Schizophrenia

Cavum Septum Pellucidum and Adhesio Interthalamica
Abnormalities in Schizophrenia

José Alexandre de Souza Crippa,¹ Geraldo Busatto Filho² and Clarissa Trzesniak¹

¹. Department of Neuropsychiatry and Medical Psychology; 2. Department of Psychiatry, Faculty of Medicine, University of São Paulo

Abstract
Although the underlying pathology of schizophrenia remains unknown, it is believed that this disorder is related to brain developmental abnormalities that predispose patients to a characteristic pattern of brain malfunction from early adult life onwards. In fact, it has been proposed that subjects with schizophrenia could show both higher prevalence of cavum septum pellucidum (CSP) and non-adhesio interthalamica (AI) than healthy comparison controls, which is consistent with the neurodevelopmental model of schizophrenia. Below, we provide a synthesis of CSP and AI findings in schizophrenia. Although most of the studies point to increased prevalence only of large CSP in patients and no differences in the incidence of absent AI between patients and controls, future studies with standardisation of the methodology and with a more judicious selection of the samples are necessary to establish the real impact of these alterations in the disorder.

Keywords
Schizophrenia, psychosis, cavum septum pellucidum, adhesio interthalamica, massa intermedia

Schizophrenia is a disabling mental disorder that affects about 1% of the general population. Although the underlying pathology of this condition remains unknown, it is believed that schizophrenia is related to brain developmental abnormalities that predispose patients to a characteristic pattern of brain malfunction from early adult life onwards.¹ In fact, magnetic resonance imaging (MRI) studies conducted over the last few years provide some of the most compelling evidence indicating the presence of brain abnormalities in schizophrenia. These studies have shown alterations in different brain regions, including the limbic system, temporal and frontal lobes, thalamus and third and lateral ventricles.² In addition, medial and midline structural abnormalities such as increased incidence of cavum septum pellucidum (CSP) and the absence of adhesio interthalamica (AI) have been repeatedly reported in literature, which is consistent with the neurodevelopmental model of schizophrenia.³ In this article, we describe the main CSP and AI MRI findings in schizophrenia and discuss the possible implications of these abnormalities to the neuropathology of the disorder.

Cavum Septum Pellucidum
The septum pellucidum, a component of the limbic system, is a thin plate of two laminae that forms the medial walls of the lateral ventricles. When these laminae fail to fuse, they form a cavity known as CSP. A CSP is present in 100% of foetuses and premature infants, but the posterior half of the leaves are normally fused by three to six months of age.⁴ The presence of a CSP later in life may reflect developmental abnormalities of structures bordering the septum pellucidum, such as the corpus callosum and hippocampus.⁵ Thus, the CSP can be considered a marker of limbic system dysgenesis, a forme fruste of midline abnormalities or both.⁶ The complete non-fusion of the two leaflets of the septum pellucidum – an anomaly termed combined CSP and cavum vergae (CV) – is considered to be the most extreme form of CSP (see Figure 1).

Since its original description by Degreef et al.,⁷ the finding of a higher prevalence of CSP in patients with schizophrenia compared with asymptomatic controls has been observed in both chronic⁸–¹⁰ and first-episode patients.¹¹ However, some studies failed to find significant differences in the prevalence of CSP between patients and controls.¹²–¹⁶ Such discrepancies could be partly explained by differences in imaging techniques, sample characteristics (e.g. race, gender, clinical aspects) and/or CSP definition criteria among the reports.

Recent thin-slice high-resolution MRI studies using more quantitative approaches with relatively objective methods have improved the accuracy of estimates of the prevalence and the length of the CSP in such studies, the CSP has been evaluated by the measurement of its area,¹⁷ width,¹⁸ length,¹⁹ thickness and volume²⁰ or categorised by anato-mo-embryological type.²¹ However, the thin slice length methodology of counting the number of slices in which CSP appears, especially in its coronal view, is now the state-of-the-art method to assess the presence and severity of this brain abnormality. Based on post mortem findings,²² CSPs with anterior-to-posterior length spanning >6mm have been defined as large.²³,²⁴ This has proved to be the most sensitive and reliable way to classify CSPs.²³,²⁴

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Using this approach, several MRI studies have reported an increased prevalence of large CSPs in schizophrenia, although the prevalence of CSPs of any size did not differ between patients and healthy volunteers in some of these studies. Based on these findings, it has been speculated that the severity of the anomaly is more critical than its frequency. Furthermore, it appears that a small CSP is frequently observed in the general population and may simply reflect normal anatomical variability. Overall, the results of these studies reinforce the proposition that the clinical significance of a CSP may depend more on its magnitude than on whether it is present or absent.

