Cavum Septi Pellucidi in Tourette Syndrome

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Background: An enlarged cavum septum pellucidum (CSP) is a putative marker of disturbed brain development, and it has been associated with a variety of neuropsychiatric disorders. The goal of this study was to characterize systematically the CSP and the related cavum vergae in individuals with Tourette syndrome (TS).

Methods: The overall size and anteroposterior length of the CSP in 161 children (97 with TS and 64 normal pediatric control subjects) and 107 adults (43 with TS and 64 normal adult control subjects) were rated on high-resolution magnetic resonance images in the coronal view. The associations of CSP size with diagnosis and symptom severity scores were assessed using ordinal logistic regression.

Results: CSP size in TS children was significantly smaller than in normal control subjects, and it was inversely associated with attention-deficit/hyperactivity disorder symptom severity in the TS subjects. CSP size was not significantly associated with the comorbid diagnoses of OCD or ADHD. These results were replicated in the independent sample of adults with TS and their same-age control subjects. The presence of a cavum vergae was not significantly associated with a diagnosis of TS.

Conclusions: These findings suggest that the pathophysiology of TS may involve abnormalities in the early development of the CSP or in the neighboring corpus callosum, septal nuclei, or limbic system. Biol Psychiatry 2003;00:000–000 © 2003 Society of Biological Psychiatry

Key Words: Cavum septi pellucidi, Tourette syndrome, magnetic resonance imaging, septal nuclei

Introduction

The cavum septum pellucidum (CSP) is a potential midline space bounded by the two leaves of the septum pellucidum. The CSP or related cavum vergae (CV) that persist postnatally are putative markers of disturbances in early brain development (Bodensteiner and Schaefer 1990; Sarwar 1989; Shaw and Alvord 1969). An increased size or prevalence of the CSP has been reported in a wide variety of clinical populations, including children with mental retardation (Bodensteiner et al 1998) or fetal alcohol syndrome (Swayze et al 1997), in individuals with affective disorders (Shioiri et al 1996), and most commonly in patients with schizophrenia (Kwon et al 1998; Nopoulos et al 1997).

Tourette syndrome (TS) is characterized by motor and vocal tics that begin in childhood and that fluctuate over time. It is frequently associated with other social and behavioral disturbances (Shapiro et al 1988; Stokes et al 1991). In both clinical and epidemiologic samples, TS frequently co-occurs with obsessive-compulsive disorder (OCD) or attention-deficit/hyperactivity disorder (ADHD) (Douglass et al 1995; Flament et al 1988; Leonard et al 1992; Peterson et al 2001a; Shapiro et al 1988). The co-occurrence of these disorders is thought to be a consequence of shared genetic and environmental risk factors that produce anatomic and functional disturbances in cortical–subcortical circuits (Leckman and Riddle 2000; Peterson et al 1999). Environmental risk factors in TS are thought to include prenatal and perinatal complications, such as maternal stress, low birth weight, and obstetric complications associated with central nervous system hypoxia or ischemia. These complications are thought to play a role in modulating the severity of tic symptoms or the likelihood of having comorbid OCD or ADHD (Hyde et al 1992; Leckman et al 1990; Santangelo et al 1994; Whitaker et al 1997).

The septal region surrounding the CSP is anatomically intimately interconnected with the cortical–subcortical circuits thought to subserve TS symptoms. Characterizing the septal region may therefore provide important information concerning anatomic and functional disturbances in the development of these circuits in TS subjects. Indeed, several isolated case reports have suggested that the CSP may be enlarged in individuals who have tic disorders (Lewis and Mezey 1985; Robertson et al 1991; Whitaker et al 2001). In both clinical and epidemiologic samples, TS frequently co-occurs with obsessive-compulsive disorder (OCD) or attention-deficit/hyperactivity disorder (ADHD) (Hyde et al 1992; Leckman et al 1990; Santangelo et al 1994; Whitaker et al 1997).

The main objective of our study was to characterize the occurrence and size of the CSP and CV in the magnetic resonance imaging (MRI) scans of 140 TS and 128 normal control subjects. We hypothesized that the CSP would differ significantly in size in TS subjects compared with control subjects. In addition, correlations of CSP size with the severity of tic, OCD, and ADHD symptoms were examined in the patient group.
Methods and Materials

Subject Recruitment and Characterization

Subjects with TS (97 children and 43 adults) were recruited from the Tic and Obsessive-Compulsive Disorders Specialty Clinic at the Yale Child Study Center. Normal control subjects (64 children and 64 adults) were recruited from a list, purchased from a telemarketing company, of families in the local community. These individuals were identified as being within a specified age range and as living in the same neighborhoods (based on zip code) as the TS subjects. Individuals from the list were randomly selected for contact. Introductory letters were sent and followed by screening phone calls. Of the eligible control subjects contacted, approximately 10% participated. After complete description of the study to the subjects, written informed consent was obtained. Assent was obtained from each child. The Yale University School of Medicine Human Investigations Committee approved the study protocol.

