical and cognitive insight and brain structure or function through conducting a meta-analysis and systematic review. Results of both are discussed below.

4.1 Clinical insight and brain volume

Three meta-analyses on eight studies showed significant positive associations between total clinical insight and i) the sum of total gray matter and white matter volume, ii) total gray matter volume, and iii) total white matter volume. Results from structural MRI-studies on global brain volumes that were excluded from these meta-analyses (because they did not report effect sizes), differ with regard to their findings. Two additional studies showed no significant associations with clinical insight in schizophrenia patients (David et al., 1995; Rossell et al., 2003).

Similar associations were demonstrated in the studies investigating brain volume using specific ROIs. Two meta-analyses on three studies each showed significant positive associations between total clinical insight and volume of the left and right frontal gyri. Additional studies that were not included in the meta-analyses also showed less (pre)frontal volume in relation to poor insight. Already in first episode schizophrenia (FES) patients, lower scores on the symptom attribution sub-dimension of insight were associated with lower cortical thickness in several frontal areas and parts of the anterior cingulate (Asmal et al., 2018). That such insight-related smaller brain volumes are not simply a consequence of medication use, was demonstrated by a study examining the association between prefrontal cortex volume and clinical insight in antipsychotic-naïve first episode patients (Shad et al., 2006). This study showed a positive relationship between awareness of symptoms and right dorsolateral prefrontal cortex volume, while attribution of symptoms was positively related with right medial orbitofrontal cortex volume (Shad et al., 2006). However, Buchy et al. (2010) did not find any association between GM and WM in the bilateral hippocampus and clinical insight in first episode patients, but in this study insight was assessed with only one item of the SUMD (Buchy et al., 2010). Attribution of symptoms has also been positively related with superior frontal gyrus volumes and

awareness with the bilateral middle frontal gyrus, right gyrus rectus and left anterior cingulate gyrus in later stages of the illness (Flashman et al., 2001). Altogether, findings across studies investigating brain volume implicate lower global brain volume in patients with poorer clinical insight that is independent of medication use or stage of illness. ROI studies suggest that in particular lower frontal volume seems to be implicated in poor insight.

Studies in which brain volume is assessed with VBM have somewhat more mixed results, and a meta-analysis on these studies was not significant. In drug-naïve first-episode patients, insight was positively related to volume of the cerebellum, inferior temporal gyrus, superior frontal gyrus, inferior frontal gyrus and lingual gyrus (Bergé et al., 2011). Three other studies included in the meta-analysis showed a positive association between insight and volume or cortical thickness in varying brain areas distributed across the brain in medicated patients with schizophrenia (Emami et al., 2016; Ha et al., 2004; Sapara et al., 2016). Emami et al (2016) found thinning of the right insula, superior temporal gyrus and parahippocampal gyrus in schizophrenia patients with low insight (Emami et al., 2016). Insight was also positively correlated with GM concentrations in the left posterior and right anterior cingulate and bilateral inferior temporal regions including the lateral fusiform gyrus (Ha et al., 2004) and widespread areas across the brain (Sapara et al., 2016). A last study reported a significant negative association between the sum of awareness and attribution of symptoms score, and volume of the left medial frontal gyrus and adjacent anterior cingulate cortex (Bassitt et al., 2007). Six other studies did not find an association between total insight and volume (Buchy et al., 2017; Gerretsen et al., 2015, 2013; McFarland et al., 2013; Morgan et al., 2010; Raij et al., 2012). Although Buchy et al. (2017) did not find any baseline associations between insight and cortical thickness, they found that a decrease of insight was associated with cortical thinning in the dorsal precentral and postcentral gyri (Buchy et al., 2017).

More symptom misattribution was associated with higher GM volume in the bilateral caudate, left thalamus, right insula, putamen and cerebellum in first episode patients, but not in schizophrenia (McFarland et al., 2013). VBM-studies that could not be included in the meta-analyses as they only investigated clinical insight sub-dimensions also showed mixed results. Cooke et al. (2008) examined the relationship between GM volume and sub-dimensions of insight in patients with schizophrenia or

schizoaffective disorder with VBM, and found that 'the ability to recognize experiences as abnormal' was positively associated with right superior temporal gyrus volume. In the same study, 'awareness of problems' was positively related to left precuneus volume, whereas 'awareness of symptoms and attributing them to illness' was related to volumes of the left superior middle temporal gyrus, the right inferior temporal gyrus and lateral parietal gyri (Cooke et al., 2008). No association between 'recognition of need for medication' and GM volume was found in that study (Cooke et al., 2008). Summarized, VBM-studies did not show a clear structural substrate of clinical insight but show abnormalities across the brain.

The finding that structural imaging studies show associations with insight seems to be at odds with the fact that insight fluctuates over time. However, one should bear in mind that the correlations between brain structure and insight were in most cases only low to moderate. This means that reduced (regional) brain volume only explains part of the variance in insight and other factors will play a role as well. Sensitivity to stigma may be one of these factors. When people are aware of the prejudice others may have about people with mental illness, they may consciously or unconsciously reject the diagnostic label or symptoms associated with it. This may result in low scores on assessment of illness. The way some-one perceives himself often changes over time, for example as a result of treatment and recovery, which may lead to changes in insight regardless of brain volume.

4.2 Clinical insight and brain function

The meta-analysis on clinical insight and fMRI did not show significant results, which might be explained by the heterogeneity of paradigms and processes that were examined in these studies. All studies showed significant correlations between BOLD response and aspects of clinical insight or significant differences in BOLD response between high and low insight groups. Some authors found associations between clinical insight and brain activity during basic neurocognitive processes. For example, poorer insight was related to lower activation in precuneus and cerebellum during a working memory task (Sapara et al., 2014). Other studies examined higher-order social or self-related cognitive processes, in which clinical insight was found to be positively related to activation in the superior (Bedford et al., 2012) and inferior frontal gyri, left insula and left inferior parietal lobule (van der

Meer et al., 2013), but negatively related to activation in the right middle frontal gyrus and precuneus during self-evaluation (Bedford et al., 2012) in schizophrenia. Schizophrenia patients with poor insight also showed less activation than patients with good insight during a verbal self-motoring task in areas such as the putamen extending to the caudate, insula and inferior frontal gyrus (Sapara et al., 2015). Gerretsen et al. (2015) found a positive association between insight and activation in the left temporoparieto-occipital junction during an illness denial task (Gerretsen et al., 2015). In an additional study focused on clinical insight sub-dimensions, Shad and Keshavan (2015) found that awareness of symptoms was associated with widespread activation in prefrontal, parietal and limbic areas and the basal ganglia during a self-awareness task. Attribution of symptoms was associated with more localised activity in the prefrontal cortex and basal ganglia (Shad and Keshavan, 2015). fMRI-studies were very heterogeneous, however, with paradigms that tap on different cognitive processes that might also involve certain regions more than others. Nonetheless, altogether, all functional imaging studies showed significant associations between clinical insight and brain functioning and (pre)frontal regions seem to be implicated most consistently in clinical insight, regardless of the specific cognitive process that was assessed during scanning.

4.3 Cognitive insight

Cognitive insight is a relatively newer construct compared to clinical insight and, therefore, our search did not yield enough studies to conduct a meta-analysis. No studies on global brain volume and cognitive insight were found. In a study in 15 FEP patients, Buchy et al., (2016) did not find a significant association between hippocampal volumes and self-reflectiveness nor self-certainty, while self-reflectiveness and self-certainty were both associated with widespread changes in cortical thickness in frontal, parietal and temporal cortices; higher self-reflection was associated with thicker cortex and self-certainty with thinner cortex (Buchy et al., 2016). A second VBM study on cognitive insight showed that self-reflectiveness was positively related to GM volume of the right ventrolateral prefrontal cortex in individuals with schizophrenia (Orfei et al., 2013). GM volume of the hippocampus was found to be negatively related to self-certainty and not to self-reflection (Buchy et al., 2010; Orfei et al., 2017). Finally, Buchy et al. (2010) also found that *total* cognitive insight was

positively related to left hippocampal volume (Buchy et al., 2010). A last study of which the sample partially overlapped with a previous publication of this group (Buchy et al., 2016) found a negative relationship between self-reflectiveness and cortical thickness of the right occipital lobe (Buchy et al., 2018).

Three fMRI- (Buchy et al., 2015; Lee et al., 2015; van der Meer et al., 2013) and one Near-infrared spectroscopy (NIRS) study (Pu et al., 2013) on cognitive insight found significant associations between BOLD response and aspects of cognitive insight. Total cognitive insight was positively associated with activation in the left dorsolateral prefrontal cortex, and negatively with activation of the left parahippocampal gyrus during reality evaluation, and positively with activity in the right posterior cingulate cortex and right inferior parietal lobule during recognition (Lee et al., 2015). Other studies did not find significant associations between BCIS composite index scores and brain activation (Pu et al., 2013; van der Meer et al., 2013).

Self-reflectiveness was positively associated with activation in the left parahippocampal gyrus activation during reality evaluation (Lee et al., 2015) and with activation in the bilateral VLPFC in 25 first-episode schizophrenia patients (Buchy et al., 2015). Self-reflectiveness was also positively associated with activity in the bilateral ventromedial prefrontal cortex during self-reflection (van der Meer et al., 2013). Finally, self-reflectiveness was positively associated with hemodynamic changes in VLPFC and right temporal areas during a verbal fluency task as measured with NIRS (Pu et al., 2013). fMRI/ NIRS studies did not find significant associations for self-certainty (Buchy et al., 2015; Lee et al., 2015; van der Meer et al., 2013).

In sum, our literature search did not yield sufficient comparable studies on cognitive insight to perform meta-analyses. A systematic review of the literature showed that hippocampal and ventrolateral prefrontal cortex abnormalities were found most often in poorer cognitive insight.

4.4 Processes involved in insight

In sum, results of meta-analyses as well as the systematic review of additional studies consistently showed poor clinical insight to be related to lower GM- as well as WM-volume, particularly in frontal areas. Areas such as the inferior and superior temporal gyrus were also often

found in structural imaging studies, while functional imaging studies implicated the inferior frontal gyrus and insula more often than other areas. Altogether, structural and functional abnormalities of widespread areas across the brain have been related to poorer clinical insight. This suggest that insight is associated with a network of brain areas, illustrating that clinical insight is a complex construct with several partly overlapping dimensions that may be associated with functioning of different overlapping brain areas and several self-related cognitive processes. These may be processes such as error monitoring and correction (Koren et al., 2004), working memory and cognitive flexibility (Nair et al., 2014) and the ability to use explicit feedback of others to improve task performance (de Vos et al., 2015), but also higher-order social cognitive and self-oriented processes such as self-reflectiveness, affective mentalizing and empathy (Pijnenborg et al., 2013). All these processes enable individuals to compare ideas about the self (including having a mental illness) with new information or feedback from others, so that one's self-representations can be flexibly corrected when these are not in line with that information. Thus, clinical insight might be the outcome of several self-related cognitive processes in combination with information about one's mental state inferred from interactions with others. Besides that, non-cognitive factors, such as stigma sensitivity (Cooke et al., 2005), are associated with poor clinical insight as well, providing further evidence that poor insight cannot not merely be explained by deficits related to malfunctioning or atrophy of isolated brain areas. Rather, complex cognitive-emotional interactions in otherwise intact circuits could also play a key role in this multifaceted but highly clinically relevant phenomenon. Relations between brain areas and sub-dimension recognizing need for medication were not found. This makes sense, since e.g. attitudes toward pharmacotherapy and side-effect or previous experiences with anti-psychotic drugs of the patient and his environment will highly impact one's attitude toward medication.

Regarding cognitive insight, we mainly found associations with the ventrolateral prefrontal cortex and hippocampal areas, both in functional and structural studies. The ventrolateral prefrontal cortex has been linked to self-reflection and controlled retrieval of stored conceptual representations (Badre and Wagner, 2007; Levy and Wagner, 2011) and working memory (Buchy et al., 2015; Wolf et al., 2006). These memory processes have been linked to the ability to hold information online and is hypothesized to play a role in the ability to compare and integrate new information about the self to

the stored self-image (Orfei et al., 2013). The hippocampus was also found to play a role in self-related processes in previous studies (Schmitz and Johnson, 2006), forming a network with the dorsal medial and dorsolateral prefrontal cortex that facilitates cognitive control and monitoring of self-related decisions. The hippocampus also plays a role in several memory processes (Sheldon and Levine, 2018) that have been associated with cognitive insight (Davies et al., 2017), in particular impaired retrieval from declarative memory. Thus, integrated results suggest that cognitive insight mainly relies on the ability to retrieve and integrate self-related information with new information, which may hamper self-reflection and may lead to idiosyncratic self-certainty.

4.5 Limitations

Whereas almost 2000 publications were reviewed, only 37 studies could be included. These studies were still rather diverse in terms of samples and measurements. As a result, meta-analyses were sometimes not possible, and meta-analyses that were conducted were likely to be underpowered, which may have caused an underestimation of the effects or a biased estimation. The majority of studies had small to modest sample sizes, and calculated many correlations without proper correction for multiple testing. This could have led to false positives. Differences in preprocessing choices, such as smoothing filter size and method of segmentation, may also influence results. In these studies, a great variety of insight measures were used, with interview-based ratings possibly measuring different aspects of insight compared to self-reported ratings (Young et al., 2003). Some studies examined insight dimensions, while others looked at total scores or performed factor analyses. Furthermore, samples varied greatly between studies. The patient population is already very heterogeneous, and illness-related factors such as illness duration and antipsychotic use also varied significantly between studies. These factors have been shown to influence insight (Garver et al., 2005; Lieberman et al., 2005), making it even harder to integrate findings.

Of note, the current conceptualization of clinical insight is, to a considerable degree, dependent on how researchers and mental health workers perceive illness and to what extent the patient agrees with this view. This means that when opinions on mental health change over time, patients have to adapt their illness perceptions in line with these changes to be perceived as having

good insight. This approach is to some extent arbitrary and problematic, insofar it "penalizes" possibly justified considerations regarding the nature of mental illness on behalf of the patient. That is, clinical insight may, to a certain extent, reflect the tendency to agree with others rather than true insight in one's mental state. In more recent publications on insight, a broader definition of insight has been proposed. Instead of the willingness to understand one's mental health problems in line with the medical model, narrative insight focuses on the ability to integrate illness one's in a personal life story (Roe et al., 2008). Narrative insight relies on the ability to integrate one's one perspective with that of others to make sense of what has happened or how one functions. Future studies may focus on neural underpinnings and processes that are involved in this ability.

4.6 Conclusions

Although studies were diverse, the results indicate that different brain areas are associated with clinical and cognitive insight. More specifically, impaired clinical insight appears to be associated with spatially diffuse global abnormalities, in particular with the frontal areas. It might rely on a broad range of (social) cognitive functions. Cognitive insight, on the other hand, appears to involve the hippocampus and ventrolateral prefrontal cortex and may thus rely more on the specific ability to retrieve and integrate self-related information.

Our results may also have clinical implications by informing interventions that aim to increase insight by stimulating relevant brain areas. In fact, there is preliminary evidence that transcranial direct current stimulation (TDCS) of the frontotemporal areas and the left temporoparietal junction is associated with an increase of both cognitive (Chang et al., 2019) and clinical (Chang et al., 2018; Sreeraj et al., 2018) insight. Future research is needed both to replicate and expand on these findings.

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Figure legends

Fig. 1. PRISMA flowchart.