There have been reports associating the presence of a large CSP in schizophrenia patients with reduced intelligence quotient (IQ), family history of the disorder, duration of the illness, poor prognosis, more negative symptoms, more severe thinking disturbance, higher suicide rates, impairment due to odd speech and greater cognitive deficits. Although we failed to find an association with the pattern of autonomic system activity, it was also demonstrated that patients with large CSP had more pronounced right-left brain asymmetry and reduced volumes of the left temporal lobe, bilateral hippocampus, bilateral amygdala and left parahippocampal gyrus. These findings indicate that patients with large CSP may show a different pattern of disturbed brain morphology and possibly more psychopathological impairment.

However, it is important to stress that CSP abnormalities are not specific to schizophrenia as they are also observed in other medical conditions of developmental origin, such as foetal alcohol, Sotos and Apert’s syndromes. In addition, while the size and prevalence of CSP are normal in subjects with panic disorder, there are also reports of an increased prevalence of CSP in post-traumatic stress, bipolar affective (BADD) and schizotypal personality (SPD) disorders. Based on the latter findings, some authors have speculated that psychosis associated with schizophrenia and BAD share, at least to some extent, neurodevelopmental abnormalities involving midline structures and that SPD may be a milder form on a continuum of schizophrenia spectrum disorders.

It is well known that the fusion of the septi pellucidi results from rapid growth of the hippocampus, corpus callosum and other midline structures that have consistently been linked to schizophrenia. Therefore, the presence of CSP in patients with schizophrenia could represent an early marker secondary to other developmental defects involving some of those brain regions. Similarly, it would be quite unlikely that a specific disturbance of a localised structure such as CSP would lead to widespread manifestations of schizophrenia and other disorders. More likely is that the developmental process by which the septum pellucidum is formed and matures may reflect the aetiology for widespread brain disturbance.

Adhesio Interthalamica

The AI, or massa intermedia, is a midline structure connecting the medial borders of both thalami across the third ventricle, which generally fuses between the 13th and 14th weeks of gestation (see Figure 2). It contains several nuclei and is normally well developed in mammals. Post mortem studies have shown that the AI is absent in approximately 15–25% of humans, but seems to be more commonly absent in males than females.

Several lines of evidence have indicated that the thalamus may play a crucial role in schizophrenia and this has raised interest in studying the AI in this disorder. As for CSP, alterations in AI could be a marker of early developmental abnormalities in midline brain structures, which could also be in line with the neurodevelopmental hypotheses of schizophrenia. Former studies have found that the absence of AI was more common among patients with schizophrenia than in healthy controls. However, other authors failed to replicate these findings using either MRI or post mortem methds.

These disagreements may be due to differences across studies with regard to imaging techniques, criteria used to define AI as present/absent and sample characteristics, making it difficult to compare the data of separate investigations directly. First, differences in slice thickness may have led to conflicting findings; for example, studies with relatively thick slices (3mm) could potentially miss a narrow connection between the thalami. Second, while some studies used only the coronal slices to define the presence of AI, others used both coronal and axial views or, more recently, the three planes. In addition, some authors considered AI as absent if it was not seen in two or more coronal slices, while another study adopted three slices as threshold. Third, differences in gender distribution, size of the samples or the ethnic groups studied may also have contributed to these discrepancies.

In order to minimise some of the methodological problems above, two recent studies in schizophrenia also measured the anterior–posterior length of the AI, counting the number of slices in which the...
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structure was clearly seen, and observed shorter AI in patients than in controls. This new quantitative approach to evaluating AI seems to be more effective than only determining its presence/absence and can lead to better comparability among studies.

