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Review article

Adhesio interthalamica alterations in schizophrenia spectrum disorders: A systematic review and meta-analysis

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ABSTRACT

Magnetic resonance imaging (MRI) studies have reported a variety of brain abnormalities in association with schizophrenia. These include a higher prevalence of an absent adhesio interthalamica (AI; also known massa intermedia), a gray matter junction that is present between the two thalami in approximately 80% of healthy subjects. In this meta-analytic review, we describe and discuss the main AI MRI findings in schizophrenia spectrum disorders (SSDs) to date. The MEDLINE and ISI Web of Knowledge[SM] databases were searched up to December 2010, for studies that used MRI to assess AI in patients with SSD and controls. From fourteen potential reports, eleven were eligible to be part of the current review. These studies included 822 patients with SSD and 718 healthy volunteers. There was a large degree of variability in the MRI methods they employed. Patients with SSD had a higher prevalence of absent AI than healthy volunteers (odds ratio = 1.98; 95% confidence interval 1.33–2.94; $p = 0.0008$). This association was evident in both male and female SSD subjects, and there was no evidence that the prevalence was related to age or duration of illness. The significance of the absence of an AI for SSD may be clarified by studies in large, longitudinal community-based samples using standardized methods.

Contents

Abbreviations: AI, Adhesio interthalamica; BDNF, Brain-derived neurotrophic factor; MRI, Magnetic resonance imaging; SANS, Scale for the Assessment of Negative Symptoms; SSD, Schizophrenia spectrum disorder; SPD, Schizotypal personality disorder.

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1. Introduction

Despite more than a century of research, the etiology of schizophrenia remains unknown. It is supposed, however, that the interaction between environmental and biological (i.e., genetic, biochemical, physiological and developmental) factors is fundamental to the aetiology of the disorder. The neurodevelopmental model of schizophrenia posits that the disorder is the behavioral outcome of an aberration in neurodevelopmental processes that begins long before the onset of clinical symptoms, and is caused by a combination of environmental and genetic factors (Murray and Lewis, 1987; Weinberger, 1987). Several post-mortem and neuroimaging studies support this hypothesis by demonstrating that many patients with schizophrenia show signs of altered brain development, such as agenesis of the corpus callosum and arachnoid cysts (Hallak et al., 2007; Kuloglu et al., 2008). In addition, rats with early neurodevelopmental lesions display aberrant behavior during adolescence (Brown and Derkits, 2010; Wilson and Terry, 2010). In recent years, longitudinal brain imaging studies of both early- and adult-onset schizophrenia spectrum disorder (SSD) populations indicate that there are progressive brain changes, particularly in adolescence, that appear to be an exaggeration of the normal developmental pattern (Pantelis et al., 2005). For example, a recent meta-analysis has confirmed the finding of progression of lateral ventricular volume enlargement in patients with schizophrenia (Kempton et al., 2010).

The adhesio interthalamica (AI), or massa intermedia, is a midline structure connecting the medial borders of both thalami across the third ventricle, which usually fuse between the 13th and 14th weeks of gestation (see Fig. 1; Rosales et al., 1968). It contains several nuclei and is normally well developed in mammals (Snyder et al., 1998). However, *post mortem* studies have shown that the AI is absent in approximately 15–25% of healthy humans (Samra and Cooper, 1968), and seems to be more frequently absent in males than females (Allen and Gorski, 1991; Malobabić et al., 1987; Samra and Cooper, 1968). The absence of the AI may be related to neurodevelopmental alterations in the growing process of surrounding structures during early gestation, a period in which other developmental risk factors for schizophrenia, such as maternal viral infection (Wright et al., 1995) or malnutrition (Susser et al., 1998), reportedly have their effect on the susceptibility for the disorder.

Even though the functional relevance of the AI to the psychopathology of schizophrenia remains obscure, some possibilities can be hinted at. First, the anatomical location of the bridge as a midline structure may be important, since several abnormal morphologies have been reported in other midline regions in schizophrenia patients, including the corpus callosum, cerebellar vermis (Shenton et al., 2001), and septum pellucidum (Trzesniak et al., 2010). Also, neurophysiological studies in rats underscore the functional importance of the AI in interhemispheric transfer (Hirayasu and Wada, 1992; Wouterlood et al., 1990). Second, several lines of evidence have indicated that the thalamus may play a crucial role in schizophrenia (Andreasen et al., 1994; Shenton et al., 2001), which has raised interest in the significance of an absent AI in the disorder. Dopamine dysfunction is thought to be a key feature of schizophrenia, and animal studies suggest that the AI might be involved in the regulation of dopamine release in the basal ganglia (Cheramy et al., 1984; Romo et al., 1984), or in the transfer of information implicated in the reciprocal regulation of the two nigrostriatal dopaminergic pathways (Leviel et al., 1981). Striking increases in neuronal activity are evident in the thalamic midline nuclei of rats in response to the antipsychotic drugs haloperidol and clozapine (Cohen and Wan, 1996; Cohen et al., 1998), and there is evidence that both dopamine receptor function and glutamate levels in the thalamus are perturbed in psychosis (Stone et al., 2009, 2010). It remains to be established to what extent these observations may explain the diverse symptoms of schizophrenia. Although clearly not sufficient to explain the complexity of this disorder, the dopamine deregulation hypothesis provides a direct relationship between the schizophrenia symptoms and their respective treatment (Toda and Abi-Dargham, 2007). Based on this, it was speculated that neurodevelopmental abnormalities in thalamus and in the AI could lead to consequent dopaminergic alterations, and contribute to the pathogenesis of the disorder (Takahashi et al., 2008a).

Magnetic resonance imaging (MRI) has become established as an important method for evaluating the presence or absence of AI. Nevertheless, there are some difficulties in interpreting the findings reported in the published MRI literature on this issue hitherto. Since the first study conducted by Snyder et al. (1998), several MRI studies have investigated AI in schizophrenia. However, the prevalence rates of AI that they have reported in SSD patients and healthy volunteers have not been consistent across studies.

The application of meta-analytic methods provides a means of combining data from multiple brain imaging studies for qualitative and quantitative analyses. Some advantages of this approach include: 1) increment in statistical power; 2) the possibility of teasing apart the influence of factors causing heterogeinity in the results reported by individual studies; and 3) the opportunity to combine findings from all studies, improving the estimation of the overall odds ratio. Taking advantage of this, we present herein a systematic review and meta-analysis providing a qualitative and quantitative integration of the MRI findings of absent AI in SSD published to date.

2. Methods

Searches were performed in the MEDLINE and ISI Web of Knowledge[SM] databases using the keywords adhesio, adhesio interthalamica or massa intermedia and schizophrenia or psychosis, up to December 2010. References of selected articles were also hand-searched for possible additional citations. All studies involving human patient samples relating MRI data of AI to SSD were incorporated in this analysis (Fig. 2).