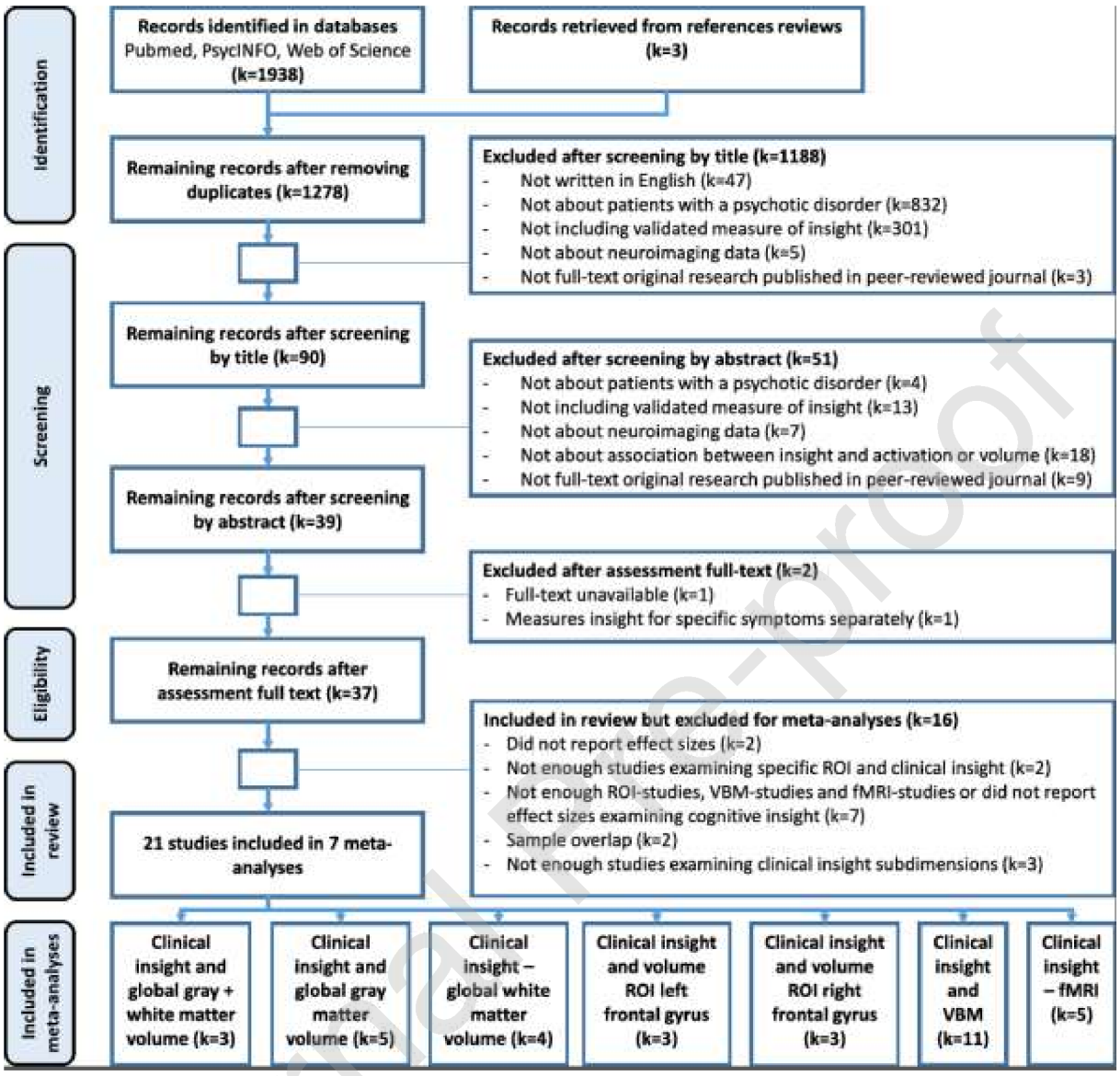


Fig. 2. Forest plot of effect sizes of studies on the association between clinical insight and total gray matter volume.

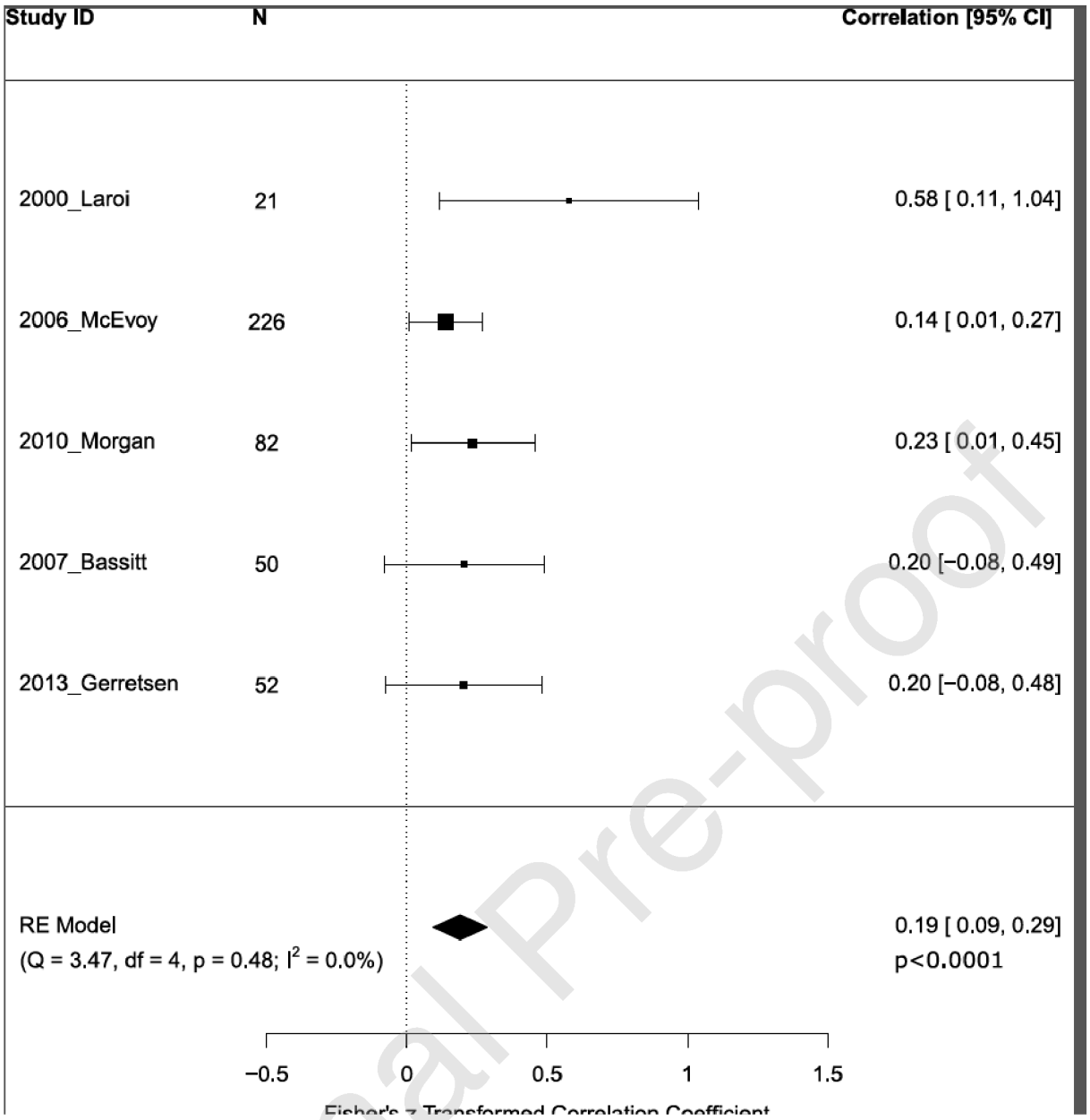


Fig. 3. Forest plot of effect sizes of studies on the association between clinical insight and total white matter volume.

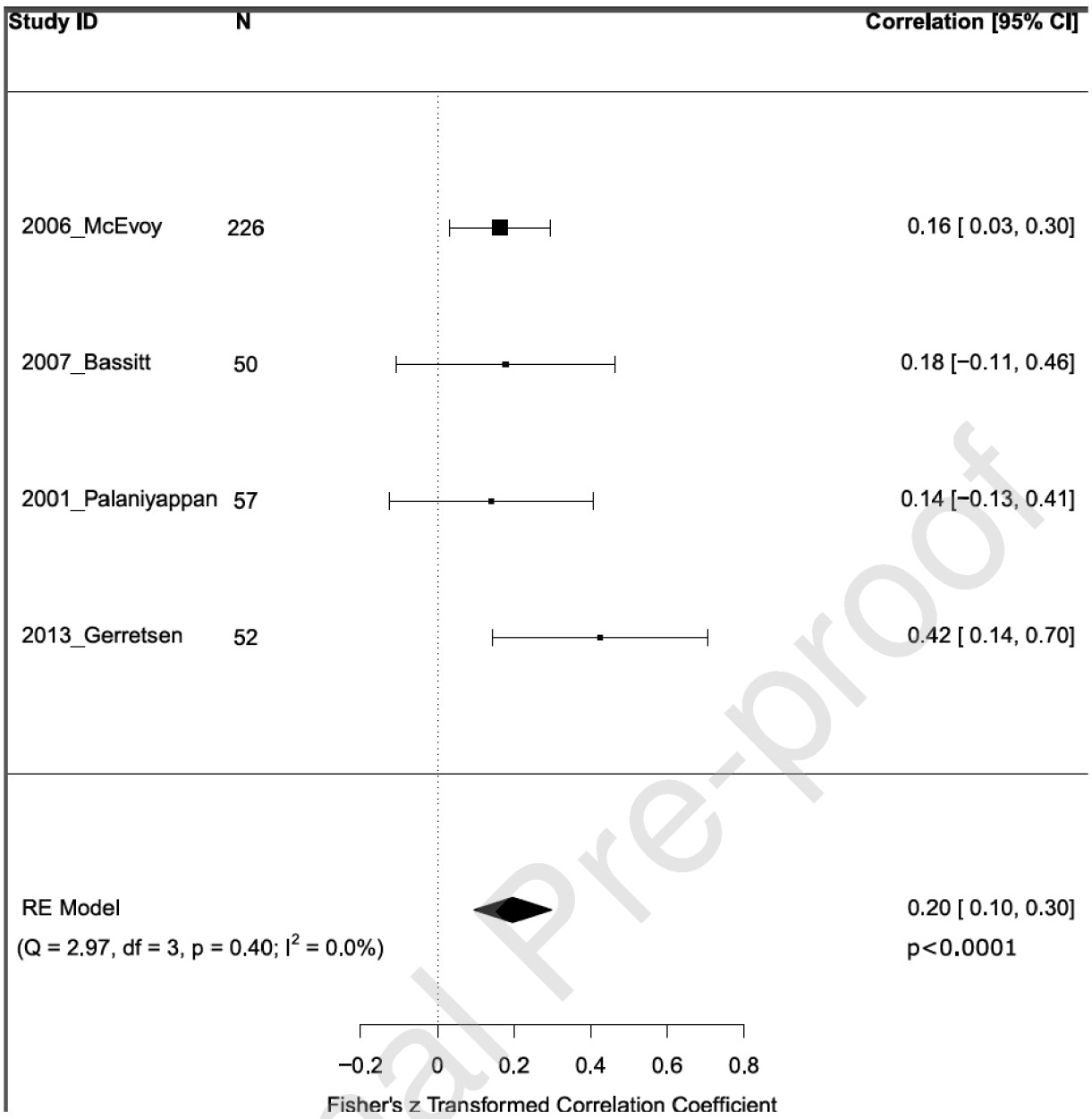


Fig. 4. Forest plot of effect sizes of studies on the association between clinical insight and total gray and white matter volume.

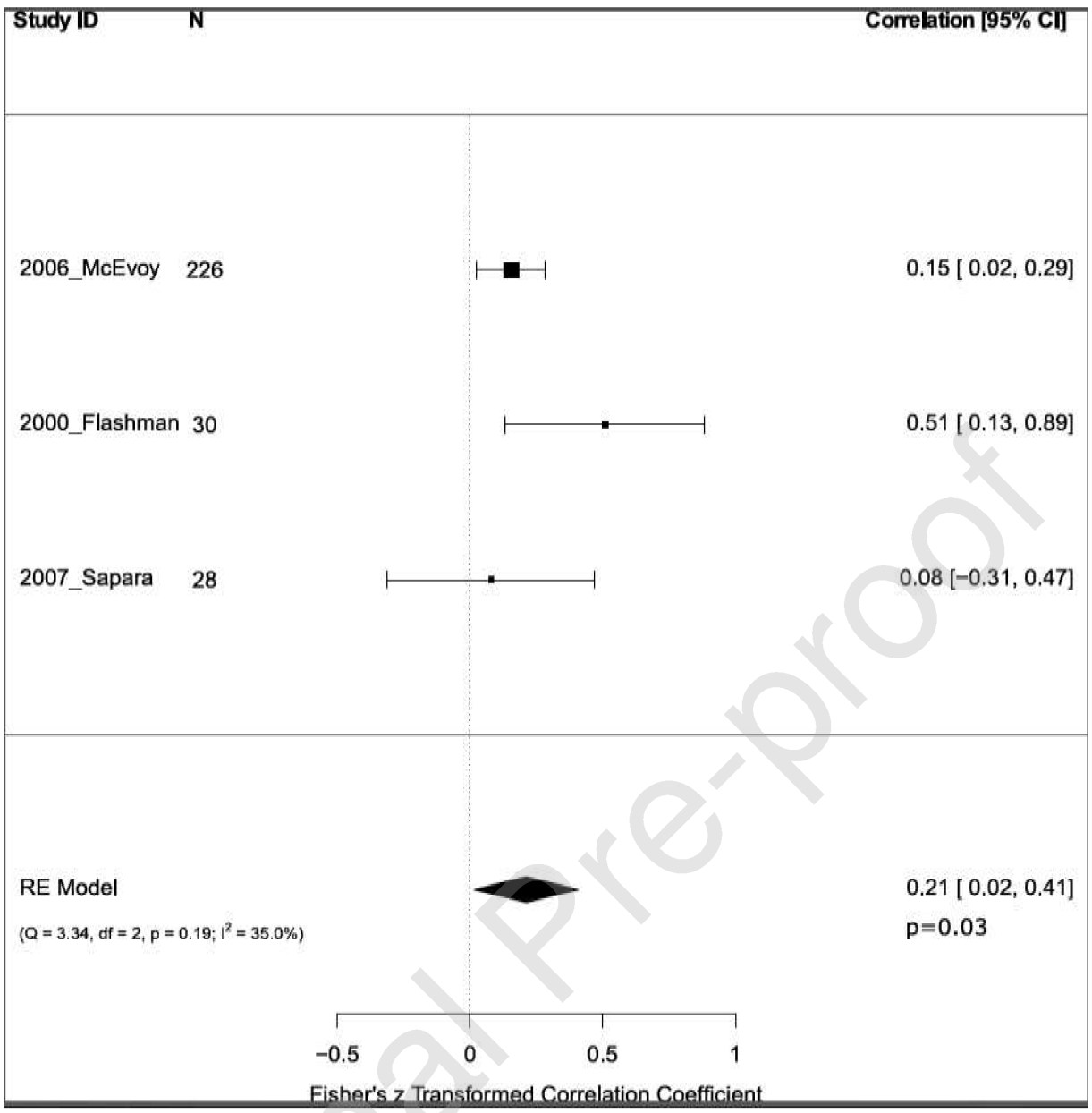


Fig. 5. Forest plot of effect sizes of studies on the association between clinical insight and gray matter volume of the left frontal gyrus.

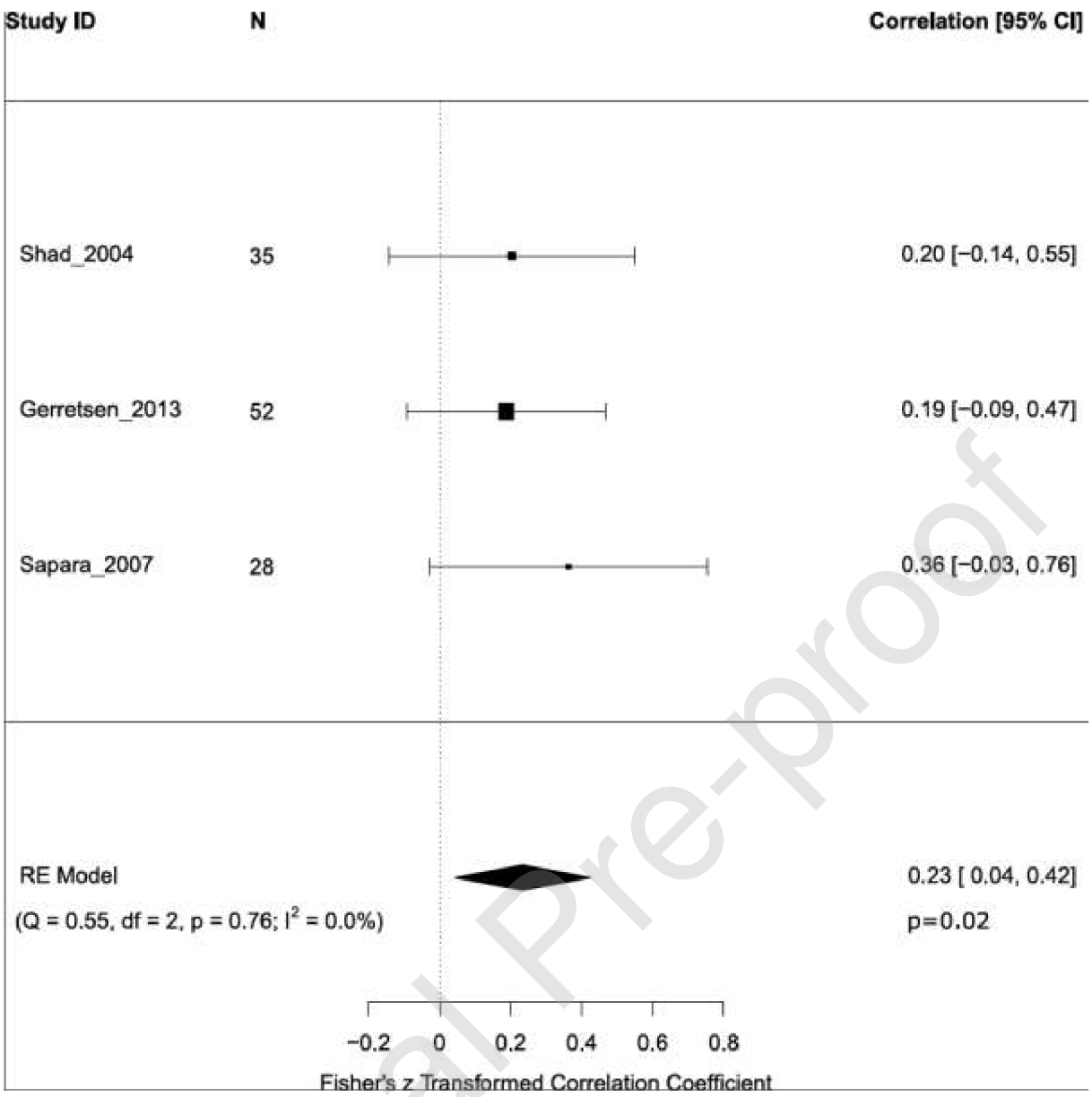


Fig. 6. Forest plot of effect sizes of studies on the association between clinical insight and gray matter volume of the right frontal gyrus.