Sexual dimorphism regarding AI has also been investigated in schizophrenia patients, but results have been contradictory. While some studies observed that AI absence was more common among male patients, Nopoulos and co-workers found a higher incidence of absent AI in female patients. In addition, it was also verified that female schizophrenia patients showed significantly lower ratings than controls.

Although the functional significance of gender differences in the prevalence of AI remains unclear, some authors have hypothesised that the female brain is more functionally symmetrical than the male brain. Moreover, it was also speculated 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.

Studies demonstrated that patients without AI had increased third ventricle volume and lower parahippocampal gyrus and amygdala volumes. Furthermore, this subgroup demonstrated more severe negative symptoms than patients with AI, although such findings have not been replicated by other authors.

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 AI as a midline structure may be important, since several abnormal morphologies have been reported in other midline regions in schizophrenia patients, including corpus callosum, cerebellar vermis and thalamus, as mentioned above. Second, animal studies revealed that the AI might be involved even in regulation of the release of dopamine in the basal ganglia or in the transfer of information implicated in the reciprocal regulation of the two nigrostriatal dopaminergic pathways. Although clearly not sufficient to explain the complexity of this disorder, the dopamine dysregulation still offers a direct relationship to symptoms and to their treatment. The dopamine hypothesis of schizophrenia is well known. Based on this, it was speculated that disturbed neural networks, including these regions during early neurodevelopment and consequent dopaminergic abnormalities, contribute to the pathogenesis of the disorder.

Relationship Between Cavum Septum Pellucidum and Adhesio Interthalamica

Given that large CSP and absent AI have independently been reported in schizophrenia and both can be linked to the neurodevelopmental model of the disorder, it is important to investigate the relationship between them. However, to the best of our knowledge only two studies evaluated the presence of both alterations in the same sample, showing absolutely little or no overlap between them. However, the lack of or weak association

between large CSP and absent AI is not surprising, since the development of the AI occurs during early gestation (around the 13th to 14th week), while the complete closure of the CSP – although requiring the normal development of other brain regions – occurs later during gestation or after birth.

Finally, it is important to emphasise that both enlarged CSP and absent AI are relatively uncommon findings in schizophrenia, since they are present in only 4% to 30% and 5% to 35% of patients, respectively. Therefore, these midline structural abnormalities should at most be regarded as early neurodevelopmental risk factors that could be associated with a future manifestation of schizophrenia in a subgroup of patients rather than as causative determinants of the disorder.

Conclusions and Future Directions

In conclusion, our review suggests that a large CSP and absence of AI in schizophrenia could be early markers of developmental abnormalities in the neural network, including midline brain and limbic regions, that may play an important role in the pathogenesis of schizophrenia. Further investigations are needed to reconcile the so far conflicting findings and to elucidate the complex clinical and functional effects of such neurodevelopmental abnormalities on the pathology of schizophrenia, for example by using large population-based investigations with longitudinal designs.

8. Clarissa Trzesniak is a Clinical Psychologist at the University of São Paulo. She previously worked at the Institute of Psychiatry of the University of London.
9. José Alexandre de Souza Crippa is an Assistant Professor in the Department of Neuropsychiatry and Medical Psychology School of Medicine at Ribeirão Preto, University of São Paulo, where he uses morphometric magnetic resonance imaging (MRI) and nuclear medicine techniques in studies investigating the pathophysiology of schizophrenia, panic, social anxiety and other neuropsychiatry disorders. He also directs the Consultation–Liaison Service and the Social and Medical Psychology School at the University of São Paulo, University of São Paulo.
10. Geraldo Busatto Filho is an Associate Professor in the Department of Psychiatry at the University of São Paulo, where he directs a neuromaging laboratory dedicated to the use of morphometric magnetic resonance imaging (MRI), nuclear medicine techniques and functional MRI in studies investigating the pathophysiology of schizophrenia, obsessive-compulsive disorder, Alzheimer’s disease and other neuropsychiatry conditions. He is also Vice President of the Directing Board of Research of the Medical School at the University of São Paulo. He previously worked at the Institute of Psychiatry of the University of London.
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