To be included in this review, the studies had to meet the following criteria: 1) to be published in English; 2) to use MRI to assess the AI; 3) to have a comparison group of healthy subjects; and 4) to be carried out in a population diagnosed as having SSD (i.e., schizophrenia, schizophreniform or schizoaffective disorders), according to the Diagnostic Statistical Manual of Mental Disorders (DSM) III-R (American Psychiatric Association, 1987), IV (American Psychiatric

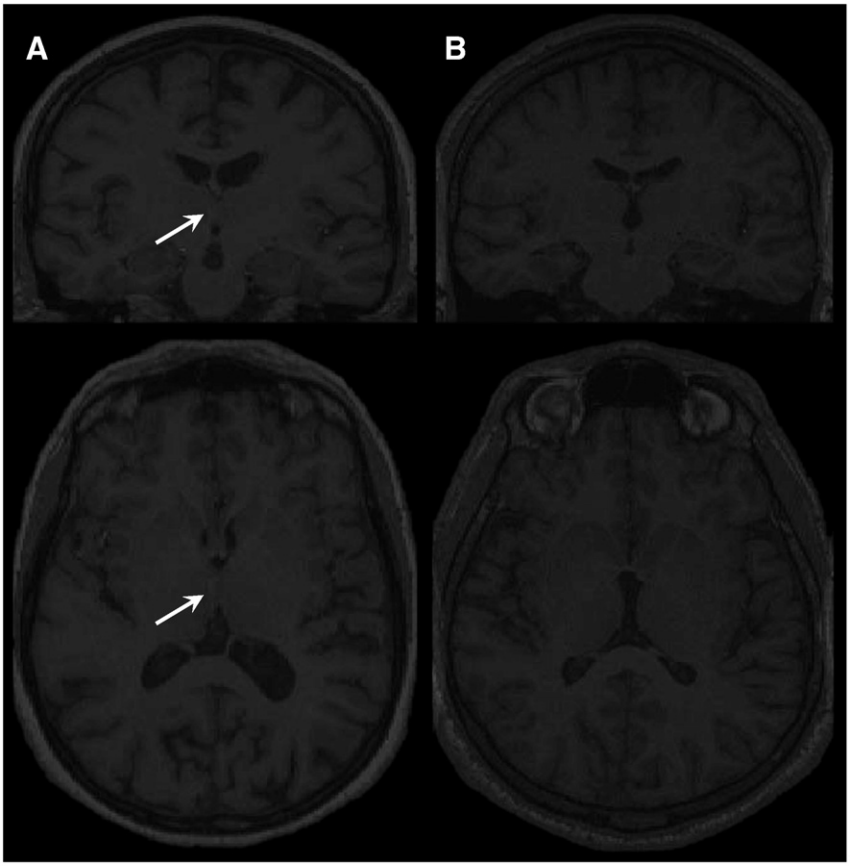

Fig. 1. Coronal (upper) and axial (lower) magnetic resonance images showing a brain with (A; arrow) and one without (B) the adhesio interthalamica.

Association, 1994), and IV-TR (American Psychiatric Association, 2000). Given that there is acceptable agreement (moderate to substantial kappa indexes) between the DSM systems, the Research Diagnostic Criteria (RDC; Spitzer et al., 1978); and the International Classification of Diseases (ICD-10) for schizophrenia (Hill et al., 1996; Jäger et al., 2004; Jakobsen et al., 2006; Cheniaux et al., 2009), we decided to include studies in which subjects were diagnosed as schizophrenia patients, according the RDC and ICD-10.

In order to select the potentially relevant studies, three independent reviewers (AGA, CT, and MHNC) evaluated the abstracts

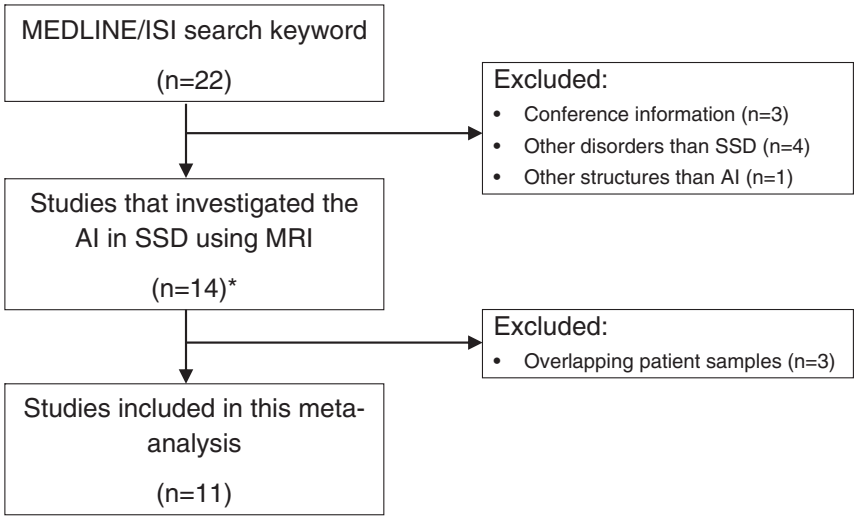

Fig. 2. Flow chart showing study selection for the meta-analysis.

identified in the literature search. Next, the same three reviewers, working independently, decided which of those papers fulfilled the inclusion criteria. Disagreement at any stage was resolved by consensus. For each study investigated, a data collection form was used, and these data were obtained independently by the three reviewers. The reviewers had access to raw data from four studies, (Ettinger et al., 2007; Agarwal et al., 2008; Takahashi et al., 2008c; Takahashi et al., 2008d). By accessing the original data, we were able to exclude measures from affective psychotic patients included in Takahashi et al. (2008d), exclude schizotypal personality disorder subjects in Takahashi et al. (2008c) and for an additional sub-analysis, extract measures from males and females included in Ettinger et al. (2007) and Agarwal et al. (2008) The MRI studies included in this review are summarized in Table 1, which lists the sociodemographic characteristics of each study sample by first author and year.

Statistical analyses were performed with STATA 10.1 (StataCorp, College Station, Texas) using the METAN command. For each study, odds ratios and 95% confidence intervals were calculated. We used a random effects model that weighted the studies according to the inverse variance, and provided the odds ratio and the corresponding confidence interval.

The proportion of patients from the included studies which presented AI compared to those which did not were broken down into 2×2 contingency tables. The between-study variability among the population effect sizes, i.e. the heterogeneity, was assessed formally by applying Cochran's q test for homogeneity (Sutton et al., 2000) and informally by assessing a sample size independent descriptive measure of inconsistency I^2 (Higgins et al., 2003). The I^2 index describes the percentage of the total variability in a set of effect sizes due to true heterogeneity, that is, between-study variability (Huedo-Medina et al., 2006). For example, a meta-analysis with $I^2=0$ means that all variability in effect size estimates is due to sampling error within studies. On the other hand, a meta-analysis with $I^2=50$ means that half of the total variability among effect sizes is caused not by sampling error but by true heterogeneity between studies. Higgins et al. (2003) proposed a tentative classification of I^2 values with the purpose of helping to interpret its magnitude. Thus, percentages of around 25% ($I^2=25$), 50% ($I^2=50$), and 75% ($I^2=75$) would indicate low, medium, and high heterogeneity, respectively.

2.1. Publication bias

We used Egger's regression test which is a formal method of assessing publication bias (Egger et al., 1997) as implemented with the STATA function METABIAS.

2.2. Subgroup meta-analyses

To assess the sexual dimorphism of the AI, two meta-analyses were performed separately comparing male patients to male controls, and female patients to female controls. To compare the effect sizes from the two groups a Z-test was used. The studies which did not specify the prevalence of absent AI according to gender were excluded from this analysis. We also performed a meta-analysis among the three studies which quantified the length of the AI (Shimizu et al., 2008; Takahashi et al., 2008c, d), in order to investigate whether this rating would be different between patients and healthy volunteers. The individuals in which the AI was absent were excluded from the calculus of its length.