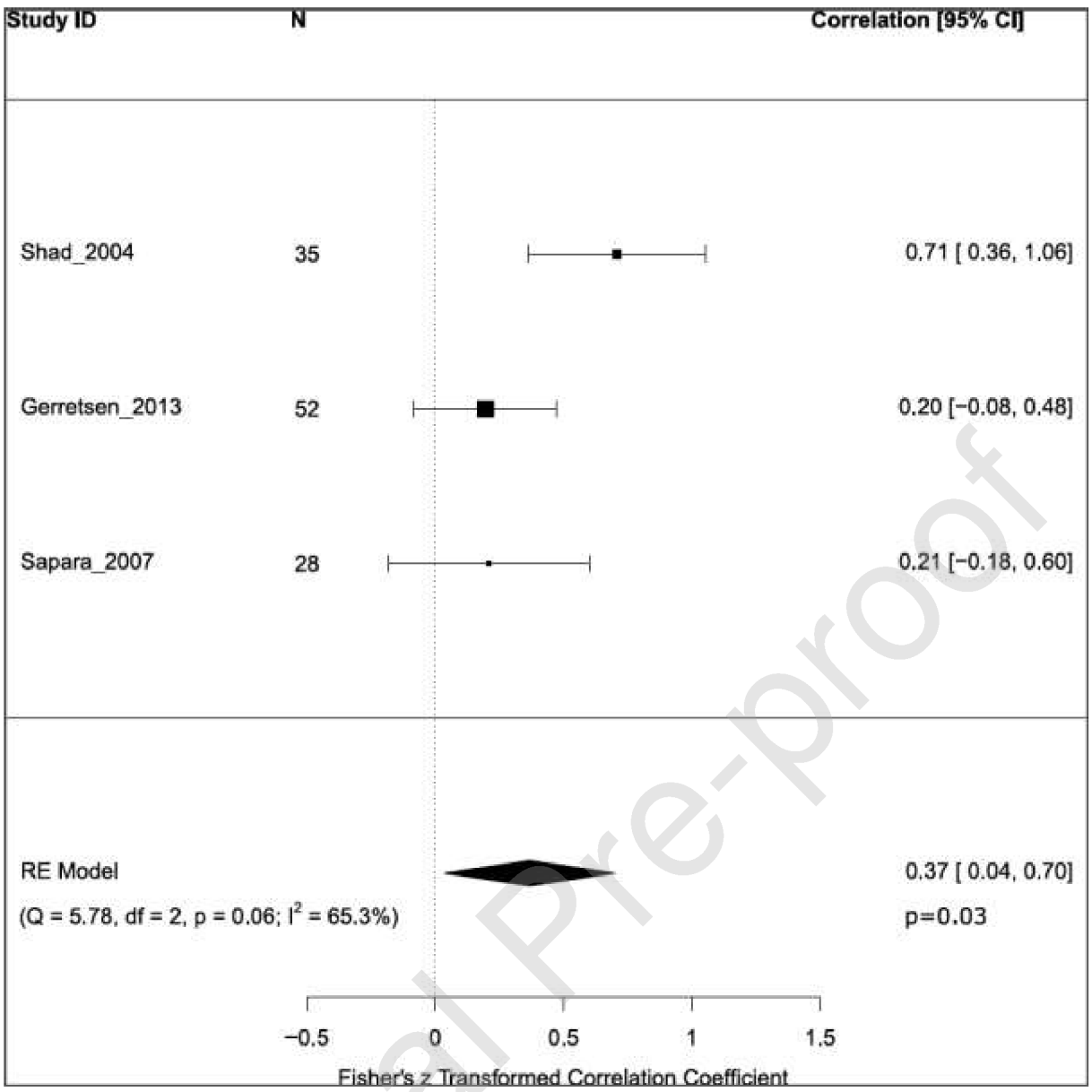
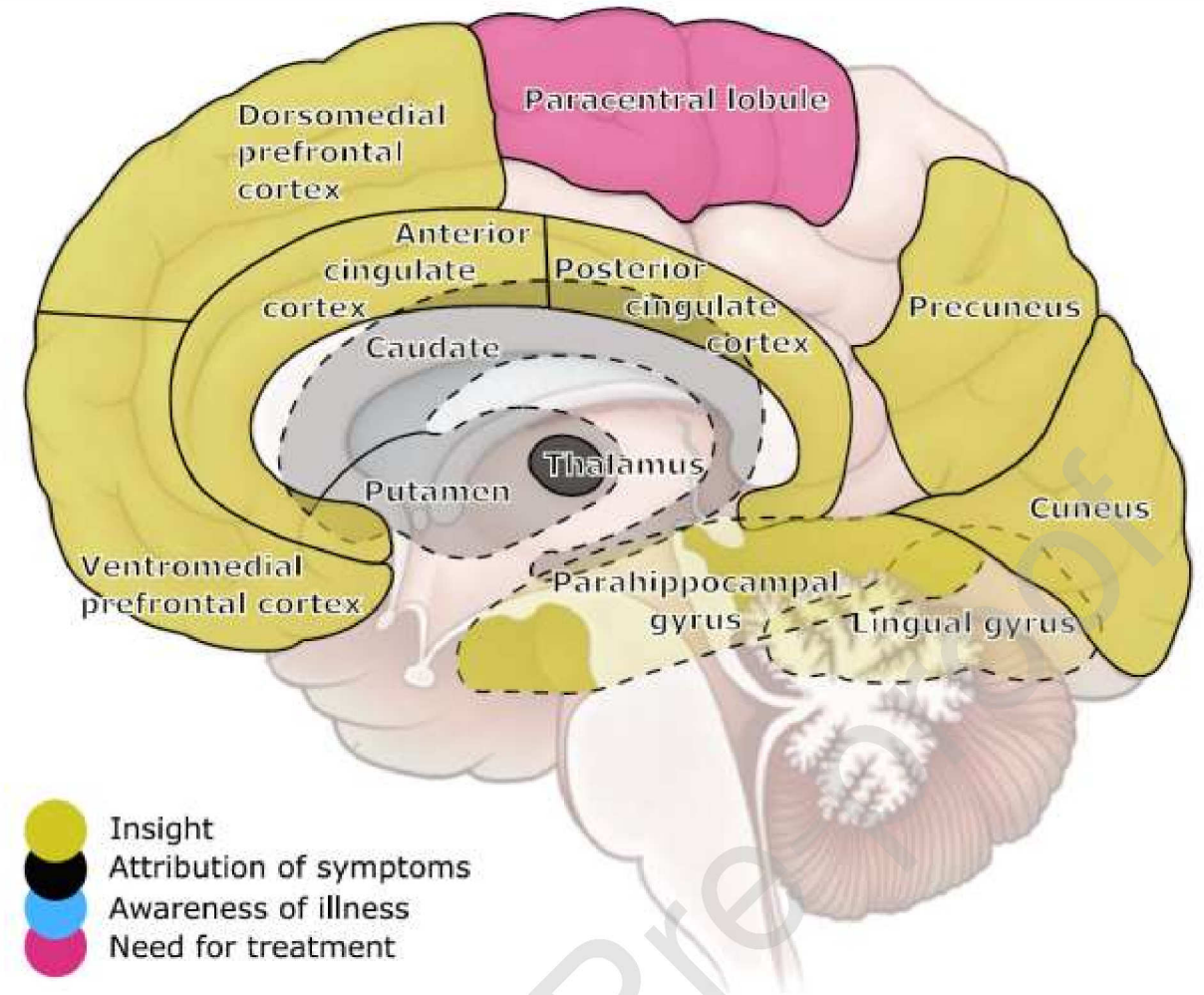


Figure 7. Schematic display of medial and lateral views of areas that showed an association between brain structure and clinical insight.

NB: regions implicated in more than two (* in five or more) separate studies: the superior frontal gyrus, middle frontal gyrus*, inferior frontal gyrus*, insula, superior temporal gyrus*, middle temporal gyrus, inferior temporal gyrus*, cerebellum, dorsomedial prefrontal cortex, anterior cingulate cortex, ventromedial prefrontal cortex, parahippocampal gyrus and cuneus.

Figure from (Larabi, 2020).



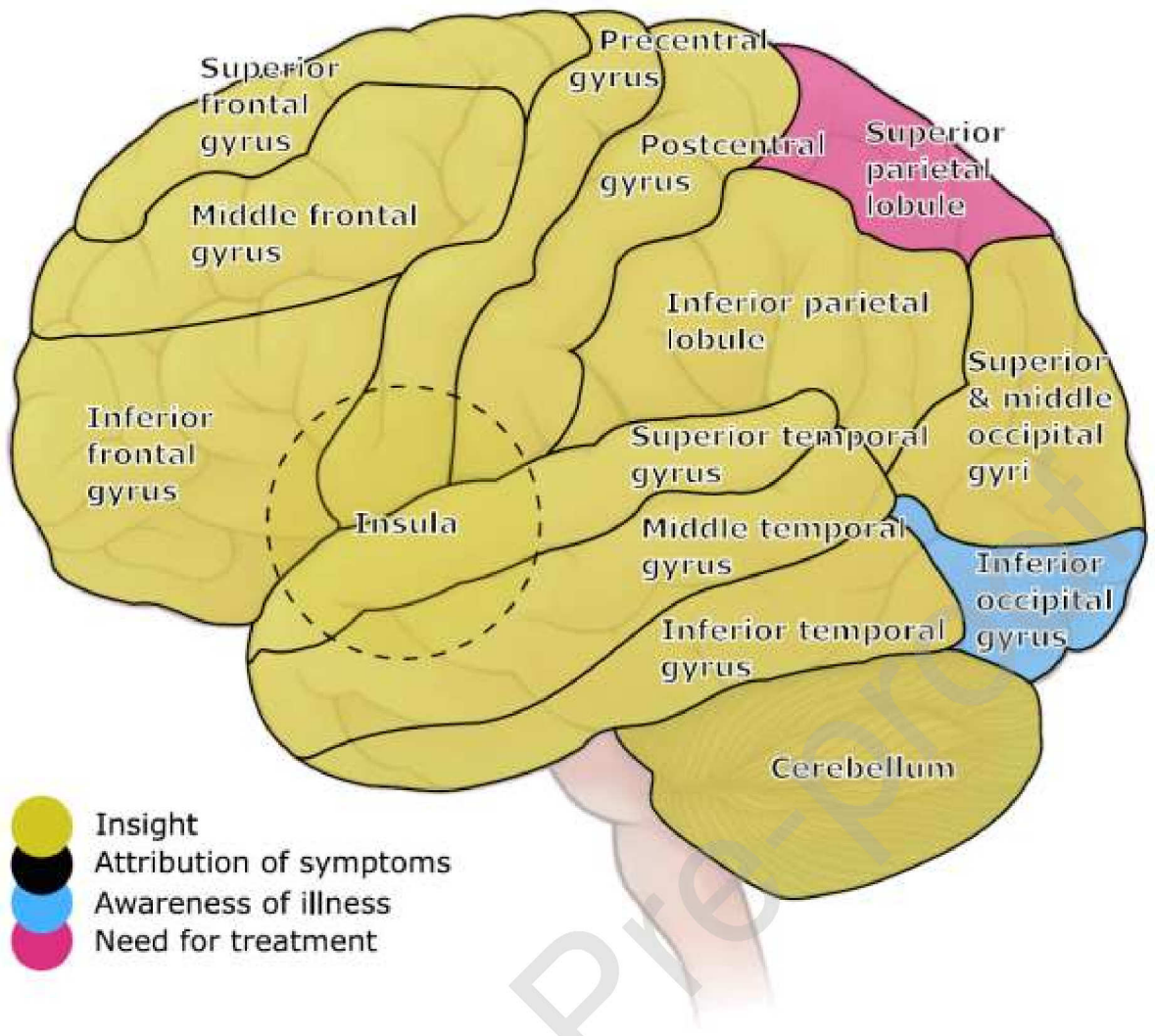
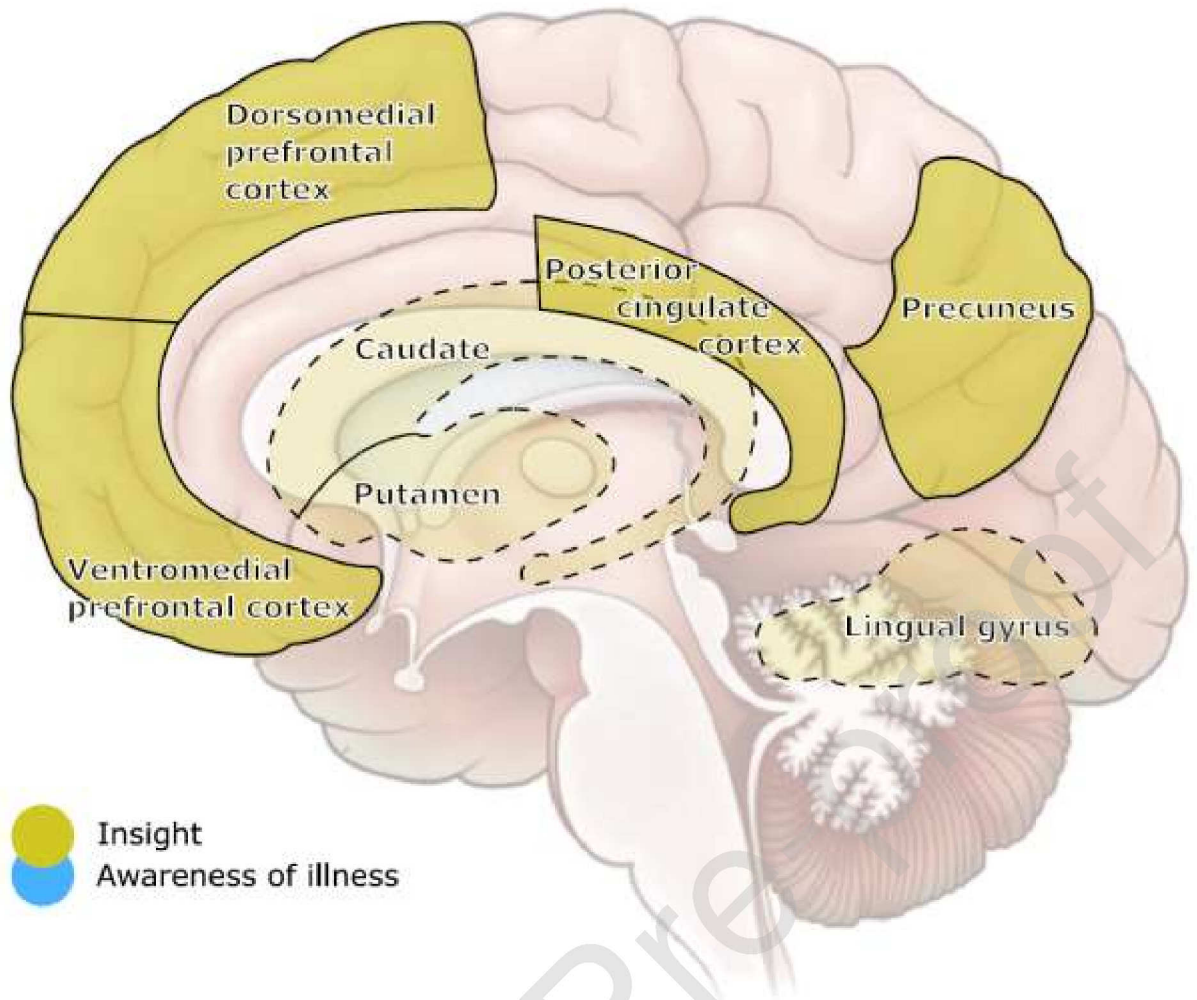


Figure 8. Schematic display of medial and lateral views of areas that showed an association between brain activation and clinical insight.

NB: Regions implicated in more than two (* in five or more) separate studies: inferior frontal gyrus*, insula*, inferior parietal lobule and precuneus.

Figure from (Larabi, 2020).