2.3. Meta-regression

The effects of mean patient age and duration of illness on the prevalence of the AI were assessed in a random effects meta-regression model by using the METAREG (Sharp, 1998) command in STATA. The default option using residual maximum likelihood (REML) was selected. Since there is evidence showing that the AI becomes shorter over the

Table 1
Demographic and clinical characterization of the samples.

Reference	Subjects	N (M/F)	Mean age + SD (years)	Duration of illness (years)	Antipsychotics	Diagnostic criteria	Comments/healthy controls origin
Snyder et al., 1998	FE SCHZ + FE SCHZA	82 (54/28)	ND	ND	ND	RDC	CTRL: members of the community and hospital staff
	CTRL	52 (30/22)	27.7 + 6.5				
Nopoulos et al., 2001	FE SCHZ + CHR SCHZ	114 (56/58)	29.9 + 10.4	ND	ND	DSM-III-R; DSM-IV	CTRL: members of the community
	CTRL	112 (53/59)	28.5 + 10.0				
Erbagci et al., 2002	CHR SCHZ	26 (11/15)	34.7 + 19.7	ND	Yes	DSM-IV	CTRL: members of the community
	CTRL	29 (11/18)	28.6 + 7.5		–		
Meisenzahl et al., 2002	CHR SCHZ	50 (50/0)	30.0 + 8.4	ND	ND	DSM-IV	CTRL: members of the community
	CTRL	50 (50/0)	30.2 + 8.8	–			
De Souza Crippa et al., 2006	CHR SCHZ	38 (26/12)	29.9 + 10.0	10.3 + 8.2	Yes	DSM-IV	CTRL: members of the community and hospital staff
	CTRL	38 (26/12)	29.7 + 9.7	–			
Ettinger et al., 2007	CHR SCHZ + CHR SCHZA	53 (40/13)	33.9 + 10.9	ND	Yes	DSM-IV	CTRL: twins members of community
	CTRL	54 (34/20)	35.7 + 10.1	–			
Ceyhan et al., 2008	CHR SCHZ	35 (18/17)	37.6 + 11.2	ND	ND	DSM-IV	CTRL: ND
	CTRL	89 (39/50)	36.6 + 1.3	–			
Shimizu et al., 2008	CHR SCHZ + CHR SCHZA + SCHZP	64 (30/34)	36.3 + 11.0	10.4 + 9.1	Yes	DSM-IV	CTRL: members of the community
	CTRL	51 (22/29)	36.1 + 8.4	–			
Takahashi et al., 2008c	CHR SCHZ	72 (38/34)	26.2 + 5.6	4.6 + 5.0	Yes	ICD-10	CTRL: members of the community, hospital staff, university students
	CTRL	81 (46/35)	24.5 + 5.7	–			
Takahashi et al., 2008d	FE SCHZ + CHR SCHZ	192 (152/40)	28.1 + 6.4	12.8 + 9.9	Yes	DSM-III-R	Gender: M>F in CHR compared with other all groups
	CTRL	87 (55/32)	26.9 + 10.1	–	–		Age: CHR SCHZ>other groups CTRL: similar sociodemographic areas as patients; members of the community
Agarwal et al., 2008	CHR SCHZ	71 (46/25)	40.5 + 11.9	13.9 + 10.8	Yes	DSM-IV	CTRL: members of the community, hospital staff, university students
	CTRL	75 (39/36)	39.7 + 10.9	–			

CHR, chronic; CTRL, controls; DSM, Diagnostic Statistical Manual; F, female; FE, first episode; ICD, International Classification of Diseases; M, male; ND, not described; RDC, Research Diagnostic Criteria; SCHZA, schizoaffectives; SCHZ, schizophrenics; SCHZP, schizophreniform; SD, standard deviation.

time (Rosales et al., 1968), we performed a meta-regression to evaluate the effects of mean patient age in the length of the structure.

2.4. Sensitivity analysis

To test how robust the results were to variations in the meta-analysis methodology, we examined the effect of the following strategies on the meta-analysis estimate: a) excluding three studies which combined schizophrenia with other psychotic disorders; b) evaluating the six studies which included chronic patients with schizophrenia only (no first-episode subjects); c) evaluating the five studies that adopted DSM-IV diagnostic criteria and had only included chronic schizophrenia patients; d) evaluating the five well-designed studies selected from the literature (inclusion criteria: number of SSD patients included (>20 subjects), an adequate matching between the samples of patients and controls, and acquisition of thinner and contiguous slices (≤1.0 mm); (Ceyhan et al., 2008; de Souza Crippa et al., 2006; Nopoulos et al., 2001; Shimizu et al., 2008; Takahashi et al., 2008c); and e) repeating the meta-analysis 11 times, each time excluding one study.

3. Results

3.1. Main meta-analysis

Fourteen studies that examined the prevalence of AI in schizophrenia, schizophreniform and/or schizoaffective disorders fulfilled the initial inclusion criteria. Among these, three (Meisenzahl et al., 2000; Takahashi et al., 2009a, b) were excluded because their samples had already been included in other studies (Meisenzahl et al., 2002; Takahashi et al., 2008c). Thus 11 studies provided comparative data from 822 patients and 718 healthy volunteers with and without AI and were included in the meta-analysis (Table 1).

All of the 11 studies analyzed in this review investigated the absence of AI in both patients and controls. The prevalence of non-AI ranged from 2.3% (Takahashi et al., 2008c) to 22.3% (Nopoulos et al., 2001) in healthy individuals, and from 4.7% (Shimizu et al., 2008) to 34.6% (Erbagci et al., 2002) in subjects with SSD. The finding of a higher occurrence of non-AI was observed both in chronic (Erbagci et al., 2002; Takahashi et al., 2008c) and in first-episode SSD patients (Nopoulos et al., 2001; Snyder et al., 1998; Takahashi et al., 2008d). Six out of 11 studies failed to find significant differences in the prevalence of absent AI between SSD patients and controls (Agarwal et al., 2008; Ceyhan et al., 2008; de Souza Crippa et al., 2006; Ettinger et al., 2007; Meisenzahl et al., 2002; Shimizu et al., 2008). As shown in Fig. 3, in our random effects quantitative meta-analysis, patients with SSDs had significantly higher prevalence of absent AI compared to controls, with non-AI being almost twice as likely to occur in SSD than healthy individuals (odds ratio = 1.98; 95% confidence interval 1.33–2.94; p = 0.0008). There was no evidence of between-study heterogeneity (I^2 = 28.6%, Q = 14.0, p = 0.17) or publication bias (p = 0.94). Undertaking power calculations using the odds ratio is problematic because the calculation depends on both the odds ratio and the prevalence of the AI in the control group. As the latter measure is highly variable it is difficult to calculate the necessary sample size to detect a significant effect with precision.