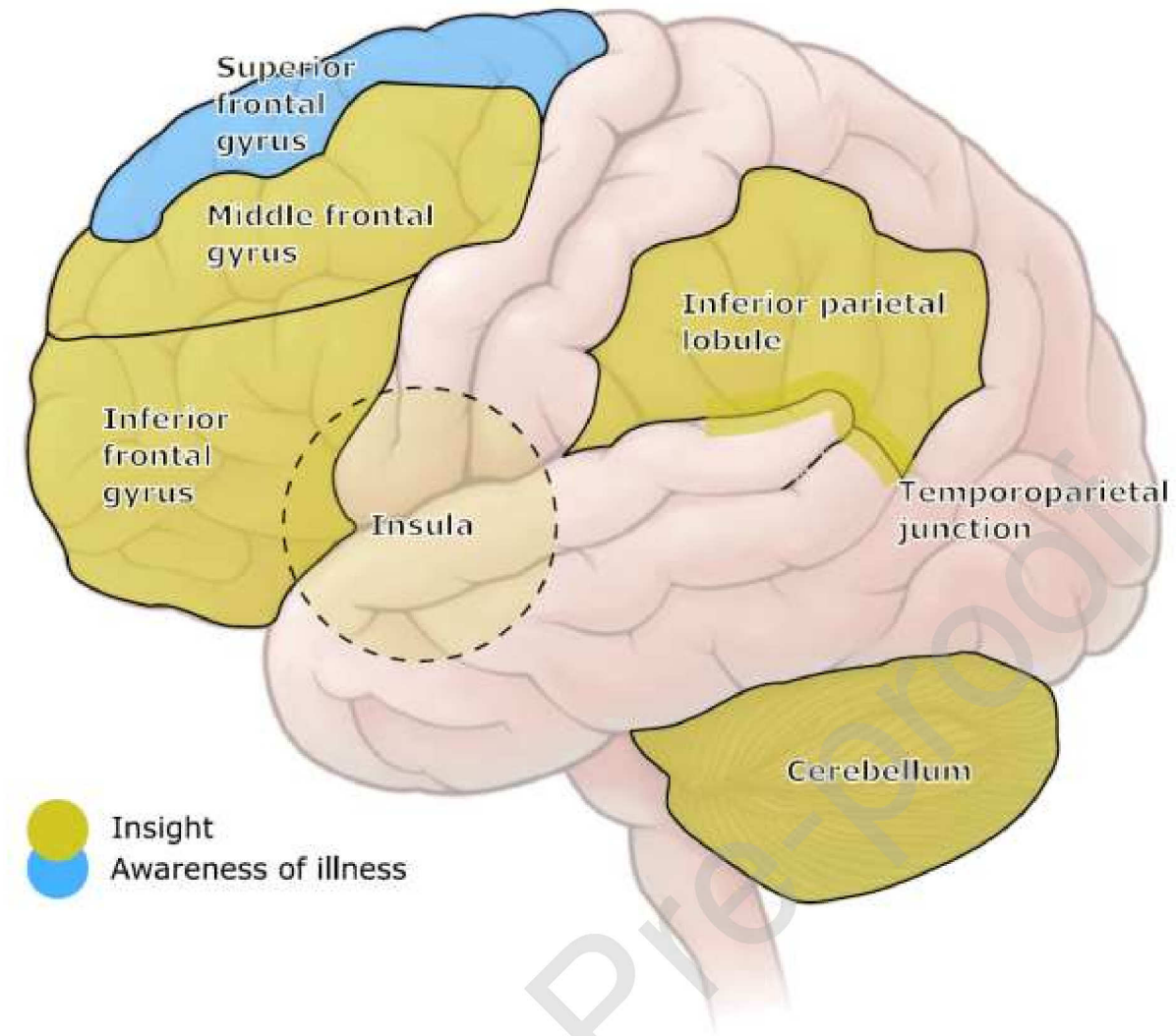
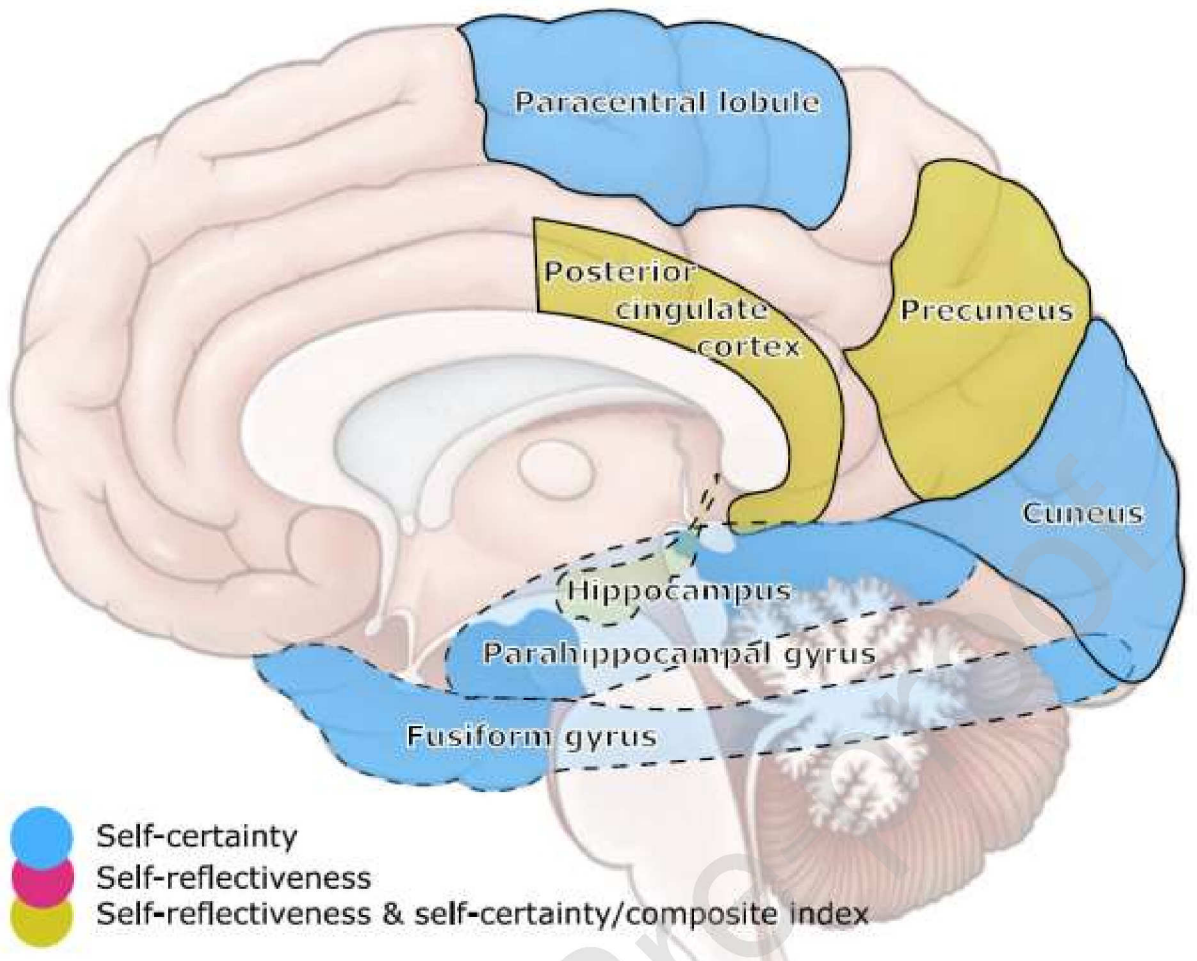


Figure 9. Schematic display of medial and lateral views of areas that showed an association between brain structure and cognitive insight.

NB: only one region (i.e. the hippocampus) was implicated in more than 2 studies.

Figure from (Larabi, 2020).



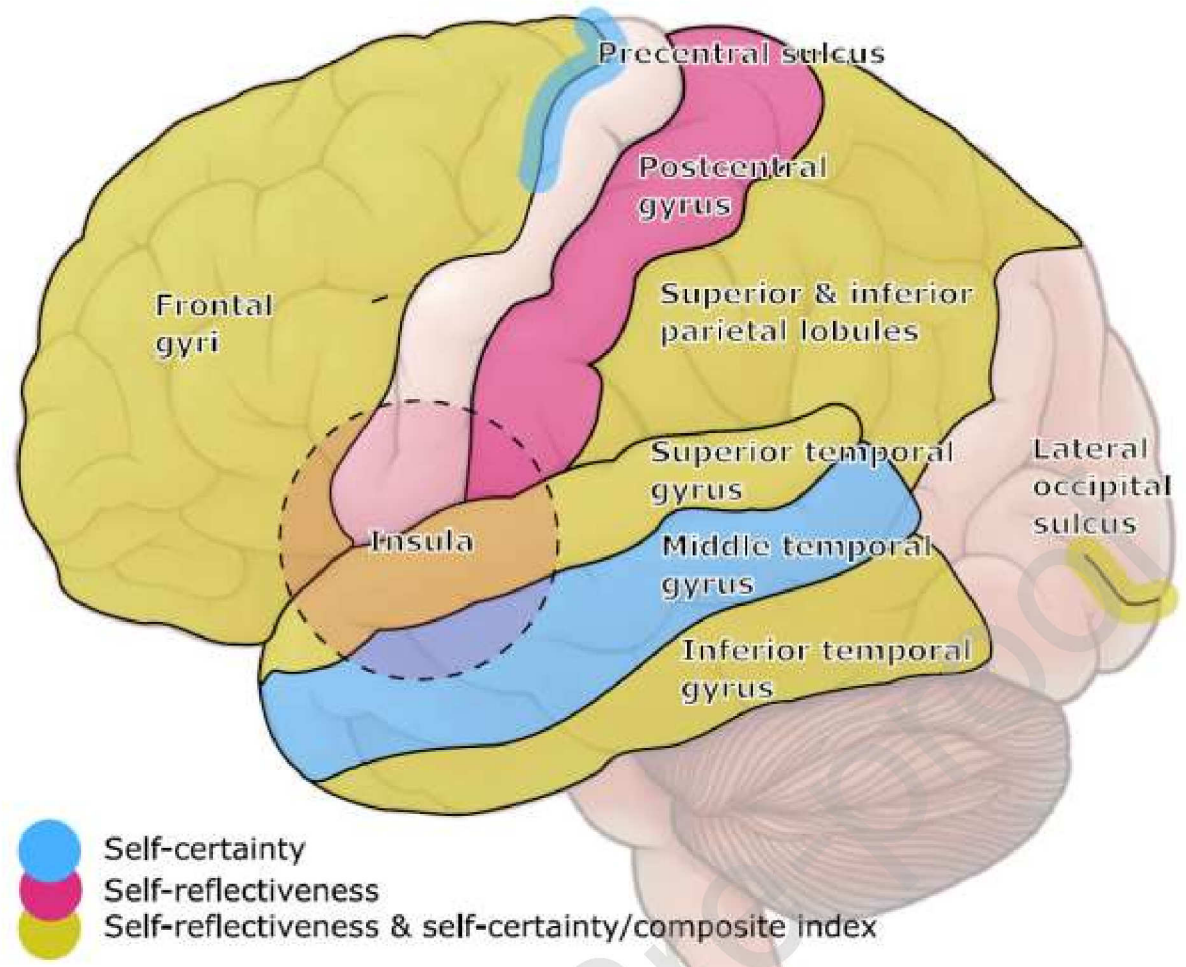
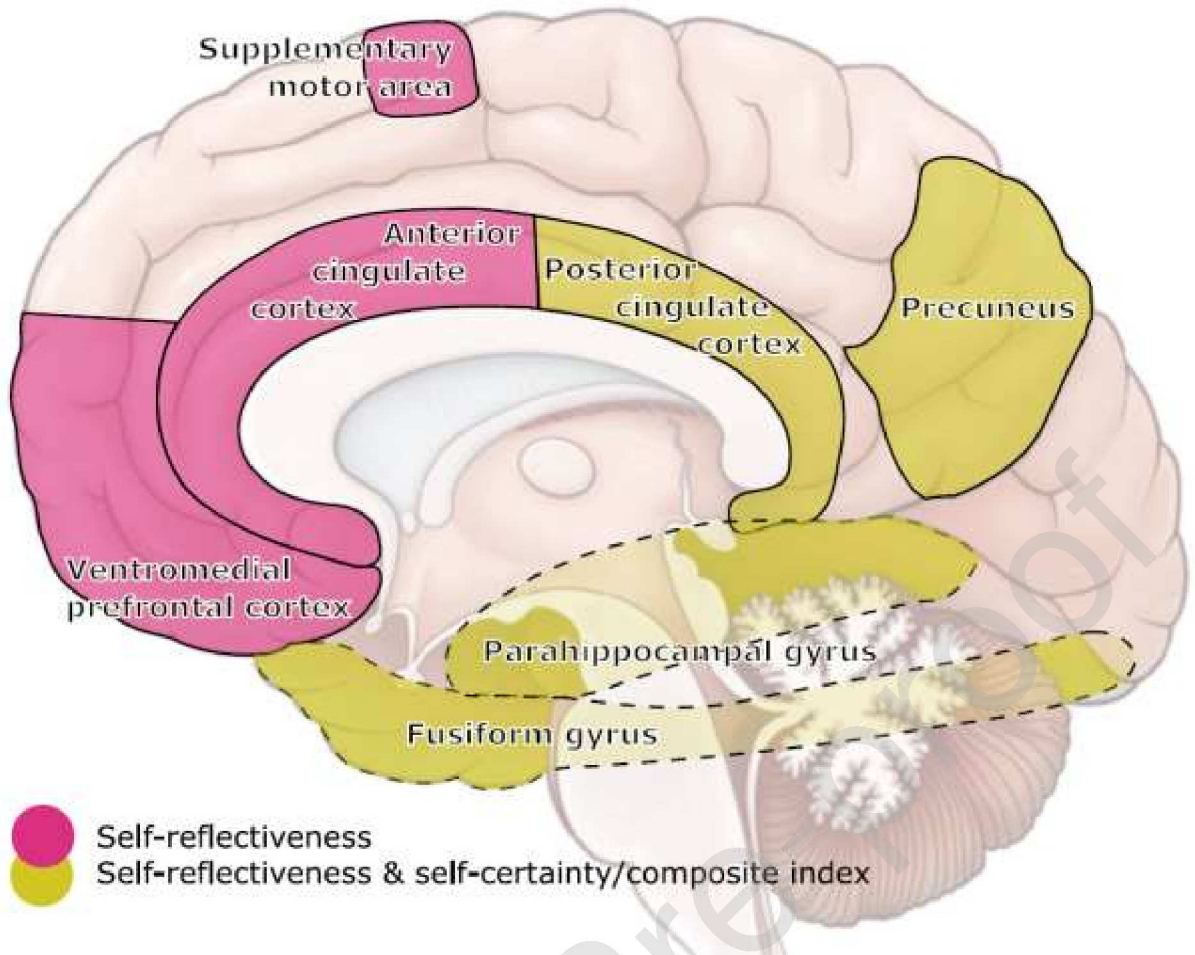
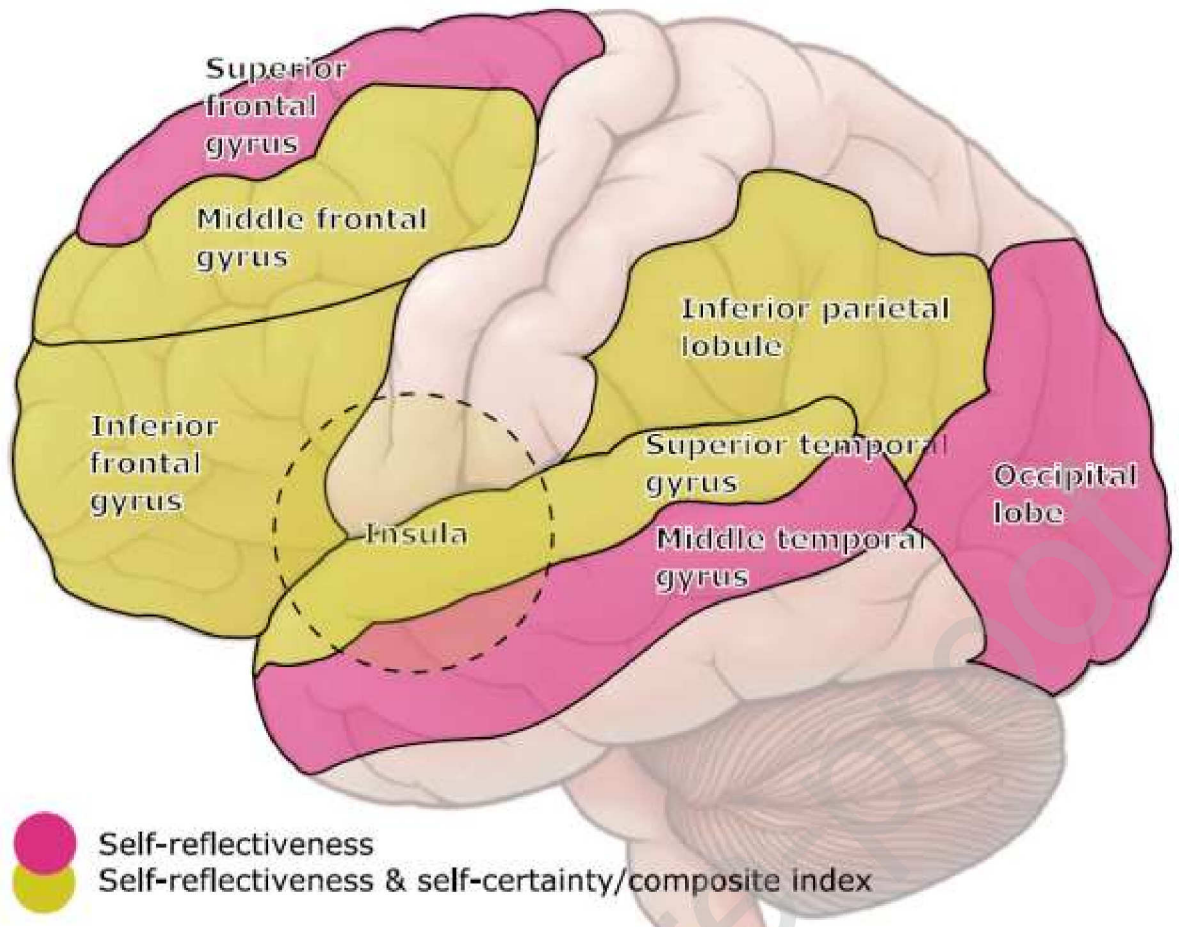


Figure 10. Schematic display of medial and lateral views of areas that showed an association between brain function and cognitive insight.

NB: only one region (i.e. the inferior frontal gyrus) was implicated in more than two studies.

Figure from (Larabi, 2020).





Tables

Table 1. Methodological characteristics of studies included in meta-analysis on clinical insight and total brain volume (k=8).

Study	Sample size & diagnosis	Neuroimaging technique	Field strength scanner	FOV	ROIs	Statistical threshold	Insight measure	Brain measure	Controlled for	Association with insight	Significance
(Flashman et al., 2000)	30 SZ	MRI: whole brain volume and intracranial volume	1.5T	WB	n.a.	$p_{unc}<.05$	SUMD total	Whole brain volume	-	Positive	Significant
							SUMD total	Intracranial volume	-	Positive	Significant
(Larøi et al., 2000)	21 SZ	CT: visual inspection ventricular enlargement and/or sulcal widening	n.a.	WB	n.a.	$p_{unc}<.05$	SUMD total	Cortical atrophy	-	Positive	Significant
(Palaniyappan et al., 2011) *	57 SZ	MRI: WM and cortical surface area	3T	WB	n.a.	$p_{Bonferroni-Holm}<.05$	Symptoms and Signs in Psychotic Illness scale sub-item	Total WM	Total area and total burden of symptoms	Positive	Not significant
							Symptoms and Signs in Psychotic Illness scale sub-item	Total cortical surface area	Total area and total burden of symptoms	Negative	Not significant
(McEvoy et al., 2006)	226 FEP	MRI: GM, WM, CSF, total brain volume (GM+WM), lateral		WB	n.a.	$p_{unc}<.05$	ITAQ total	Total GM+WM	Investigator, age, gender and ethnicity	Positive	Significant
							ITAQ total	Total GM	Investigator, age, gender and ethnicity	Positive	Significant

Study	Sample size & diagnosis	Neuroimaging technique	Field strength scanner	FOV	ROIs	Statistical threshold	Insight measure	Brain measure	Controlled for	Association with insight	Significance
		ventricular volume					ITAQ total	Total WM	Investigator, age, gender and ethnicity	Positive	Significant
							ITAQ total	Total CSF	Investigator, age, gender and ethnicity	Negative	Not significant
							ITAQ total	Lateral ventricular volume	Investigator, age, gender and ethnicity	Negative	Not significant
(Bassitt et al., 2007) *	50 SZ	MRI: GM, WM	1.5T	WB	n.a.	p_{unc}<.001	SUMD combined awareness and attribution item	Total GM	-	Positive	Not significant
							SUMD combined awareness and attribution item	Total WM	-	Positive	Not significant
(Saparra et al., 2007) *[a]	28 SZ	MRI: GM, WM	1.5T	WB	n.a.	p_{unc}<.05	BIS total	Total GM+WM	-	Positive	Not significant
							BIS Insight into symptoms	Total GM+WM	-	Positive	Not significant
							BIS Insight into illness	Total GM+WM	-	Positive	Not significant
							BIS Need for treatment	Total GM+WM	-	Negative	Not significant
							SAI-E total	Total GM+WM	-	Positive	Not significant
							SAI-E Insight into symptoms	Total GM+WM	-	Positive	Not significant

Study	Sample size & diagnosis	Neuroimaging technique	Field strength scanner	FOV	ROIs	Statistical threshold	Insight measure	Brain measure	Controlled for	Association with insight	Significance
							SAI-E Insight into illness	Total GM+WM	-	Positive	Not significant
							SAI-E Need for treatment	Total GM+WM	-	Positive	Not significant
							SAI-E Insight into consequences	Total GM+WM	-	Positive	Not significant
(Morgan et al., 2010) *	82 first-onset psychosis	MRI: GM, ventricular volume	1.5T	WB	n.a.	$p_{clustered\text{-}mass}<.01$	SAI-E total	Total GM	Age	Positive	Not significant
							SAI-E total	Ventricular volume	Age		Not significant
							SAI-E Relabeling of symptoms	Total GM or ventricular volume	Age		Not significant
(Gerretsen et al., 2013) *	52 SZ	MRI: WM, GM	1.5T	WB	n.a.	$p_{Bonferroni}<.01$	PANSS G12	Total WM	Age, gender, total intracranial volume	Positive	Significant
							PANSS G12	Total GM	Age, gender, total intracranial volume	Negative	Not significant

*Included in multiple meta-analyses as multiple methods are reported.
[a]Only the association with the SAI-E measure was included in the meta-analysis, as the association with the BIS measure was from the same sample.
NB: higher insight is reflected by higher scores on some insight measures but lower scores on other insight measures. Note that in the "Association with insight" column, the association with insight is stated and not with the insight *measure* (e.g. positive association: lower volume with lower insight).

Table 2. Clinical characteristics of studies included in meta-analysis on clinical insight and total brain volume (k=8)

Study	Diagnosis	Insight measure	Sample size (number of males)	Age	Mean illness duration (years)	Type of medication; mean CPZ equivalents (mg)	PANSS score	In/out patients
(Flashman et al., 2000)	DSM-IV diagnosis of schizophrenia (n=24), schizoaffective disorder (n=5) or psychotic disorder not otherwise specified (n=1)	SUMD total	30 (22)	34.9 ± 11.9				27 in 3 out
(Larøi et al., 2000)	DSM-IV diagnosis of schizophrenia	SUMD total	21 (11)	36 ± 10.2	12.77 ± 11.36	All on neuroleptics with mean of 2.2 ± 1 defined daily dose		In/out
(Palaniyappan et al., 2011)	DSM-IV diagnosis of schizophrenia	Symptoms and Signs in Psychotic Illness scale sub-item	57 (50)	26.10 ± 7.49	4.3	All on atypical antipsychotics; 288.7		
(McEvoy et al., 2006)[b]	DSM-IV diagnosis of schizophrenia (n=133), schizophreniform disorder (n=69) or schizoaffective disorder (n=24)	ITAQ total	226 (184)	23.86 ± 4.71	1.20 ± 1.15	168 on antipsychotics	80.48 ± 14.65	
(Bassitt et al., 2007)*	DSM-IV diagnosis of schizophrenia	SUMD combined awareness and attribution item	50 (38)	31.7 ± 7.1	11.4 ± 7.4	All on antipsychotics: typical (n=4), second-generation (n=17), clozapine (n=21), combination of either typical plus second-generation (n=6) or typical plus clozapine (n=2)	59.1 ± 14.4	Out

Study	Diagnosis	Insight measure	Sample size (number of males)	Age	Mean illness duration (years)	Type of medication; mean CPZ equivalents (mg)	PANSS score	In/out patients
(Sapara et al., 2007)*	DSM-IV diagnosis of schizophrenia	BIS total, BIS 3 subscales, SAI-E total, SAI-E 4 subscales	28 (24)	39 ± 10.51	13.68 ± 10.05	Typical (n=4), atypical (n=23) or both typical and atypical (n=1) antipsychotics	63.11 ± 11.47	Out
(Morgan et al., 2010)*	ICD-10 diagnosis of first-episode psychosis: schizophrenia (n=39), schizoaffective disorder (n=6), bipolar disorder (n=17), depressive psychosis (n=10), or other psychosis (n=10)	SAI-E total	82 (50)	27.15 ± 7.58	0.25 ± 0.25	Typical (n=21), atypical (n=19), mixed (n=29) or none (n=13)		In/out
(Gerretsen et al., 2013)*	DSM-IV-TR diagnosis of schizophrenia	PANSS G12	52 (33)	41.5 ± 14.5	17.0 ± 14.1		43.0 ± 11.6	

*Included in multiple meta-analyses as multiple methods are reported.

Table 3. Methodological characteristics of studies excluded from meta-analysis on clinical insight and total brain volume (k=4)

Reason exclusion	Study	Sample size & diagnosis	Neuroimaging technique	Field strength scanner	FOV	ROIs	Statistical threshold	Insight measure	Brain measure	Controlled for	Association with insight	Significance
Not enough studies examining clinical insight subdimensions	(Cooke et al., 2008)*	52 SZ/SA	MRI: GM	1.5T	WB	n.a.	p_{FWE}<.05	SAI-E+BIS Awareness of Problems	Total GM	-	Positive	Significant
								SAI-E + BIS Symptom Relabeling	Total GM	-	Positive	Significant
								SAI-E+BIS Awareness of and Attribution to Illness	Total GM	-	Positive	Not significant
								SAI-E + BIS Recognition of the Need for Medication	Total GM	-	Positive	Not significant
Does not report effect sizes	(David et al., 1995)	59 SZ, 32 affective psychosis, 27 SF / DD / atypical psychosis, 10 schizoaffective psychosis (total n=128)	CT: ventricular volume	n.a.	WB	n.a.	p_{unc}<.05	PSE item 104	Ventricular volume	-		Not significant
Does not report effect sizes	(Rossell et al., 2003)	71 SZ	MRI: GM, WM, CSF, total brain	1.5T	WB	n.a.	p_{unc}<.05	SAI-E total	Total GM	-		Not significant
								SAI-E total	Total WM	-		Not significant
								SAI-E total	Total CSF	-		Not significant

Reason exclusion	Study	Sample size & diagnosis	Neuroimaging technique	Field strength scanner	FOV	ROIs	Statistical threshold	Insight measure	Brain measure	Controlled for	Association with insight	Significance
			volume (GM+WM)				SAI-E total	Total GM+WM	-			Not significant
Full-text unavailable	(Takai et al., 1992)	57 SZ	MRI: ventricular-brain ratio		WB	n.a.	PSE item 104	Association between ventricular enlargement and insight	-		Negative	Significant

*Included in multiple meta-analyses as multiple methods are reported.
NB: higher insight is reflected by higher scores on some insight measures but lower scores on other insight measures. Note that in the "Association with insight" column, the association with insight is stated and not with the insight *measure* (e.g. positive association: lower volume with lower insight).

Table 4. Clinical characteristics of studies excluded from meta-analysis on clinical insight and total brain volume (k=4).

Reason exclusion	Study	Diagnosis	Insight measure	Sample size (number of males)	Age	Mean illness duration (years)	Type of medication; mean CPZ equivalents (mg)	PANSS score	In/out patients
Not enough studies examining clinical insight dimensions	(Cooke et al., 2008)*	DSM-IV diagnosis of schizophrenia (n=47) or schizoaffective disorder (n=5)	Combined BIS+SAI-E	52 (40)	38.35 ± 9.89	13.9 ± 9.6	Atypical (n=42) or typical antipsychotics (n=10)	66.2 ± 13.7	Out
Does not report effect sizes	(David et al., 1995)[a]	DSM-III-R diagnosis of schizophrenia (n=59), affective psychosis (n=32), schizophreniform disorder/delusional disorder/atypical psychosis (n=27 SF/DD/atypical psychosis) or schizoaffective disorder (n=10)	PSE item 104	128 (83)	26.4 ± 6.5	2.2 ± 2.0			In
Does not report effect sizes	(Rossell et al., 2003)	DSM-IV diagnosis of schizophrenia	SAI-E total	71 (71)	33.7 ± 8.50	11.19 ± 7.75	648.2 ± 535.6		In/out
Full-text unavailable	(Takai et al., 1992)	Diagnosis of schizophrenia	PSE item 104	57					

*Included in multiple meta-analyses as multiple methods are reported.

Table 5. Methodological characteristics of studies included in meta-analysis on clinical insight and volume regions of interest (ROIs) (k=3).

Study	Sample size & diagnosis	Neuroimaging technique	Field strength scanner	FOV	ROIs	Statistical threshold	Insight measure	Brain measure	Controlled for	Association with insight	Significance
(Shad et al., 2004)	35 SZ/SA	MRI: GM volume	1.5T	4 ROIs (region)	Left and right dorsolateral prefrontal cortex and hippocampus	p_{unc}<.05	Insight item of HDRS	Right dorsolateral prefrontal cortex	Intracranial volume	Positive	Significant
							Insight item of HDRS	Left dorsolateral prefrontal cortex	Intracranial volume	Positive	Not significant
							Insight item of HDRS	Left hippocampus	Intracranial volume	Negative	Not significant
							Insight item of HDRS	Right hippocampus	Intracranial volume	Negative	Not significant
(Sapara et al., 2007)*	28 SZ	MRI: GM volume	1.5T	15 ROIs (region)	Total, left and right: prefrontal cortex, superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, orbitofrontal gyrus	p_{unc}<.05	BIS total, BIS Insight into symptoms, BIS Insight into illness, BIS Need for treatment, SAI-E total, SAI-E Insight into symptoms, SAI-E Insight into illness, SAI-E Need for treatment,	BIS total & total prefrontal cortex, total inferior frontal gyrus, total/right/left orbitofrontal gyrus	-	Positive	Significant

Study	Sample size & diagnosis	Neuroimaging technique	Field strength scanner	FOV	ROIs	Statistical threshold	Insight measure	Brain measure	Controlled for	Association with insight	Significance
						SAI-E Insight into consequences					
						BIS Insight into Illness & Total/left/right prefrontal cortex, right superior frontal gyrus, total inferior frontal gyrus, total/right orbitofrontal gyrus	-			Positive	Significant
						BIS Insight into symptoms & right orbitofrontal gyrus	-			Positive	Significant
						SAI-E total & left prefrontal cortex	-			Positive	Significant
						SAI-E Insight into illness & left prefrontal cortex, total/right/left	-			Positive	Significant

Study	Sample size & diagnosis	Neuroimaging technique	Field strength scanner	FOV	ROIs	Statistical threshold	Insight measure	Brain measure	Controlled for	Association with insight	Significance
								orbitofrontal gyrus			
								SAI-E Insight into symptoms & right orbitofrontal gyrus	-	Positive	Significant
								SAI-E Need for treatment & left middle frontal gyrus	-	Positive	Significant
(Gerretsen et al., 2013)*	52 SZ	MRI: GM and WM volume	1.5T	12 ROIs (region)	GM and WM of left and right frontal, parietal, and temporal lobes	$p_{Bonferroni}<.01$	PANSS G12	WM parietal lobe	Age, gender, total intracranial volume	Positive	Significant
								GM and WM frontal and temporal lobes, WM parietal lobe	Age, gender, total intracranial volume		Not significant

*Included in multiple meta-analyses as multiple methods are reported.
NB: higher insight is reflected by higher scores on some insight measures but lower scores on other insight measures. Note that in the "Association with insight" column, the association with insight is stated and not with the insight *measure* (e.g. positive association: lower volume with lower insight).

Table 6. Clinical characteristics of studies included in meta-analysis on clinical insight and volume regions of interest (ROIs) (k=3).

Study	Diagnosis	Insight measure	Sample size (number of males)	Age	Mean illness duration (years)	Type of medication; mean CPZ equivalents (mg)	PANSS score	In/out patients
(Shad et al., 2004)	DSM-IV diagnosis of schizophrenia (n=30) or schizoaffective disorder (n=5)	Insight item of HDRS	35 (24)	25.76 ± 7.25	2.79 ± 4.25			In
(Sapara et al., 2007)*	DSM-IV diagnosis of schizophrenia	BIS total, BIS 3 subscales, SAI-E total, SAI-E 4 subscales	28 (24)	39 ± 10.51	13.68 ± 10.05	Typical (n=4), atypical (n=23) or both typical and atypical (n=1) antipsychotics	63.11 ±11.47	Out
(Gerretsen et al., 2013)*	DSM-IV-TR diagnosis of schizophrenia	PANSS G12	52 (33)	41.5 ± 14.5	17.0 ± 14.1		43.0 ± 11.6	

*Included in multiple meta-analyses as multiple methods are reported.