3.2. Subgroup meta-analyses

Eight out of 11 studies in the main meta-analysis reported data separately for males and females and one study involved only male subjects. A meta-analysis of female samples (214 patients and 262 control subjects) revealed that female patients with SSD showed a higher incidence of absent AI than healthy females (8 studies, odds ratio = 2.66, 95% confidence interval = 1.41–4.99, p = 0.002). In the meta-analysis of male subjects (437 patients and 353 control individuals), an increased occurrence of absent AI in male SSD patients was also found (9 studies, odds ratio = 1.72, 95% confidence interval = 1.03–2.88, p = 0.040). There was no significant difference between the effect sizes for males and females (Z = 1.05, p = 0.30).

When the meta-analysis was restricted to studies that assessed the length of the AI, significant reduction of this structure was found in patients (effect size g = 0.979, 95%CI 0.719 to 1.239, p < 0.001). There was no between-study heterogeneity (I^2 = 43.5%, Q = 3.54, p = 0.17) nor evidence of publication bias (p = 0.40). For a study to be sufficiently powered to detect a difference in AI length (alpha = 0.05, power = 0.80), 18 patients and 18 controls would be need to be recruited.

3.3. Meta-regression

The meta-regression analysis showed no significant moderating effect of mean patient age (10 studies; r = −0.045; p = 0.39) or

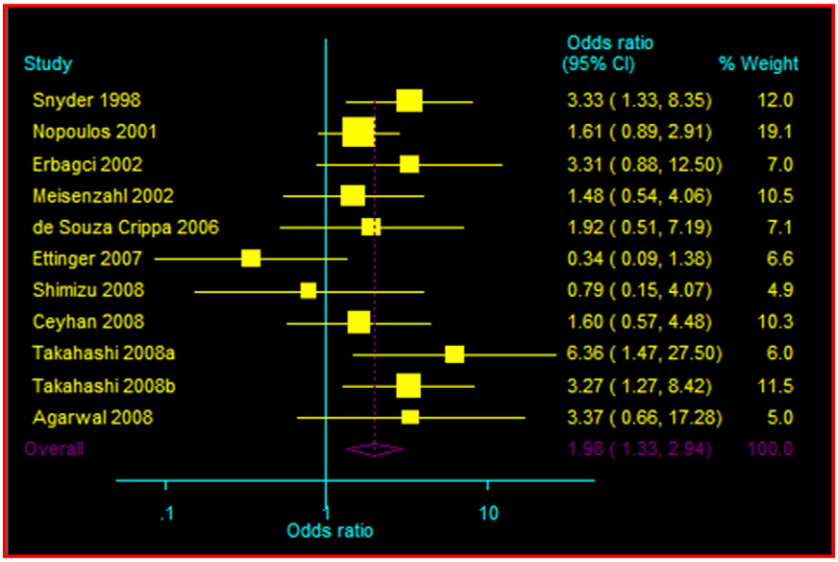

Fig. 3. The odds ratio of the 11 studies that investigated the prevalence of absent adhesio interthalamica in patients with schizophrenia spectrum disorder and healthy volunteers. The mean data shows significant differences between patients and healthy comparison subjects (p = 0.0008). AI, adhesio interthalamica; OR, odds ratio.

duration of illness (5 studies; r = 0.010; p = 0.93) on the prevalence of AI. Likewise, there was no evidence of effects of mean patient age (3 studies; r = 017; p = 0.73) on the length of the AI. The number of studies included in the meta-regression analyses is fewer than the main meta-analysis given that not all of the eleven studies provided the appropriate clinical data.

3.4. Sensitivity analysis

The result of the main meta-analysis remained significant (odds ratio = 1.15 to 3.38, all $p \leq 0.02$) when we: a) excluded studies which had samples including patients with psychotic disorders other than schizophrenia; b) evaluated the six studies which included chronic patients with schizophrenia only (no first episode subjects); c) evaluated five studies that adopted DSM-IV diagnostic criteria and only included chronic schizophrenia patients; d) evaluated the five well-designed studies selected from the literature (criteria described in Section 2.4); and e) repeated the meta-analysis 11 times each time excluding one study.

4. Discussion

Our analyses indicate that the incidence of non-AI is higher in SSD patients than in healthy volunteers. We therefore propose that the lack of AI could have clinical significance in SSD. In addition, patients without an AI may also differ from patients with AI with respect to other MRI features and clinical measures. Thus, it has previously been reported that SSD subjects with absent AI have greater third (Meisenzahl et al., 2002; Snyder et al., 1998) and lateral ventricle volume (Takahashi et al., 2008d); and smaller amygdala (Takahashi et al., 2008a). Besides, in the studies reviewed herein, patients with no AI have previously been found to have higher scores on the Scale for the Assessment of Negative Symptoms (SANS; Meisenzahl et al., 2002), a longer duration of illness, and had received higher doses of antipsychotic medication (Takahashi et al., 2008d).

Despite the above findings, it is important to emphasize that the absence of AI occurs in only a subgroup of individuals with SSD, with prevalence rates ranging from 4.7% (Shimizu et al., 2008) to 34.6% (Erbagci et al., 2002), respectively. Therefore, this absence should at most be regarded as an early neurodevelopmental risk factor that may be related to the presence of schizophrenia in a subgroup of patients, rather than being a causative determinant of the disorder. In fact, Takahashi et al. (2008d) observed that although alterations of the AI were present at ultra-high risk psychosis subjects, they were not specific to high risk individuals who will subsequently develop psychosis. This suggests that the absence of an AI is a correlate of increased vulnerability to psychosis, but is not a predictor of psychotic illness per se (Takahashi et al., 2008d). Similarly, it is unlikely that a disturbance in a localized structure such as the AI would lead to widespread manifestations of schizophrenia and other disorders. A more plausible possibility is that abnormalities in the process by which the AI is formed and matures are markers of an overall aberrance of early neurodevelopment of more widespread proportions and etiopathological significance to psychosis.

It is also important to stress that AI abnormalities are not specific to schizophrenia, since these findings have also been observed in other psychiatric disorders, such as borderline personality (Takahashi et al., 2009a), major depression (Takahashi et al., 2009b), bipolar disorder (Takahashi et al., 2010), and schizotypal personality disorder (SPD, Takahashi et al., 2008c). It was already speculated that psychosis associated with schizophrenia and bipolar affective may share neurodevelopmental abnormalities involving midline structures (Kasai et al., 2004), and that SPD may be a milder form on a continuum of SSD (Kwon et al., 1998). In fact, it is possible that alterations in AI are a marker of general psychopathology. AI abnormalities could be an indicator of disturbed neural networks including the thalamic and related regions during neurodevelopment, which might be core components of the vulnerability to neuropsychiatric disorders. Thus, further work should investigate the specificity of AI findings in various psychiatric disorders, including anxiety disorders.

4.1. Methodological aspects: sample characteristics

The wide discrepancy in the reported prevalence of the AI in association with SSD may be, in great part, explained by differences in the methodology across the studies published to date. Besides schizophrenia, some samples included other related conditions, such as schizoaffective or schizophreniform disorder (Ettinger et al., 2007; Snyder et al., 1998; Shimizu et al., 2008). Likewise, different types of diagnostic criteria were adopted (i.e., RDC, ICD-10, DSM-III-R, and DSM-IV; Table 1). There is no clear consensus on the reliability for SSD amongst classificatory systems. Whereas the coefficient of diagnostic congruence (kappa) appears to be higher than 0.5 for schizophrenia (Hill et al., 1996; Jäger et al., 2004; Jakobsen et al., 2006; Cheniaux et al., 2009), it is lower for other conditions such as schizoaffective disorder (Cheniaux et al., 2009). For this reason, we decided to include only schizophrenia samples from studies which adopted diagnostic systems other than DSM. In the same way, some degree of variability is observed in the DSM classifications over time; nevertheless, this instability seems to be fairly low, especially when comparing DSM-III-R and DSM-IV criteria for schizophrenia (Jakobsen et al., 2006). Although heterogeneity across diagnoses and diagnostic criteria may be considered a confounding factor, the sensitivity analyses indicated that this did not affect the main result of this meta-analysis.