Table 7. Methodological characteristics of studies excluded from meta-analysis on clinical insight and volume ROIs (k=6).

Reason exclusion	Study	Sample size & diagnosis	Neuroimaging technique	Field strength scanner	FOV	ROIs	Statistical threshold	Insight measure	Brain measure	Controlled for	Association with insight	Significance
Not enough studies examining sub-dimensions and these ROIs	(Asmal et al., 2018)	92 FES	MRI: cortical thickness	3T	24 frontal ROIs (region)	Superior frontal gyrus, rostral and caudal divisions of the middle frontal gyrus, pars opercularis, pars triangularis, pars orbitalis, lateral and medial divisions of the orbitofrontal cortex, frontal pole, precentral gyrus, rostral and caudal anterior cingulate	$p_{FDR}<.02$	BIS Symptom relabeling	Left and right rostral middle frontal, left caudal anterior cingulate, right superior frontal, and left and right pars triangularis	Age, gender	Positive	Significant
Not enough studies examining sub-dimensions	(Flashman et al., 2001)	15 SZ/ SA	MRI: GM volume	1.5T	16 ROIs (region)	Left and right: frontal pole, superior frontal gyrus, middle	$p_{unc}<.01$	SUMD Unawareness	Bilateral middle frontal gyrus, right gyrus rectus and left	Intracranial volume	Positive	Significant

Reason exclusion	Study	Sample size & diagnosis	Neuroimaging technique	Field strength scanner	FOV	ROIs	Statistical threshold	Insight measure	Brain measure	Controlled for	Association with insight	Significance
and these ROIs						frontal gyrus, inferior frontal gyrus, orbital frontal gyrus, precentral gyrus, gyrus rectus, and anterior cingulate			anterior cingulate cortex			
								SUMD Misattribution	Bilateral superior frontal gyrus	Intracranial volume	Positive	Significant
Longitudinal design	(Parellada et al., 2011)	53 SZ/SF	MRI: GM volume	1.5T	Total GM and GM of 8 ROIs (region)	Left and right frontal, parietal lobe, temporal, and occipital lobe	$p_{unc}<.05$	SUMD total	Positive association between insight at 2 years and GM volume frontal and parietal lobe at baseline	Age	Positive	Significant
ROIs do not overlap with equivalent studies	(Buchy et al., 2010)	54 FEP	MRI: volume	1.5T	8 ROIs (region)	Left and right hippocampus total	$p_{unc}<.05$	SUMD item 1	-	-		Not significant
						Left and right hippocampus	$p_{Bonferroni}<.02$	SUMD item 1	-	-		Not significant

Reason exclusion	Study	Sample size & diagnosis	Neuroimaging technique	Field strength scanner	FOV	ROIs	Statistical threshold	Insight measure	Brain measure	Controlled for	Association with insight	Significance
						head, body and tail						
ROIs do not overlap with equivalent studies	(Palaniyappan et al., 2011)	57 SZ	MRI: GM and WM volume	3T	4 ROIs (region)	GM and WM left and right posterior insula	$p_{Bonferroni-holm}<.05$	Symptoms and Signs in Psychotic Illness scale sub-item	Right posterior insula	Total WM volume and total burden of symptoms	Positive	Significant
								Symptoms and Signs in Psychotic Illness scale sub-item	Left posterior insula	Total area and total burden of symptoms	Positive	Not significant
								Symptoms and Signs in Psychotic Illness scale sub-item	GM left and right posterior insula	Total area and total burden of symptoms		Not significant
Not enough studies on sub-dimensions and these ROIs	(Shad et al., 2006)	14 FES	MRI: GM volume	1.5T	6 ROIs (region)	Left and right: dorsolateral prefrontal cortex, medial and lateral orbitofrontal cortex	$p_{unc}<.05$	SUMD unawareness	Right dorsolateral prefrontal cortex		Positive	Significant
								SUMD misattribution	Right medial orbitofrontal cortex		Negative	Significant

NB: higher insight is reflected by higher scores on some insight measures but lower scores on other insight measures. Note that in the "Association with insight" column, the association with insight is stated and not with the insight *measure* (e.g. positive association: lower volume with lower insight).

Table 8. Clinical characteristics of studies excluded from meta-analysis on clinical insight and volume ROIs (k=6).

Reason exclusion	Study	Diagnosis	Insight measure	Sample size (number of males)	Age	Mean illness duration (years)	Type of medication; mean CPZ equivalents (mg)	PANSS score	In/out patients
Not enough studies examining dimensions and these ROIs	(Asmal et al., 2018)	DSM-IV diagnosis of first-episode psychosis: schizophreniform disorder (n=29), schizophrenia (n=62) or schizoaffective disorder (n=1)	BIS Symptom relabeling	92 (64)	24.68 ± 6.75		None (n=54) or minimally treated (n=38)	92.66 ± 15.28	
Not enough studies examining dimensions and these ROIs	(Flashman et al., 2001)	DSM-IV diagnosis of schizophrenia (n=12) or schizoaffective disorder (n=3)	SUMD unawareness, SUMD misattribution	15 (11)	31.9 ± 11	6.8	All on neuroleptics		13 in, 2 out
Longitudinal design	(Parellada et al., 2011)	DSM-IV diagnosis of schizophrenia (n=44) or schizophreniform disorder (n=9)	SUMD total	52 (39)	15.43 ± 1.95	0.18 ± 0.15		88.26 ± 17.46	
ROIs do not overlap with equivalent studies	(Buchy et al., 2011)[a]	DSM-IV diagnosis of first-episode psychosis: schizophrenia (n=33), schizoaffective	SUMD item 1	54 (43)	23.4 ± 3.7		Atypical (n=48), typical (n=1) or none (n=5); 235.9 ± 277.7		

Reason exclusion	Study	Diagnosis	Insight measure	Sample size (number of males)	Age	Mean illness duration (years)	Type of medication; mean CPZ equivalents (mg)	PANSS score	In/out patients
		disorder (n=8), schizophreniform disorder (n=1), psychosis not otherwise specified (n=6), delusional disorder (n=1), bipolar disorder (n=4) or undetermined (n=1)							
ROIs do not overlap with equivalent studies	(Palaniyappan et al., 2011)	DSM-IV diagnosis of schizophrenia	Symptoms and Signs in Psychotic Illness scale sub-item	57 (50)	26.10 ± 7.49	4.3	All on atypical antipsychotics; 288.7		
Not enough studies on subdimensions and these ROIs	(Shad et al., 2006)	DSM-IV diagnosis of first-episode psychosis	SUMD unawareness, SUMD misattribution	14 (12)	26.23 ± 7.50	2 ± 2.42	None		In

[a]Number of diagnoses, number of men/women, mean age and illness duration are only described for full sample of n=61.

Table 9. Methodological characteristics of studies included in meta-analysis on clinical insight and voxel-based morphometry (VBM) or cortical thickness (k=11).

Study	Sample size & diagnosis	Neuroimaging technique	Field strength scanner	FOV	ROIs	Statistical threshold	Insight measure	Brain measure	Controlled for	Association with insight	Significance
(Ha et al., 2004)	35 SZ	VBM	1.5T	WB	n.a.	p_{unc}<.001 + k>50	PANSS G12	Left posterior cingulate gyrus, right anterior cingulate gyrus, bilateral inferior temporal gyri	Illness duration, age of onset and PANSS scores	Positive	Significant
(Bassitt et al., 2007)*	50 SZ	VBM	1.5T	ROI (coordinate)	Prefrontal cortex including dorsolateral prefrontal cortex, dorsomedial prefrontal cortex, orbitofrontal cortex, anterior cingulate cortex	p_{FWE} <.05 and small-volume correction	SUMD combined awareness and attribution item	Left medial frontal gyrus and adjacent anterior cingulate cortex	Total gray matter	Negative	Significant
(Morgan et al., 2010)*	82 first-onset psychosis	VBM	1.5T	WB	n.a.	$p_{cluster\text{-}mass\ corrected}$<.01	SAI-E total SAI-E Relabeling	n.a.	Age and total gray matter volume Age and total gray		Not significant

Study	Sample size & diagnosis	Neuroimaging technique	Field strength scanner	FOV	ROIs	Statistical threshold	Insight measure	Brain measure	Controlled for	Association with insight	Significance
(Bergé et al., 2011)	21 FEP	VBM		WB	n.a.	p_{unc}<.0001 + k>100	SUMD global items (3)	Bilateral superior medial frontal, left cerebellum 4-5, right inferior frontal operculum, right inferior temporal, right superior frontal, right lingual, right cerebellum crus 2	Age, gender, and GM volume	Positive	Significant
(Raij et al., 2012)*	21 SZ	VBM	3T	WB	n.a.	p_{unc}<.0001 +$_{pFWE\_cluster}$<.05	SUMD total	n.a.	-		Not significant
(Gerretsen et al., 2013)*	52 SZ	VBM	1.5T	3 ROIs (coordinate)	Right frontal lobe, right parietal lobe, right temporal lobe	p_{unc}<.001 + k>20+$_{pFWE}$ <.05	PANSS G12	n.a.	Age, gender, total intracranial volume		Not significant
(McFarland et al., 2013)	Experiment 1: 32 FEP	VBM	1.5T	WB	n.a.	p_{FDR}<.05	SUMD symptom misattribution	Bilateral caudate, left thalamus, right insula, right putamen and cerebellum	-	Negative	Significant
							SUMD Awareness	n.a.	-	n.a.	Not significant
	Experiment 2: 30 SZ	VBM	1.5T	WB	n.a.	p_{FDR}<.05	SUMD Awareness	n.a.	-	n.a.	Not significant

Study	Sample size & diagnosis	Neuroimaging technique	Field strength scanner	FOV	ROIs	Statistical threshold	Insight measure	Brain measure	Controlled for	Association with insight	Significance
							, SUMD Symptom misattribution		-		
							SUMD total	n.a.	-	n.a.	Not significant
(Gerretsen et al., 2015)*	18 SZ/SA	CTh	1.5T	WB	n.a.	$p_{FDR}<.01$	SAI-E subtotal	n.a.	Age, gender	n.a.	Not significant
(Emami et al., 2016)	66 SZ	CTh 2 groups: low insight (SAI-E item 7: 0–2; n=33), and high insight (item 7: 2-4; n = 33)	3T	WB	n.a.	$p_{unc}<.01$		Between-group analysis (high vs low insight): right superior temporal gyrus, parahippocampal gyrus, and insula	Age, gender	Positive	Significant
(Sapara et al., 2016)	40 SZ	VBM	1.5T	WB	n.a.	$p_{unc}<.005$ + $p_{FWE\_cluster}<.05$	BIS total Between group analysis: impaired insight (BIS total minus item 4 ≤ 8)	Between-group analysis (preserved vs impaired insight): bilateral superior temporal gyrus, bilateral precentral gyrus, bilateral inferior frontal gyrus,	Education, IQ	Positive	Significant

Study	Sample size & diagnosis	Neuroimaging technique	Field strength scanner	FOV	ROIs	Statistical threshold	Insight measure	Brain measure	Controlled for	Association with insight	Significance
							versus preserved insight (BIS total minus item 4>13).	right postcentral gyrus, bilateral parahippocampus, left middle frontal gyrus, left middle temporal gyrus, bilateral cuneus, right cerebellum			
(Buchy et al., 2017)	128 FEP	CTh	1.5T	WB	n.a.	p_{unc}<.005	SUMD sum of items 1, 2a and 2b	n.a.	Age, gender, handedness, subcortical brain volume, medication adherence	n.a.	Not significant

*Included in multiple meta-analyses as multiple methods are reported.
NB: higher insight is reflected by higher scores on some insight measures but lower scores on other insight measures. Note that in the "Association with insight" column, the association with insight is stated and not with the insight *measure* (e.g. positive association: lower volume with lower insight).

Table 10. Clinical characteristics of studies included in meta-analysis on clinical insight and voxel-based morphometry (VBM) or cortical thickness (k=11).

Study	Diagnosis	Insight measure	Sample size (number of males)	Age	Mean illness duration (years)	Type of medication; mean CPZ equivalents (mg)	PANSS score	In/out patients
(Ha et al., 2004)	DSM-IV diagnosis of schizophrenia	PANSS G12	35 (21)	27.8 ± 6.2	4.9 ± 3.7	All on atypical antipsychotics: risperidone (n=21), olanzapine (n=9), clozapine (n=3)	75 ± 18.5	In/out
(Bassitt et al., 2007)*	DSM-IV diagnosis of schizophrenia	SUMD combined awareness and attribution item	50 (38)	31.7 ± 7.1	11.4 ± 7.4	All on antipsychotics; typical (n=4), second-generation (n=17), clozapine (n=21), combination of either typical plus second-generation (n=6) or typical plus clozapine (n=2)	59.1 ± 14.4	Out
(Morgan et al., 2010)*	ICD-10 diagnosis of first-onset psychosis: schizophrenia (n=39), schizoaffective disorder (n=6), bipolar disorder (n=17), depressive psychosis (n=10), other psychosis (n=10)	SAI-E total, SAI-E Relabeling of symptoms	80 (50)	27.15 ± 7.58	0.25 ± 0.25	Typical (n=21), atypical (n=19), mixed (n=29) or none (n=13)		In/out
(Bergé et al., 2011)	DSM-IV diagnosis of first-episode psychosis	SUMD global items (3)	21 (12)	24.81 ± 4.3	0.01 ± .01	None	84.43 ± 15.7	In

Study	Diagnosis	Insight measure	Sample size (number of males)	Age	Mean illness duration (years)	Type of medication; mean CPZ equivalents (mg)	PANSS score	In/out patients
(Raij et al., 2012)*	DSM-IV of schizophrenia	SUMD total	21 (15)	27 ± 4	4.08 ± 1.83	559 ± 506	69 ± 9	
(Gerretsen et al., 2013)*	DSM-IV-TR diagnosis of schizophrenia	PANSS G12	52 (33)	41.5 ± 14.5	17.0 ± 14.1		43.0 ± 11.6	
(McFarland et al., 2013)	DSM-IV diagnosis of first-episode psychosis: schizophreniform disorder (n=9), schizophrenia (n=7), delusional disorder (n=2), schizoaffective disorder (n=1), bipolar disorder (n=6), psychosis not otherwise specified (n=3), depression with psychotic features (n=3), brief psychotic episode (n=1)	SUMD symptom misattribution, SUMD unawareness	32 (23)	27.8 ± 7.6	1.23 ± 1.39	None (n=3) or atypical antipsychotics: Olanzapine (n=15), Risperidone (n=3), Quetiapine (n=5), Paliperidone (n=4), Aripiprazole (n=2)	Negative=14.8 ± 5.7; Positive=17.3 ± 3.8; General=32.4 ± 5.9	In/out
	DSM-IV diagnosis of schizophrenia	SUMD symptom misattribution, SUMD unawareness	30 (22)	35.1 ± 8.7	12.08 (5.09)		Negative=15.9 ± 7.9; Positive=14.3 ± 7.9; General=27.4 ± 12.2	In/out
(Gerretsen et al., 2015)*	DSM-IV diagnosis of schizophrenia or schizoaffective disorder	SAI-E subtotal	18 (11)	41.7 ± 12.2	18.9 ± 13.6	Clozapine (n=3), risperidone (n=6), risperidone IM (n=1), quetiapine (n=3), olanzapine (n=3), aripiprazole		In/out

Study	Diagnosis	Insight measure	Sample size (number of males)	Age	Mean illness duration (years)	Type of medication; mean CPZ equivalents (mg)	PANSS score	In/out patients
						(n=3), loxapine (n=1), zuclopenthixol decanoate (n=1), Haldol decanoate (n=1); 346.8 ± 211.1		
(Emami et al., 2016)	DSM-IV diagnosis of schizophrenia	SAI-E item 7	66 (51)	34.94 ± 7.96	12.73 ± 7.49	664.865 ± 664.91		9 in, 57 out
(Sapara et al., 2016)	DSM-IV diagnosis of schizophrenia - with preserved insight	BIS total (excluding item 4)	20 (16)	36.15 ± 10.54	10.25	Atypical (n=18; 9 olanzapine, 5 risperidone, 3 clozapine, 1 quetiapine) or typical (n=2; 1 sulpiride, 1 haloperidol); 461.21 ± 333.95	67.70 ± 14.90	Out
	DSM-IV diagnosis of schizophrenia - with impaired insight	BIS total (excluding item 4)	20 (16)	37.8 ± 7.85	13.95	Atypical (n=13; 7 olanzapine, 3 clozapine, 1 aripiprazole, 1 amisulpride, 1 risperidone) or typical (n=5; 2 flupenthixol, 1 fluphenazine, 1 sulpiride, 1 haloperidol or both (n=2; 1 on clozapine +	66.75 ± 14.02	Out

Study	Diagnosis	Insight measure	Sample size (number of males)	Age	Mean illness duration (years)	Type of medication; mean CPZ equivalents (mg)	PANSS score	In/out patients
						levomepromazine, 1 zuclopenthixol + aripiprazole); 556.63 ± 366.49		
(Buchy et al., 2017)	DSM-IV diagnosis of first-episode psychosis: schizophrenia (n=75), schizophreniform (n=2), schizoaffective disorder (n=13), bipolar disorder I (n=15), bipolar disorder II (n=1), major depression with psychotic features (n=8), delusional disorder (n=3), psychosis not otherwise specified (n=11)	SUMD sum of items 1, 2a and 2b	128 (90)	24.2 ± 4	5.9 ± 5.1	804.9 ± 4.3		

*Included in multiple meta-analyses as multiple methods are reported.