The methods for the recruitment of healthy comparison groups could also be considered a source of bias, since most studies recruited hospital staff (Agarwal et al., 2008; de Souza Crippa et al., 2006; Snyder et al., 1998; Takahashi et al., 2008c), university students (Agarwal et al., 2008; Takahashi et al., 2008c); or members of community by advertisements (Agarwal et al., 2008; Erbagci et al., 2002; Meisenzahl et al., 2002; Nopoulos et al., 2001; Shimizu et al., 2008; Snyder et al., 1998; Takahashi et al., 2008c). Moreover, Ceyhan et al. (2008) did not specify the source of their healthy control sample. On the other hand, Ettinger et al. (2007) used healthy twin volunteers to compare with both concordant and discordant twins for schizophrenia, and Takahashi et al. (2008d) recruited healthy individuals from the similar sociodemographic areas as the patients.

4.1.1. Gender effects

Sexual dimorphism regarding AI has also been investigated in schizophrenia, but the results have been contradictory. While there are some reports describing that a lack of AI was commoner among male patients (de Souza Crippa et al., 2006; Takahashi et al., 2008a), Nopoulos et al. (2001) found a higher prevalence of absent AI in female patients. In addition, it was verified that females with schizophrenia had a shorter length (Shimizu et al., 2008) and area of AI (Ceyhan et al., 2008) than female controls. Nonetheless, when all the subjects were pooled together, the AI length was found to be shorter in males (Takahashi et al., 2008c, d). In our subgroup meta-analysis, we could not find evidence for a strong differential effect between males and females. Although the functional significance of gender differences related to the AI remains unclear, some authors have hypothesized that the female brain is more functionally symmetrical than the male brain (Mcglone, 1980). Moreover, it was proposed that brain commissures such as AI, which are sexually dimorphic in the normal brain, may somehow be more developmentally vulnerable and manifest abnormal morphology in schizophrenia (Nopoulos et al., 2001). These gender alterations in a structure that connects the two cerebral hemispheres may underlie functional sex differences in cognitive skills, developmental language disorders, and functional asymmetries (Allen and Gorski, 1991).

4.1.2. Use of antipsychotics

There is no mention about the use of antipsychotics in four studies (Ceyhan et al., 2008; Meisenzahl et al., 2002; Nopoulos et al., 2001; Snyder et al., 1998). This lack of information regarding treatment status possibly relates to the view that the absence of AI is entirely established during the first weeks of gestation, and therefore non-AI incidence indices would not be affected by the use of antipsychotic medications. Nonetheless, neuroleptic medication probably influences volumetric brain structure (Chakos et al., 2005; Tomelleri et al., 2009), and might also influence length and area ratings of the AI. In fact, Takahashi et al. (2008d) reported a negative correlation between daily medication dosage and the length of the AI in chronic schizophrenia patients.

4.1.3. Age and duration of illness

Age also seems to be an influential factor for the AI. Post-mortem investigations by Rosales et al. (1968) demonstrated an involution process of the AI with age in the healthy population, which may start from the third decade onwards. Therefore, the absence of AI should increase with advancing age, and its length would be expected to decrease over time. Indeed, there have been reports of negative correlations between age and both the area (Ceyhan et al., 2008) and the length (Takahashi et al., 2008d) of the AI, both in schizophrenia and in healthy controls. Consequently, especially in older individuals, atrophy in this midline structure could be the result of dynamic brain changes, rather than being a fixed consequence of abnormal neurodevelopment. In our meta-regression analyses, we did not observe any relationship between mean patient age and either the prevalence or the length of the AI. However, further investigation about the association between age and the AI length is advisible, given the reduced number of studies which provided these data (Shimizu et al., 2008; Takahashi et al., 2008c, d). In addition, in two (Takahashi et al., 2008c, d) of these three studies, patients were quite young (mean age of 26.2 and 26.9 years, respectively) and probably the involution of the AI had not yet started in these samples when they were accessed.

There is evidence that there are progressive volumetric changes in brain structures in the vicinity of the AI, such as the thalamus and total ventricular volume, when first-episode psychosis patients are directly compared with chronic subjects with SSD (for a review, see Ellison-Wright et al., 2008). This indicates that it is important to control for the duration of illness in MRI studies evaluating AI. Interestingly, it has been observed that chronic patients had a shorter AI and a higher prevalence of absence of this structure than first-episode psychosis patients (Takahashi et al., 2008d). Similarly, the duration of illness has been found to negatively correlate with both the length (Takahashi et al., 2008a) and area of the AI (Ceyhan et al., 2008) in chronic schizophrenia.

4.2. Methodological aspects: Experimental Designs and Characterization of the AI

The variation in the acquisition parameters across different MRI studies may influence the results obtained in the studies of AI in SSDs. In relation to the intensity of the magnetic field, only one study used a 1.0 T scanner (Snyder et al., 1998). In contrast, other nine utilized scanners with a magnetic field of 1.5 T (Agarwal et al., 2008; Ceyhan et al., 2008; de Souza Crippa et al., 2006; Erbagci et al., 2002; Ettinger et al., 2007; Meisenzahl et al., 2002; Nopoulos et al., 2001; Takahashi et al., 2008c, d), while Shimizu et al. (2008) carried out their research with a 3.0 T equipment. Higher magnetic fields probably contributed to improve the quality of the MRI data acquired.

There has been a great degree of variability in the thickness of MRI slices acquired across different studies to date, ranging from 1.0 mm to 5.0 mm (Table 2). There is also variation in the inter-slice gaps across MRI studies, ranging from none to 5 mm. Thinner and contiguous slices are considered the 'gold-standard' method, since these allow more accurate estimates not only of the prevalence of non-AIs, but also their length. It is well-known that thicker slices, such as 3.0 to 5.0 mm, and gaps may occasionally miss narrow connection between the thalami and report higher prevalence of absent AI, as well as leading to partial volume effects. However, our sensitivity analysis demonstrated that the exclusion of studies conducted with thicker slices (>1.0 mm) and gaps did not affect the main result of this meta-analysis.

There is also great disparity in the way for classifying the absence of the AI (Table 2). For example, while some studies only used the coronal slices to evaluate the presence of the AI, others utilized either both coronal and axial or coronal and sagittal views. More recently, the three planes have also been employed as parameters (Table 2). In addition, some authors considered AI as absent if it was not seen in two or more coronal slices (de Souza Crippa et al., 2006; Erbagci et al., 2002; Snyder et al., 1998), while others adopted three slices on both coronal and axial planes as threshold (Takahashi et al., 2008c, d). Limitations in such qualitative forms of assessing AI are likely to contribute to the contradictory findings among the articles published to date.

In order to minimize these discrepancies, recent studies in SSD have also measured the anterior–posterior length of the AI (Shimizu et al., 2008; Takahashi et al., 2008c, d) by counting the number of coronal slices in which the structure clearly appears. Through this technique, the number of slices can be multiplied by their thickness, allowing the calculation of the length of the AI. This new quantitative approach seems to be more effective than only determining the AI's presence/absence and might lead to better comparability across studies. It is important to highlight that all of these studies that employed this approach observed that SSD patients have shorter AI than controls. In addition, our subgroup meta-analysis that included the data of these three articles showed that the length of the AI is greatly shorter in patients.

4.3. Correlations with quantitative and qualitative variables

There have been reports showing that the absence AI in SSD is related to increased volume of both the third (Meisenzahl et al., 2002; Snyder et al., 1998) and lateral (Takahashi et al., 2008d) ventricles, as well as to decrease in bilateral amygdala (Takahashi et al., 2008a). Although not always replicated, patients without AI have also shown more negative symptons (Meisenzahl et al., 2002), and were receiving more antipsychotics (Takahashi et al., 2008a) than those with the structure. Taken together, these findings suggest that schizophrenia patients without AI may present more psychopathological and brain structural alterations, possibly reflecting distinct patterns of disturbed brain morphology. In addition, the AI area was found to be negatively correlated with both age and duration of illness in SSD (Ceyhan et al., 2008). The length of the AI was negatively correlated to SANS scores (Takahashi et al., 2008a), and to age, duration of illness, dose of medication and lateral ventricular enlargement (Takahashi et al., 2008d) in SSD. Interestingly, Shimizu et al. (2008) did not observe correlations between the length of the AI and whole thalamic volumes in both patients and controls groups, even though patients showed smaller volumes of the mediodorsal nuclei of the thalami and shorter AI. It was not found evidence for the genotypic combination effect of the dopamine D3 receptor and brain-derived neurotrophic factor (BDNF) single nucleotide polymorphisms on the AI in schizophrenia (Takahashi et al., 2008b). Finally, although the cavum septum pellucidum (CSP) is considered to be an early neurodevelopmental abnormality (for a review, see Trzesniak et al., 2010), there was no overlap between the presence of a large CSP and an absence of AI (de Souza Crippa et al., 2006). This is not, however, surprising, as the development of the AI occurs during early gestation (around 13th and 14th weeks), while the complete closure of the CSP – although requiring the normal development of other brain regions – occurs later or after the birth.

Table 2
Findings in adhesio interthalamica in schizophrenia spectrum disorder.

Reference	Magnetic field (T)	Slice length/gap (mm)	Criteria of the detection of the AI	Subjects	Prevalence of absence of the AI (%) [a]	Findings: absence of the AI	Comments
Snyder et al., 1998	1.0	3.1	Absence: AI not seen on more than 2 coronal MRI slices	FE SCHZ + FE SCHZA CTRL	34.2 13.5	↑ in PAT	PAT without AI: ↑ third ventricle
Nopoulos et al., 2001	1.5	1.0	Absence: AI not seen on more than 2 coronal and axial slices	FE SCHZ + CHR SCHZ CTRL	31.6 22.3	↑ fem PAT × fem CTRL	CTRL: absent AI commoner in males than in females
Erbagci et al., 2002	ND	3.0/5.0	Absence: AI not seen on more than 2 coronal MRI slices	CHR SCHZ CTRL	34.6 13.8	↑ in PAT	
Meisenzahl et al., 2002	1.5	1.5	Qualitatively in the coronal and axial plane	CHR SCHZ CTRL	22.0 16.0	NS	SCHZ/CTRL without AI: ↑ third ventricle SCHZ without AI: ↑ SANS
de Souza Crippa et al., 2006	1.5	1.0	Absence: AI not seen on more than 2 coronal MRI slices	CHR SCHZ CTRL	18.4 10.5	NS	SCHZ: absent AI commoner in males absent AI not associated with large CSP
Ettinger et al., 2007	1.5	1.5	Qualitatively in the coronal, axial and sagittal planes	CHR SCHZ + CHR SCHZA CTRL	5.7 14.8	NS	
Ceyhan et al., 2008	1.5	1.0	Absence: AI not seen on coronal and sagittal MRI slices	CHR SCHZ CTRL	20.0 13.5	NS	CTRL: absent AI ↑ males CTRL and SCHZ: AI area (−) correlated to age SCHZ: AI area (−) correlated to duration of illness ↓ AI area in SCHZ ↓ AI area in SCHZ female than CTRL female
Shimizu et al., 2008	3.0	1.0	Qualitatively in the coronal, axial and sagittal planes length: number of coronal slices in which AI was visualized	CHR SCHZ + CHR SCHZA + SCHZP CTRL	4.7 5.9	NS	↓ AI length in PAT ↓ AI length in female PAT × female CTRL AI length not correlated with thalamic volume
Takahashi et al., 2008c	1.5	1.0	Absence: AI not identified in less than three both coronal and axial MRI contiguous slices	CHR SCHZ CTRL	23.6 8.6	↑ in PAT	↓ AI length in SCHZ ↓ AI length in males than females in general
Takahashi et al., 2008d	1.5	1.5	Absence: AI not identified in less than three both coronal and axial MRI contiguous slices	FE SCHZ + CHR SCHZ CTRL	13.0 2.3	↑ in CHR × FE SCHZ and CTRL	Absent AI commoner in males ↓ AI length in both FE and CHR SCHZ/shorter in CHR ↓ AI length in males than females in general CHR SCHZ without AI: receiving more antipsychotics/longer duration of illness subjects without AI: larger lateral ventricles SCHZ: AI length (−) correlated to illness duration, dose of medication; ventricular enlargement All groups: AI length (−) correlated to age
Agarwal et al., 2008	1.5	5.0/1.5	ND	CHR SCHZ CTRL	8.5 2.7	NS	

(−), negatively; ↓, decrease; ↑, increase; AI, adhesio interthalamica; CSP, cavum septum pellucidum; CTRL, controls; FE, first episode; fem, female; mm, millimeter; MRI, magnetic resonance imaging; ND, not declared; NS, no significant; PAT, patients; SANS, Scale for the Assessment of Negative Symptoms; SCHZ, schizophrenia; SCHZA, schizoaffectives; SCHZP, schizophreniform; T, Tesla.

[a] The prevalence of absent AI was calculated as follows: 100 × (number of subjects with absent AI/number of all subjects).

4.4. Limitations

The main difficulty in analyzing the 11 articles included in the meta-analysis arose from the variation in the methodological variables across studies, as discussed above. Additionally, even though these MRI investigations were rigorous in many ways – particularly the recent ones – few of them reached satisfactory criteria for inclusion in the meta-analysis, both in respect to the clinical and demographic characteristics of the samples studied, and in the parameters of image acquisition. The less than ideal use of thick slices (3.0–5.0 mm) and inter-slice gaps in the imaging acquisition protocols, variability in the criteria used for categorizing absence of the AI, and the use of heterogeneous patients sampler and/or samples unmatched for critical demographic variables are among the factors likely to add variability to the findings reported across different studies. Using optimal inclusion criteria regarding the number of SSD patients included (>20 subjects), an adequate matching between the samples of patients and controls, and acquisition of thinner and contiguous slices (≤1.0 mm), five well-designed studies can be selected from the literature (Ceyhan et al., 2008; de Souza Crippa et al., 2006; Nopoulos et al., 2001; Shimizu et al., 2008; Takahashi et al., 2008c).