Table 11. Methodological characteristics of studies excluded from meta-analysis on clinical insight and voxel-based morphometry (VBM) or cortical thickness (k=4).

Reason exclusion	Study	Sample size & diagnosis	Neuroimaging technique	Field strength scanner	FOV	ROIs	Statistical threshold	Insight measure	Brain measure	Controlled for	Association with insight	Significance
Sample overlap with (Buchy et al., 2017)	(Buchy et al., 2011)	79 FEP	VBM	1.5T	WB	n.a.	p_{FDR}<.05	SUMD items 1 and 2 (items 2a+2b)		-	n.a.	Not significant
			CTh	1.5T	WB	n.a.	p_{FDR}<.05	SUMD item 1 (Awareness of illness)	Left middle frontal gyrus, left inferior frontal gyrus, bilateral precentral gyrus, left inferior temporal gyrus, and right inferior occipital gyrus	-	Positive	Significant
								SUMD items 2a+2b (Awareness of treatment need and efficacy)	Left middle frontal gyrus, left medial frontal gyrus, left rectal gyrus, bilateral precuneus, left paracentral lobule, bilateral supramarginal gyrus, bilateral superior temporal gyrus, left middle temporal gyrus, left inferior temporal gyrus, bilateral parahippocampal gyrus, left middle	-	Positive	Significant

Reason exclusion	Study	Sample size & diagnosis	Neuroim aging technique	Field strength scanner	FOV	ROIs	Statistical threshold	Insight measure	Brain measure	Controlled for	Association with insight	Significance
									occipital gyrus, right inferior frontal gyrus, right superior parietal lobule, right paracentral lobule, right fusiform gyrus and right lingual gyrus			
Differentiates between attribution of different types of symptoms and compares brain areas	(Buchy et al., 2012)	52 FEP	CTh	1.5T	WB	n.a.	$p_{FDR}<.05$	SUMD item 3b (attribution of hallucinations)	Left: inferior temporal gyrus, middle occipital gyrus, precentral gyrus, cingulate gyrus, parahippocampal gyrus	-	Positive	Significant
								SUMD item 3b (attribution of hallucinations)	Right: middle temporal gyrus, superior temporal gyrus, inferior parietal lobule, superior temporal gyrus/angular gyrus/middle temporal gyrus, inferior temporal gyrus, cingulate gyrus, parahippocampal gyrus/uncus	-	Negative	Significant

Reason exclusion	Study	Sample size & diagnosis	Neuroim aging technique	Field strength scanner	FOV	ROIs	Statistical threshold	Insight measure	Brain measure	Controlled for	Association with insight	Significance
							SUMD item 4b (attribution of delusions)	Left: middle frontal gyrus, inferior frontal gyrus	-	Positive	Significant	
							SUMD item 4b (attribution of delusions)	Left: precentral gyrus, cingulate gyrus, postcentral gyrus, inferior parietal lobule, superior temporal gyrus, inferior temporal gyrus, middle temporal gyrus, superior and medial frontal gyri, uncus, orbital gyrus, middle frontal gyrus, inferior frontal gyrus Right: middle frontal gyrus, superior frontal gyrus, precentral gyrus, postcentral gyrus/inferior parietal lobule, superior temporal gyrus, angular gyrus/inferior parietal lobule/precuneus, middle temporal gyrus, orbital gyrus, medial frontal gyrus,	-	Negative	Significant	

Reason exclusion	Study	Sample size & diagnosis	Neuroim aging technique	Field strength scanner	FOV	ROIs	Statistical threshold	Insight measure	Brain measure	Controlled for insight	Association with	Significance
									cingulate gyrus, cuneus, precuneus/cingulate gyrus, superior frontal gyrus			
								SUMD item 5b (attribution of flat affect)	Left: superior and middle frontal gyri/precuneus, inferior frontal gyrus, precentral gyrus, inferior temporal gyrus, middle occipital gyrus, postcentral gyrus/superior parietal lobule, paracentral lobule/cingulate gyrus/superior and medial frontal gyri/postcentral gyrus, parahippocampal gyrus	-	Positive	Significant
								SUMD item 5b (attribution of flat affect)	Right: superior, middle and medial frontal gyri/precentral gyrus/paracentral lobule, cuneus	-	Negative	Significant

Reason exclusion	Study	Sample size & diagnosis	Neuroim aging technique	Field strength scanner	FOV	ROIs	Statistical threshold	Insight measure	Brain measure	Controlled for	Association with insight	Significance
								SUMD item 6b (attribution of asociality)	Left: superior frontal gyrus, inferior frontal gyrus, middle frontal gyrus, inferior parietal lobule, parahippocampal gyrus. Right: precentral gyrus.	-	Positive	Significant
								SUMD item 6b (attribution of asociality)	Right: anterior cingulate, superior temporal gyrus	-	Negative	Significant
Not enough studies examining sub-dimensions	(Cooke et al., 2008)*	52 SZ /SA	VBM	1.5T	WB	n.a.	p_{unc}<.001 + small-volume correction + p_{FWE}<.05)	SAI-E+BIS Awareness of Problems	Left precuneus	Total GM volume	Positive	Significant
								SAI-E + BIS Symptom Relabeling	Right superior temporal gyrus	Total GM volume	Positive	Significant
								SAI-E+BIS Awareness of and Attribution to Illness	Left superior temporal gyrus, left middle temporal gyrus, right inferior temporal gyrus, right intraparietal lobule, right supramarginal gyrus	Total GM volume	Positive	Significant
								SAI-E + BIS Recognition of the Need for Medication		Total GM volume		Not significant

Reason exclusion	Study	Sample size & diagnosis	Neuroim aging technique	Field strength scanner	FOV	ROIs	Statistical threshold	Insight measure	Brain measure	Controlled for	Association with insight	Significance
Metacognitive insight	(Spalletta et al., 2014)	57 SZ	VBM	3T	WB	n.a.	$p_{FWE}<.05$	Insight scale	GM: pars orbitalis and triangularis of the left inferior frontal gyrus, right middle frontal gyrus, bilateral precentral gyri, bilateral putamen, right insula	Age and years of education	Positive	Significant
									WM: bilateral cingulum, left anterior and superior corona radiata, right superior longitudinal fasciculus, left portion of the callosal forceps minor	Age and years of education	Positive	Significant

*Included in multiple meta-analyses as multiple methods are reported.
NB: higher insight is reflected by higher scores on some insight measures but lower scores on other insight measures. Note that in the "Association with insight" column, the association with insight is stated and not with the insight *measure* (e.g. positive association: lower volume with lower insight).

Table 12. Clinical characteristics of studies excluded from meta-analysis on clinical insight and voxel-based morphometry (VBM) or cortical thickness (k=4).

Reason exclusion	Study	Diagnosis	Insight measure	Sample size (number of males)	Age	Mean illness duration (years)	Type of medication; mean CPZ equivalents (mg)	PANSS score	In/out patients
Sample overlap with (Buchy et al., 2017)	(Buchy et al., 2011)	DSM-IV diagnosis of first-episode psychosis: schizophrenia (n=44), schizoaffective disorder (n=12), schizophreniform disorder (n=2), psychosis not otherwise specified (n=9), bipolar disorder (n=8), major depression with psychotic features (n=3) or undetermined (n=1)	SUMD items 1 and 2 (items 2a+2b)	79 (57)	23.3 ± 3.7		292.1 ± 356.4	Negative=13.6 ± 5.0; Positive=12.3 ± 5.3; General=26.6 ± 7.1	In/out
Differentiates between attribution of different types of symptoms and compares brain areas	(Buchy et al., 2012)	DSM-IV diagnosis of first-episode psychosis: schizophrenia (n=30), schizoaffective disorder (n=9), schizophreniform disorder (n=1), psychosis not otherwise specified (n=6), bipolar disorder (n=4), major depression with psychotic features (n=2)	SUMD items 3b, 4b, 5b, 6b	52 (40)	23.2 ± 3.8		Risperidone (n=23), Olanzapine (n=14), Clozapine (n=2), Seroquel (n=6), Ziprasidone (n=1), Paliperidone (n=4), Seroquel XR (n=1); 310.9 ± 405.4		
Not enough studies examining subdimensions	(Cooke et al., 2008)*	47 SZ, 5 SA (total n=52; DSM-IV)	Combined BIS+SAI-E	40/12	38.35 ± 9.89	13.9 ± 9.6	Atypical (n=42) or typical antipsychotics (n=10)	66.2 ± 13.7	Out
Metacognitive insight	(Spalletta et al., 2014)	57 SZ (DSM-IV-TR)	Insight scale	42/15	37.2 ± 11.4	11.3 ± 9.1	All on stable oral doses of one or more atypical	Negative=19.0 ± 6.0; Positive=22.3 ± 6.5;	Out

Reason exclusion	Study	Diagnosis	Insight measure	Sample size (number of males)	Age	Mean illness duration (years)	Type of medication; mean CPZ equivalents (mg)	PANSS score	In/out patients
							antipsychotic drug; 22.5 ± 40.1	General=44.8 ± 10.6	

Table 13. Methodological characteristics of studies included in meta-analysis on clinical insight and functional magnetic resonance imaging (fMRI) (k=5).

Study	Sample size & diagnosis	Neuroimaging technique	Field strength scanner	FOV	ROIs	Statistical threshold	Insight measure	Brain measure	Controlled for	Association with insight	Significance
(Bedford et al., 2012)	11 SZ	fMRI self-evaluation task with positive/negative traits and mental/physical illness terms Contrast: self vs other	1.5T	ROI (Coordinate)	Regions identified as potentially relevant to self-evaluation in patients versus controls	$p_{cluster\_mass\_corrected}$<.01	SAI-E Awareness of illness	Left superior frontal gyrus	-	Positive	Significant
							SAI-E total	Left superior frontal gyrus	-	Positive	Not significant
							SAI-E total	Right middle frontal gyrus	-	Negative	Significant
							SAI-E total	Bilateral precuneus	-	Negative	Significant
(van der Meer et al., 2013)	47 SZ	fMRI self-reflection task Contrast: self-reflection >semantic	3T	ROI (Coordinate)	Medial prefrontal cortex, insula, intraparietal lobule, posterior cingulate cortex	p_{unc}< .001 + k>10	SAI-E subtotal	Left inferior frontal gyrus, left anterior insula, and left inferior parietal lobule	-	Positive	Significant
							SAI-E Awareness	Left inferior frontal gyrus, left anterior insula, and left inferior parietal lobule	-	Positive	Significant
							SAI-E Relabeling	Left inferior frontal gyrus, left anterior insula, and left	-	Positive	Significant

Study	Sample size & diagnosis	Neuroimaging technique	Field strength scanner	FOV	ROIs	Statistical threshold	Insight measure	Brain measure	Controlled for	Association with insight	Significance
								inferior parietal lobule			
							SAI-E Need for treatment	n.a.	-		Not significant
(Sapara et al., 2014)[a]	32 SZ	fMRI parametric 'n-back' task Between groups: preserved insight (BIS ≥13) vs poor insight (BIS ≤8) Contrast: 2back > rest	1.5T	WB	n.a.	p_{unc}<.005		Between-group (preserved > poor insight): precuneus	-	Positive	Significant
						p_{unc} <.005 + $_{pFWE\_cluster}$< .05		Between-group (preserved > poor insight): cerebellum	-	Positive	Significant
(Gerretsen et al., 2015)*	18 SZ/SA	fMRI illness denial task based on SAI-E Contrast: total	1.5T	ROIs (Coordinate)	Medial prefrontal cortex, dorsolateral prefrontal cortex, insula, anterior	$p_{FWE\_cluster}$ <.05	SAI-E subtotal	Left temporoparieto-occipital junction	Positive symptoms (SAPS total)	Negative	Significant

Study	Sample size & diagnosis	Neuroimaging technique	Field strength scanner	FOV	ROIs	Statistical threshold	Insight measure	Brain measure	Controlled for	Association with insight	Significance
		awareness vs neutral			temporal lobe, and temporo-parieto-occipital junction						
(Sapara et al., 2015)[a]	26 SZ	fMRI task verbal self-monitoring Between groups: preserved insight (BIS ≥13) vs poor insight (BIS ≤8) Contrast: other (=monitoring someone else's voice as non-self)	1.5T	WB	n.a.	p_{unc}<.05 + BIS total $p_{FWE\_cluster}$ <.05	Between-group (preserved > poor insight): left putamen, caudate, insula, inferior frontal gyrus	-		Positive	Significant

*Included in multiple meta-analyses as multiple methods are reported.

[a]19 patients (9 with poor insight and 10 with preserved insight) that were included in Sapara et al. (2015) were also included in Sapara et al. (2014).

NB: higher insight is reflected by higher scores on some insight measures but lower scores on other insight measures. Note that in the "Association with insight" column, the association with insight is stated and not with the insight *measure* (e.g. positive association: lower volume with lower insight).

Table 14. Clinical characteristics of studies included in meta-analysis on clinical insight and functional MRI (k=5).

Study	Diagnosis	Insight measure	Sample size (number of males)	Age	Mean illness duration (years)	Type of medication; mean CPZ equivalents (mg)	PANSS score	In/out patients
(Bedford et al., 2012)	DSM-IV-TR diagnosis of schizophrenia	SAI-E awareness of illness, SAI-E total	11 (7)	39 ± 11	12 ± 8	Mainly atypical anti-psychotics	82.0 ± 16.4	4 in 7 out
(van der Meer et al., 2013)	DSM-IV diagnosis of schizophrenia	SAI-E subtotal, SAI-E Awareness, SAI-E Relabeling, SAI-E Need for treatment	47 (35)	34.3 ± 10.7		Olanzapine (n=14), Aripiprazole (n=14), Clozapine (n=10), Quetiapine (n=7), Risperidone (n=2), Haloperidol (n=1), Perfenazine (n=1), Pemozide (n=1), none (n=2) or unknown (n=4)	58.0 ± 13.4	In/out
(Sapara et al., 2014)[a]	DSM-IV diagnosis of schizophrenia - with preserved insight	BIS excluding item 4	18 (14)	35.3 ± 9.92	10.35	459.93 ± 363.67	66.50 ± 11.91	Out
	DSM-IV diagnosis of schizophrenia - with poor insight	BIS excluding item 4	14 (9)	37.7	15.34	497.07 ± 348.63	67.29 ± 14.53	Out

Study	Diagnosis	Insight measure	Sample size (number of males)	Age	Mean illness duration (years)	Type of medication; mean CPZ equivalents (mg)	PANSS score	In/out patients
(Gerretsen et al., 2015)*	DSM-IV diagnosis of schizophrenia or schizoaffective disorder	SAI-E subtotal	18 (11)	41.7 ± 12.2	18.9 ± 13.6	Clozapine (n=3), risperidone (n=6), risperidone IM (n=1), quetiapine (n=3), olanzapine (n=3), aripiprazole (n=3), loxapine (n=1), zuclopenthixol decanoate (n=1), Haldol decanoate (n=1); 346.8 ± 211.1		In/out
(Sapara et al., 2015)[a]	DSM-IV diagnosis of schizophrenia - with preserved insight	BIS total excluding item 4	13 (11)	31.15 ± 9.77	9.92 ± 7.22	Atypical (n=10), typical (n=1) or both (n=2); 467.08 ± 400.46	71.92 ± 15.87	Out
	DSM-IV diagnosis of schizophrenia - with poor insight		13 (9)	37.85 ± 7.43	15.15 ± 9.64	Atypical (n=7), typical (n=4) or both (n=2); 623.80 ± 392.59	64.69 ± 16.11	

*Included in multiple meta-analyses as multiple methods are reported.
[a]19 patients (9 with poor insight and 10 with preserved insight) that were included in Sapara et al. (2015) were also included in Sapara et al. (2014).

Table 15. Methodological characteristics of studies excluded from meta-analysis on clinical insight and functional MRI (k=3).