Although only Takahashi et al. (2008c) have found higher prevalence of the AI in patients, a subgroup meta-analysis of these five studies confirmed our main results.

It is important to highlight some limitations of the present review. As with all meta-analyses, the findings are dependent on the quality of the primary studies. Unfortunately we did not have access to information regarding obstetric complications of the subjects, cumulative dose of antipsychotics during image acquisition, or other data which may have contributed to a better understanding of how absent AI might affect psychosis. Besides, several types of study bias could arise during publication of the primary studies (Naylor, 1997). In our review, we did not detect evidence for publication bias. In addition, we excluded duplicated samples and results when there was indication of more than one publication based on the same dataset. However, it is not possible to eliminate the likelihood that our findings were influenced by confounding factors, or methodological heterogeneity among the articles, as discussed above.

5. Conclusion

In summary, the results of the present meta-analysis strongly suggest that there is a greater prevalence of absent AI in SSD individuals than in healthy controls, and that when present, the AI in patients is shorter than in controls. Nonetheless, further investigations using quantitative analyzes are warranted to reconcile some conflicting findings in the literature to date. First, there is a need for studies evaluating the prevalence of psychosis in large, homogeneous, community-based samples of individuals presenting with AI. The AI findings in psychosis may not simply be a function of abnormal neurodevelopment, but may also reflect a progressive atrophy of this structure, either due to the disorder itself and/or effects of age, and antipsychotic treatment. As SSD are clinically heterogeneous, standardization of MRI methods and a more careful selection of the subjects — such as population-based investigations with longitudinal designs, are likely to generate more reliable conclusions concerning the role of AI in SSD.

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References

Agarwal N, Rambaldelli G, Perlini C, Dusi N, Kitis O, Bellani M, et al. Microstructural thalamic changes in schizophrenia: a combined anatomic and diffusion weighted magnetic resonance imaging study. J Psychiatr Neurosci 2008;33:440–8.
Allen LS, Gorski RA. Sexual dimorphism of the anterior commissure and massa intermedia of the human brain. J Comp Neurol 1991;312;97–104.
American Psychiatric Association. Diagnostic and statistical manual of mental disordersRevised 3rd ed. Washington, DC: American Psychiatric Association; 1987.
American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association; 1994.
American Psychiatric Association. Diagnostic and statistical manual of mental disordersRevised 4th ed. Washington, DC: American Psychiatric Association; 2000.
Andreasen NC, Arndt S, Swayze V, Cizadlo T, Flaum M, Oleary D, et al. Thalamic abnormalities in schizophrenia visualized through magnetic-resonance image averaging. Science 1994;266:294–8.
Brown AS, Derkits EJ. Prenatal infection and schizophrenia: a review of epidemiologic and translational studies. Am J Psychiatry 2010;167(3):261–80.
Ceyhan M, Adapinar B, Aksaray G, Ozdemir F, Colak E. Absence and size of massa intermedia in patients with schizophrenia and bipolar disorder. Acta Neuropsychiatry 2008;20:193–8.
Chakos MH, Schobel SA, Gu HB, Gerig G, Bradford D, Charles C, et al. Duration of illness and treatment effects on hippocampal volume in male patients with schizophrenia. Br J Psychiatry 2005;186:26–31.
Cheniaux E, Landeira-Fernandez J, Versiani M. The diagnoses of schizophrenia, schizoaffective disorder, bipolar disorder and unipolar depression: interraterreliability and congruence between DSM-IV and ICD-10. Psychopathology 2009;42(5):293–8.
Cheramy A, Romo R, Godeheu G, Glowinski J. Effects of electrical-stimulation of various midline thalamic nuclei on the bilateral release of dopamine from dendrites and nerve-terminals of neurons in the nigro-striatal dopaminergic pathways. Neurosci Lett 1984;44:193–8.
Cohen BM, Wan WH. The thalamus as a site of action of antipsychotic drugs. Am J Psychiatry 1996;153:104–6.
Cohen BM, Wan WH, Froimowitz MP, Ennulat DJ, Cherkerzian S, Konieczna H. Activation of midline thalamic nuclei by antipsychotic drugs. Psychopharmacology 1998;135:37–43.
de Souza Crippa JA, Zuardi AW, Busatto GF, Sanches RF, Santos AC, Araujo D, et al. Cavum septum pellucidum and adhesio interthalamica in schizophrenia: an MRI study. Eur Psychiatry 2006;21:291–9.
Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Br Med J 1997;315:629–34.
Ellison-Wright I, Glahn DC, Laird AR, Thelen SM, Bullmore E. The anatomy of first-episode and chronic schizophrenia: an anatomical likelihood estimation meta-analysis. Am J Psychiatry 2008;165:1015–23.
Erbagci H, Yildirim H, Herken H, Gumusburun E. A magnetic resonance imaging study of the adhesio interthalamica in schizophrenia. Schizophr Res 2002;55:89–92.
Ettinger U, Picchioni M, Landau S, Matsumoto K, van Haren NE, Marshall N, et al. Magnetic resonance imaging of the thalamus and adhesio interthalamica in twins with schizophrenia. Arch Gen Psychiatry 2007;64:401–9.
Hallak JE, Crippa JA, Pinto JP, Machado de Sousa JP, Trzesniak C, Dursun SM, et al. Total agenesis of the corpus callosum in a patient with childhood-onset schizophrenia. Arq Neuropsiquiatr 2007;65:1216–9.
Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
Hill C, Keks N, Roberts S, Opeskin K, Dean B, MacKinnon A, et al. Problem of diagnosis in postmortem brain studies of schizophrenia. Am J Psychiatry 1996;153(4):533–7.
Hirayasu Y, Wada JA. Convulsive seizures in rats induced by N-methyl-D-aspartate injection into the massa intermedia. Brain Res 1992;577:36–40.
Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? Psychol. Methods 2006;11(2):193–206.
Jäger M, Bottlender R, Strauss A, Möller HJ. Classification of functional psychoses and its implication for prognosis: comparison between ICD-10 and DSM-IV. Psychopathology 2004;37(3):110–7.
Jakobsen KD, Frederiksen JN, Parnas J, Werge T. Diagnostic agreement of schizophrenia spectrum disorders among chronic patients with functional psychoses. Psychopathology 2006;39(6):269–76.
Kasai K, McCarley RW, Salisbury DF, Onitsuka T, Demeo S, Yurgelun-Todd D, et al. Cavum septi pellucidi in first-episode schizophrenia and first-episode affective psychosis: an MRI study. Schizophr Res 2004;71(1):65–76.
Kempton MJ, Stahl D, Williams SC, DeLisi LE. Progressive lateral ventricular enlargement in schizophrenia: a meta-analysis of longitudinal MRI studies. Schizophr Res 2010;120:54–62.
Kuloglu M, Caykoylu A, Yilmaz E, Ekinci O. A left temporal lobe arachnoid cyst in a patient with schizophrenia-like psychosis: a case report. Prog Neuropsychopharmacol Biol Psychiatry 2008;32:1353–4.
Kwon JS, Shenton ME, Hirayasu Y, Salisbury DF, Fischer IA, Dickey CC, et al. MRI study of cavum septi pellucidi in schizophrenia, affective disorder, and schizotypal personality disorder. Am J Psychiatry 1998;155:509–15.
Leviel V, Chesselet MF, Glowinski J, Cheramy A. Involvement of the thalamus in the asymmetric effects of unilateral sensory stimuli on the two nigrostriatal dopaminergic pathways in the cat. Brain Res 1981;223:257–72.
Malobabić S, Puskas L, Blagotić M. Size and position of the human adhaesio interthalamica. Gegenbaurs Morphol Jahrb 1987;133(1):175–80.
Mcglone J. Sex-differences in human-brain asymmetry — a critical survey. Behav Brain Sci 1980;3:215–27.
Meisenzahl EM, Frodl T, Zetzsche T, Leinsinger G, Heiss D, Maag K, et al. Adhesio interthalamica in male patients with schizophrenia. Am J Psychiatry 2000;157:823–5.
Meisenzahl EM, Frodl T, Zetzsche T, Leinsinger G, Maag K, Hegerl U, et al. Investigation of a possible diencephalic pathology in schizophrenia. Psychiatry Res 2002;115:127–35.
Murray RM, Lewis SW. Is schizophrenia a neurodevelopmental disorder? Br Med J 1987;295(6600):681–2.
Naylor CD. Meta-analysis and the meta-epidemiology of clinical research. BMJ 1997;315:617–9.
Nopoulos PC, Rideout D, Crespo-Facorro B, Andreasen NC. Sex differences in the absence of massa intermedia in patients with schizophrenia versus healthy controls. Schizophr Res 2001;48:177–85.
Pantelis C, Yucel M, Wood SJ, Velakoulis D, Sun D, Berger G, et al. Structural brain imaging evidence for multiple pathological processes at different stages of brain development in schizophrenia. Schizophr Bull 2005;31:672–96.