Reason exclusion	Study	Sample size & diagnosis	Neuroimaging technique	Field strength scanner	FOV	ROIs	Statistical threshold	Insight measure	Brain measure	Controlled for	Association with insight	Significance
Repeated measurements design	(Lee et al., 2006)	14 SZ	fMRI social cognition task involving empathic and forgivability judgments	1.5T	WB	n.a.	p_{unc}<.005	SAI total	After recovery from the acute episode, patients exhibited increased activation in the left medial prefrontal cortex, which was, in turn, significantly correlated with improved insight and social functioning	-	Positive	Significant

Reason exclusion	Study	Sample size & diagnosis	Neuroimaging technique	Field strength scanner	FOV	ROIs	Statistical threshold	Insight measure	Brain measure	Controlled for	Association with insight	Significance
Did not assess insight with a validated measure	(Raij et al., 2012)	21 SZ	fMRI insight task	3T	ROI (Coordinate)	Medial pre-frontal cortex	$P_{corr} < 0.005$	n.a.	Sch(schizophrenia)>rest contrast: Sch-evaluation scores (insight) and left posterior cingulate cortex and bilateral medial prefrontal cortex	Dis-organization, delusions, depression scores, and WAIS similarities	Positive	Significant
									Sch>cc (common cold) contrast: Sch-evaluation scores (insight) with the right frontopolar cortex	Dis-organization, delusions, depression scores, and WAIS similarities	Positive	Significant
Not enough studies examining subdimensions	(Shad and Keshavan, 2015)	17 SZ	fMRI self-awareness task (self- versus other-	3T	WB	n.a.	$p_{FWE\_cluster} <.05$	SUMD Awareness	Left frontal inferior operculum, right precuneus,	-	Negative	Significant

Reason exclusion diagnosis	Study	Sample size & scanner	Neuroimaging technique	Field strength	FOV	ROIs	Statistical threshold	Insight measure	Brain measure	Controlled for	Association with insight	Significance
			referential stimuli) Contrast: self>other						left lingual gyrus, left inferior parietal lobule			
								SUMD Mis-attribution	Left frontal inferior triangle, right putamen and left lingual gyrus	-	Negative	Significant

NB: higher insight is reflected by higher scores on some insight measures but lower scores on other insight measures. Note that in the "Association with insight" column, the association with insight is stated and not with the insight *measure* (e.g. positive association: lower volume with lower insight).

Table 16. Clinical characteristics of studies excluded from meta-analysis on clinical insight and functional MRI (k=3).

Reason exclusion	Study	Diagnosis	Insight measure	Sample size (number of males)	Age	Mean illness duration (years)	Type of medication; mean CPZ equivalents (mg)	PANSS score	In/out patients
Repeated measurements design	(Lee et al., 2006)	DSM-IV diagnosis of schizophrenia	SAI total	14 (13)	31.7 ± 7.3)	9.8 ± 5.4)	First scan: atypical (clozapine [n=4], olanzapine [n=4], or risperidone [n=1]), or typical antipsychotics (n=5); 354.3 ± 200.4. Second scan: same as first scan, except for one patient was switched from a depot typical antipsychotic to an oral atypical antipsychotic (clozapine) between the first and second scans; 406.4 ± 205.6		In
Did not use validated measure of insight	(Raij et al., 2012)	DSM-IV diagnosis of schizophrenia		21 (15)	27 ± 4	4.08 ± 1.83	559 ± 506	69 ± 9	
Not enough studies examining subdimensions	(Shad and Keshavan, 2015)	DSM-IV diagnosis of schizophrenia	SUMD unawareness, SUMD misattribution	17 (14)	40.0 ± 10.3	17.88 ± 5.63	346.3 ± 234.0	64.76 ± 14.67)	

Table 17. Methodological characteristics of studied excluded from meta-analysis on cognitive insight and volume ROIs (k=3).

Reason exclusion	Study	Sample size & diagnosis	Neuroimaging technique	Field strength scanner	FOV	ROIs	Statistical threshold	Insight measure	Brain measure	Controlled for	Association with insight	Significance
Not enough studies	(Buchy et al., 2010)*	61 FEP	MRI: volume	1.5T	8 ROIs (region)	Left and right total hippocampus, left and right hippocampal head, body and tail	p_{unc}<.05	BCIS composite index	Left hippo-campus	-	Positive	Significant
								BCIS SC	Left and right total hippo-campus	-	Negative	Significant
								BCIS SR		-		Not significant
Not enough studies	(Buchy et al., 2016)	15 FEP	MRI: volume	3T	12 ROIs (region)	Left and right: presubiculum, CA1, CA2/3, fimbria, subiculum, CA4/Dentate gyrus, hippocampal fissure, and hippocampus	p_{unc}<.001	BCIS SR, BCIS SC		Age, intracranial volume		Not significant
Not enough studies	(Orfei et al., 2017)	45 SZ	MRI: volume	3T	9 ROIs hippo-campus (region)	right CA1, fimbria, hippocampal fissure, presubiculum, hippocampus and left fimbria, fissure,	p_{unc}<.05	BCIS SC	SC and left hippo-campus presubiculum	Age, gender and olanzapine equivalents	Negative**	Significant
								BCIS SR				Not significant

Reason exclusion	Study	Sample size & diagnosis	Neuroimaging technique	Field strength scanner	FOV	ROIs	Statistical threshold	Insight measure	Brain measure	Controlled for	Association with insight	Significance
						presubiculum and hippocampus						

*Included in multiple meta-analyses as multiple methods are reported.

**NB: note that poor cognitive insight is reflected by lower BCIS composite index and self-reflectiveness scores, and higher self-certainty scores.

Table 18. Clinical characteristics of studied excluded from meta-analysis on cognitive insight and volume ROIs (k=3).

Study	Diagnosis	Insight measure	Sample size (number of males)	Age	Mean illness duration (years)	Type of medication; mean CPZ equivalents (mg)	PANSS score	In/out patients	Reason exclusion
(Buchy et al., 2010)*	DSM-IV diagnosis of first-episode psychosis: schizophrenia (n=37), schizoaffective disorder (n=9), schizophreniform disorder (n=1), psychosis not otherwise specified (n=7), delusional disorder (n=1), bipolar disorder (n=5), undetermined (n=1)	BCIS composite index, BCIS SR, BCIS SC	61 (43)	23.4 ± 3.7		Atypical (n = 54), typical (n=1) or none (n=6); 235.9 ± 277.7	Negative=13.5 ± 4.8; Positive=12.1 ± 5.2		Not enough studies
(Buchy et al., 2016)	Diagnosis of first-episode psychosis: schizophrenia (n=10), psychosis not otherwise specified (n=3), brief psychotic disorder (n=1) and delusional disorder (n=1)	BCIS SR, BCIS SC	15 (13)	22.7 ± 2.6		None (n=3); 234.1 ± 320.8	Negative=12.6 ± 3.5; Positive=14.7 ± 7.5		Not enough studies
(Orfei et al., 2017)	DSM-IV-TR diagnosis of schizophrenia	BCIS	45 (30)	40.1 ± 11.5	13.6 ± 11.2	All on one or more atypical antipsychotics	Negative=18.1 ± 6.2; Positive=22.0 ± 5.6; General=43.6 ± 10.4.	Out	Not enough studies

*Included in multiple meta-analyses as multiple methods are reported.

Table 19. Methodological characteristics of studied excluded from meta-analysis on cognitive insight and voxel-based morphometry or cortical thickness (k=3).

Reason exclusion	Study	Sample size & diagnosis	Neuro-imaging technique	Field strength scanner	FOV	ROIs	Statistical threshold	Insight measure	Brain measure	Controlled for	Association with insight	Significance
Not enough studies	(Orfei et al., 2013)	45 SZ	VBM	3T	WB	n.a.	p_{FWE}<.05	BCIS SR	Right VLPFC	Age and years of education	Positive	Significant
								BCIS composite index		Age and years of education		Not significant
								BCIS SC		Age and years of education		Not significant
MNI coordinates unavailable and sample overlap with (Buchy et al., 2016)	(Buchy et al., 2016)*	15 FEP	CTh	3T	WB	n.a.	p_{FDR}<.01	BCIS SR	Bilateral: inferior parietal, superior frontal gyrus. Left: lateral occipital, insula, rostral middle frontal gyrus, supramarginal gyrus, postcentral gyrus, posterior cingulate, superior parietal. Right: pars opercularis, superior temporal gyrus, precuneus, caudal middle frontal gyrus, inferior temporal gyrus, entorhinal cortex, medial orbitofrontal gyrus,	Age, intracranial volume	Positive	Significant

Reason exclusion	Study	Sample size & diagnosis	Neuro-imaging technique	Field strength scanner	FOV	ROIs	Statistical threshold	Insight measure	Brain measure	Controlled for	Association with insight	Significance
									superior temporal sulcus.			
								BCIS SC	Bilateral: parahippocampal gyrus, inferior temporal, middle temporal gyrus, superior frontal gyrus, middle temporal sulcus, supramarginal gyrus, superior parietal, superior temporal sulcus, inferior parietal, cuneus, posterior cingulate, fusiform gyrus, superior frontal sulcus, Left: pars orbitalis, precuneus, lateral occipital, medial orbitofrontal, superior parietal, precentral sulcus, transverse temporal. Right: pars opercularis, pars triangularis, rostral middle frontal, precuneus,	Age, intracranial volume	Negative**	Significant

Reason exclusion	Study	Sample size & diagnosis	Neuro-imaging technique	Field strength scanner	FOV	ROIs	Statistical threshold	Insight measure	Brain measure	Controlled for	Association with insight	Significance
									paracentral gyrus, rostral middle frontal.			
MNI coordinates unavailable and sample overlap with (Buchy et al., 2016)	(Buchy et al., 2018)	130 FEP	CTh	3T	WB	n.a.	Random field-theory corrected p	BCIS SR	Right occipital lobe	Age, sex, handedness, total subcortical volume, SAPS Delusions	Negative	Significant
								BCIS SC	n.a.	Age, sex, handedness, total subcortical volume, SAPS Delusions	n.a.	Not significant

*Included in multiple meta-analyses as multiple methods are reported.
**NB: note that poor cognitive insight is reflected by lower BCIS composite index and self-reflectiveness scores, and higher self-certainty scores.

Table 20. Clinical characteristics of studied excluded from meta-analysis on cognitive insight and voxel-based morphometry or cortical thickness (k=3).

Reason exclusion	Study	Diagnosis	Insight measure	Sample size (number of males)	Age	Mean illness duration (years)	Type of medication; mean CPZ equivalents (mg)	PANSS score	In/out patients
Not enough studies	(Orfei et al., 2013)	DSM-IV-TR diagnosis of schizophrenia	BCIS composite index, BCIS SR, BCIS SC	45 (29)	38.8 ± 11.4	12.4 ± 9.7	All on atypical antipsychotics; 17.5 ± 21.5	Negative=19.0 ± 6.6; Positive=22.9 ± 6.3; General=47.3 ± 10.7	Out
Not enough studies	(Buchy et al., 2016)	Diagnosis of first-episode psychosis: schizophrenia (n=10), psychosis not otherwise specified (n=3), brief psychotic disorder (n=1) and delusional disorder (n=1	BCIS SR, BCIS SC	15 (13)	22.7 (2.6)		On medication (n=12); None (n=3); 234.1 (320.8)	Negative=12.6 ± 3.5; Positive=14.7 ± 7.5	
MNI coordinates unavailable and sample overlap with (Buchy et al., 2016)	(Buchy et al., 2018)	DSM-IV diagnosis of first-episode psychosis: schizophrenia (n=78), schizophreniform disorder (n=2), schizoaffective disorder (n=13), bipolar disorder I (n=14), bipolar disorder II (n=1), major depression with psychotic features (n=8), delusional disorder (n=3), psychosis not otherwise specified (n=11)	BCIS SR, BCIS SC	130 (93)	24.1 ± 4.1	5.8 ± 5.1		792.7 ± 772.6	

Table 21. Methodological characteristics of studied excluded from meta-analysis on cognitive insight and functional MRI (k=5).

Reason exclusion	Study	Sample size & diagnosis	Neuro-imaging technique	Field strength scanner	FOV	ROIs	Statistical threshold	Insight measure	Brain measure	Con-trolled for	Asso-ciation with insight	Significance
Sample: healthy individuals	(Buchy et al., 2014)	22 healthy controls	fMRI external source memory 2 contrasts: person > object and place > object		WB	n.a.	$p_{FDR\_cluster}$< .05	BCIS SR	Person > object contrast: SR and right VLPFC	-	Positive	Significant
								BCIS SC	Person > object contrast: SC and midbrain	-	Positive **	Significant
Not enough studies	(van der Meer et al., 2013)	47 SZ	fMRI self-reflection task Contrast: self-reflection > semantic	3T	ROIs (coordinate)	Medial prefrontal cortex insula, intraparietal lobule and posterior cingulate cortex	p_{unc}<.001 + k>10	BCIS SR	Bilateral ventromedial prefrontal cortex	-	Positive	Significant
								BCIS SC	n.a.	-		Not significant
								BCIS composite index	n.a.	-		Not significant
Not enough studies	(Pu et al., 2013)	30 SZ	52-channel NIRS verbal fluency task	n.a.	ROIs (coordinate)	prefrontal and temporal cortical regions	p_{FDR}<.05	BCIS composite index	n.a.	-		Not significant
								BCIS SR	Bilateral supplementary motor area, pars opercularis, pars triangularis, superior temporal gyrus,	-	Positive	Significant

Reason exclusion	Study	Sample size & diagnosis	Neuro-imaging technique	Field strength scanner	FOV	ROIs	Statistical threshold	Insight measure	Brain measure	Con-trolled for	Asso-ciation with insight	Significance
									middle temporal gyrus, supramarginal gyrus			
								BCIS SC	n.a.	-		Not significant
Not enough studies	(Buchy et al., 2015)	25 FES	fMRI task novel virtual reality paradigm (external source memory) 2 Contrasts: place > object and person > object	3T	ROI (coordinate)	Bilateral ventrolateral prefrontal cortex	p_{unc}<0.05 + k>20	BCIS SR	Contrast place>object: bilateral ventrolateral prefrontal cortex	-	Positive	Significant
								BCIS SC		-		Not significant
Not enough studies	(Lee et al., 2015)	20 SZ	fMRI task reality evaluation and recognition 2 contrasts: reality evaluation unreal>real	3T	WB	n.a.	p_{FWE}<.05	BCIS composite index score, BCIS SR	Reality evaluation unreal vs real: BCIS composite index score and left dorsolateral prefrontal cortex	-	Positive	Significant
									Reality evaluation unreal vs real:	-	Negative	Significant

Reason exclusion	Study	Sample size & diagnosis	Neuro-imaging technique	Field strength scanner	FOV	ROIs	Statistical threshold	Insight measure	Brain measure	Con-trolled for	Asso-ciation with insight	Significance
			and recognition unreal>real						BCIS composite index score or BCIS SR and left parahippocampal gyrus			
									Recognition unreal vs real: BCIS composite index score and right posterior cingulate cortex	-	Positive	Significant
									Recognition unreal vs real: BCIS composite index score and right inferior parietal lobule	-	Positive	Significant

**NB: note that poor cognitive insight is reflected by lower BCIS composite index and self-reflectiveness scores, and higher self-certainty scores.

Table 22. Clinical characteristics of studied excluded from meta-analysis on cognitive insight and functional MRI (k=5).

Reason exclusion	Study	Diagnosis	Insight measure	Sample size (number of males)	Age	Mean illness duration (years)	Type of medication; mean CPZ equivalents (mg)	PANSS score	In/out patients
Healthy individuals	(Buchy et al., 2014)	n.a.	BCIS SR, BCIS SC	23 (18)	24.4 ± 3.9	n.a.	n.a.	n.a.	n.a.
Not enough studies	(van der Meer et al., 2013)	DSM-IV diagnosis of schizophrenia	SAI-E subtotal, SAI-E Awareness, SAI-E Relabeling, SAI-E Need for treatment	47 (35)	34.3 ± 10.7		Olanzapine (n=14), Aripiprazole (n=14), Clozapine (n=10), Quetiapine (n=7), Risperidone (n=2), Haloperidol (n=1), Perfenazine (n=1), Pemozide (n=1), none (n=2) or unknown (n=4)	58.0 ± 13.4	In/out
Not enough studies	(Pu et al., 2013)	DSM-IV-TR diagnosis of schizophrenia	BCIS composite index, BCIS SR, BCIS SC	30 (21)	32.1 ± 10.47	10.5 ± 8.20	Olanzapine (n=9), aripiprazole (n=9), blonanserin (n=6), risperidone (n=2), perospirone (n=2), quetiapine (n=2); 513.4 ± 362.98	62.6 ± 16.60	Out
Not enough studies	(Buchy et al., 2015)	DSM-IV diagnosis of first-episode psychosis	BCIS SR	25 (20)	24.4 ± 4.1	1.4 ± 1.4			In/out
Not enough studies	(Lee et al., 2015)	DSM-IV diagnosis of schizophrenia	BCIS composite index, BCIS SR	20 (10)	37.1 ± 6.5	11.6 ± 5.1	All on medication; 399.6 ± 291.9	Negative=13.0 ± 4.7; Positive=12.4 ± 4.6; General=27.1 ± 7.6.	Out