Romo R, Cheramy A, Godeheu G, Glowinski J. Distinct commissural pathways are involved in the enhanced release of dopamine induced in the contralateral caudate nucleus and substantia nigra by unilateral application of GABA in the cat thalamic motor nuclei. Brain Res 1984;308:43–52.
Rosales RK, Lemay MJ, Yakovley PI. The development and involution of massa intermedia with regard to age and sex. J Neuropathol Exp Neurol 1968;27:166.
Samra KA, Cooper IS. Radiology of the massa intermedia. Radiology 1968;91:1124–8.
Sharp S. Metaanal regression. Stata Tech Bull 1998;42:16–22.
Shenton ME, Dickey CC, Frumin M, McCarley RW. A review of MRI findings in schizophrenia. Schizophr Res 2001;49:1-52.
Shimizu M, Fujiwara H, Hirao K, Namiki C, Fukuyama H, Hayashi T, et al. Structural abnormalities of the adhesio interthalamica and mediodorsal nuclei of the thalamus in schizophrenia. Schizophr Res 2008;101:331–8.
Snyder PJ, Bogerts B, Wu H, Bilder RM, Deoras KS, Lieberman JA. Absence of the adhesio interthalamica as a marker of early developmental neuropathology in schizophrenia: an MRI and postmortem histologic study. J Neuroimaging 1998;8:159–63.
Spitzer RL, Endicott J, Robins E. Research diagnostic criteria: rationale and reliability. Arch Gen Psychiatry 1978;35(6):773–82.
Stone JM, Day F, Tsagaraki H, Valli I, McLean MA, Lythgoe DJ, et al. Glutamate dysfunction in people with prodromal symptoms of psychosis: relationship to gray matter volume. Biol Psychiatry 2009;15:533–9.
Stone JM, Bramon E, Pauls A, Sumich A, McGuire PK. Thalamic neurochemical abnormalities in individuals with prodromal symptoms of schizophrenia — relationship to auditory event-related potentials. Psychiatry Res 2010;30:174–6.
Susser E, Brown AS, Klonowski E, Allen RH, Lindenbaum J. Schizophrenia and impaired homocysteine metabolism: a possible association. Biol Psychiatry 1998;44:141–3.
Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F. Methods for meta-analysis in medical research. New York: Wiley; 2000.
Takahashi T, Suzuki M, Nakamura K, Tanino R, Zhou SY, Hagino H, et al. Association between absence of the adhesio interthalamica and amygdala volume in schizophrenia. Psychiatry Res 2008a;162:101–11.
Takahashi T, Suzuki M, Tsunoda M, Kawamura Y, Takahashi N, Maeno N, et al. The association of genotypic combination of the DRD3 and BDNF polymorphisms on the adhesio interthalamica and medial temporal lobe structures. Prog Neuropsychopharmacol Biol Psychiatry 2008b;32:1236–42.
Takahashi T, Suzuki M, Zhou SY, Nakamura K, Tanino R, Kawasaki Y, et al. Prevalence and length of the adhesio interthalamica in schizophrenia spectrum disorders. Psychiatry Res 2008c;164:90–4.
Takahashi T, Yucel M, Yung AR, Wood SJ, Phillips LJ, Berger GE, et al. Adhesio interthalamica in individuals at high-risk for developing psychosis and patients with psychotic disorders. Prog Neuropsychopharmacol Biol Psychiatry 2008d;32:1708–14.
Takahashi T, Chanen AM, Wood SJ, Walterfang M, Harding IH, Yucel M, et al. Midline brain structures in teenagers with first-presentation borderline personality disorder. Prog Neuropsychopharmacol Biol Psychiatry 2009a;33:842–6.
Takahashi T, Yucel M, Lorenzetti V, Nakamura K, Whittle S, Walterfang M, et al. Midline brain structures in patients with current and remitted major depression. Prog Neuropsychopharmacol Biol Psychiatry 2009b;33:1058–63.
Takahashi T, Malhi GS, Wood SJ, Yucel M, Walterfang M, Nakamura K, et al. Midline brain abnormalities in established bipolar affective disorder. J Affect Disord 2010;122:301–5.
Toda M, Abi-Dargham A. Dopamine hypothesis of schizophrenia: making sense of it all. Curr Psychiatry Rep 2007;9:329–36.
Tomelleri L, Jogia J, Perlini C, Bellani M, Ferro A, Rambaldelli G, et al. Brain structural changes associated with chronicity and antipsychotic treatment in schizophrenia. Eur Neuropsychopharmacol 2009;19:835–40.
Trzesniak C, Oliveira IR, Kempton MJ, Galvão-de Almeida A, Chagas MH, Ferrari MC, et al. Are cavum septum pellucidum abnormalities more common in schizophrenia spectrum disorders? A systematic review and meta-analysis. Schizophr Res 2011;125;1–12.
Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. Arch Gen Psychiatry 1987;44(7):660–9.
Wilson C, Terry Jr AV. Neurodevelopmental animal models of schizophrenia: role in novel drug discovery and development. Clin Schizophr Relat Psychoses 2010;4(2):124–37.
Wouterlood FG, Saldana E, Witter MP. Projection from the nucleus reuniens thalami to the hippocampal region: light and electron microscopic tracing study in the rat with the anterograde tracer Phaseolus vulgaris-leucoagglutinin. J Comp Neurol 1990;296:179–203.
Wright P, Takei N, Rifkin L, Murray RM. Maternal influenza, obstetric complications, and schizophrenia. Am J Psychiatry 1995;152:1714–20.