Subjects were aged 5–63 years, and they were predominantly right-handed (Oldfield 1971). Subjects included individuals with a primary diagnosis of TS with or without comorbid OCD or ADHD, and normal control subjects. Of the 97 child subjects with TS, 20 had comorbid OCD, 19 had comorbid ADHD, and 10 had both OCD and ADHD. Of the 43 adults with TS, 20 also had OCD, 4 had ADHD, and 3 had both OCD and ADHD. A DSM-IV diagnosis of TS was based on an extensive clinical examination. All other neuropsychiatric diagnoses in TS and control subjects were established through administration of the Schedule for Tourette Syndrome and Other Behavioral Disorders (Pauls and Hurst 1996), a structured interview that includes the Kiddie-Schedule for Affective Disorders and Schizophrenia, Epidemiologic Version (Ambrosini et al 1989; Kaufman et al 1997), the adult Schedule for Affective Disorders and Schizophrenia (Endicott and Spitzer 1978), and more detailed sections on TS and OCD for both children and adults. Exclusionary criteria for TS subjects included another movement disorder or a major psychiatric disorder other than OCD or ADHD that antedated the onset of tics. For all control subjects, exclusionary criteria included any history of tic disorder, OCD, ADHD, or current Axis I disorder. Additional exclusionary criteria for both groups included a history of seizure or head trauma with loss of consciousness, ongoing substance abuse or previous substance dependence, or intelligence quotient below 80 (Wechsler 1974, 1981).

At the time of the study, 59 child TS subjects (61%) were taking psychotropic medication that included typical neuroleptics (n = 15), atypical neuroleptics (n = 3), stimulants (n = 4), α-agonists (n = 21), serotonin-specific reuptake inhibitors (n = 8), or tricyclic antidepressants (n = 7). Of the adult TS subjects, 27 (63%) were taking medication, which included typical neuroleptics (n = 3), atypical neuroleptics (n = 1), α-agonists (n = 4), serotonin-specific reuptake inhibitors (n = 9), or tricyclic antidepressants (n = 1).

Ratings of current (at the time of scan) and worst-ever severity of tic and OCD symptoms were obtained using the Yale Global Tic Severity Scale (DuPaul 1991). Socioeconomic status at birth (SES) was estimated using the Hollingshead Four-Factor Index of Social Status (Hollingshead 1975).

MRI Scanning

Magnetic resonance images of the brain were obtained using a single GE Sigma 1.5-Tesla scanner (General Electric, Milwaukie, WI). Head position was standardized using canthomeatal landmarks. A three-dimensional, spoiled gradient recall sequence was obtained for analyses of the CSP and CV (repetition time = 24 msec; echo time = 5 msec; flip angle, 45 degrees; frequency encoding superior/inferior; no wrap; 256 × 192 matrix; field of view = 30 cm; two excitations; slice thickness = 1.2 mm; and 124 contiguous slices encoded for sagittal slice reconstructions). Scan time was 19.7 min.

CSP Measures

Magnetic resonance images were analyzed on Sun Ultra 10 workstations using ANALYZE 7.5 software (Biomedical Imaging Resource, Mayo Foundation, Rochester, MN). Scans were cropped and magnified 12-fold in each dimension to aid in coding of the CSP. The same observer (KK) rated all scans blind to diagnosis and subject characteristics. Images were assessed by a neuroradiologist to exclude clinically significant abnormalities.

Ratings of Coronal Grade. Scans were rated in the coronal view, and the CSP was graded on an ordinal scale of 0–4, with descriptive anchors based on the overall size of the visible cavity (0 = absent, 1 = questionably equivocal, 2 = mild CSP, 3 = moderate CSP, 4 = large CSP). Ratings conformed with previously published methods (Degreef et al 1992; Fukuzako et al 1996; Jurjus et al 1993) and were performed on the coronal slice that showed the greatest evidence of a cavity. A rating of 0 was assigned if an intact septum pellucidum was clearly visible in all slices (i.e., no CSP was present), a rating of 1 was assigned if the septum was unclear (i.e., questionable CSP), and ratings of 2–4 were assigned based on size of the visible cavity (i.e., based on the area, height, and width of the cavity in the coronal view). Reliability of the ratings was aided by comparison with a set of standard CSP images from each ordinal grade (see Figure 1). Reliability was quantified using CSP ratings obtained independently from 30 randomly selected scans by two raters familiar with CSP anatomy. Inter-rater reliability was excellent (weighted κ = 0.72) (Fleiss 1981; Kramer and Feinstein 1981). The presence of a CV, a potential caudal extension of the CSP (Schwidde 1952), was similarly assessed in each scan.

Ratings of CSP Length. The anteroposterior length of the CSP was measured by counting the number of coronal slices containing evidence of the CSP according to previously described methods (Nopoulos et al 1998): 0 = absent, 1 = CSP seen in one slice only, 2 = CSP seen in two slices, etc. Because discrete slices are counted, CSP length (similar to CSP grade) is, strictly speaking, an ordinal measure, and not a continuous one.
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**Figure 1. Images of representative cavum septi pellucidi.** Each subjects’ brain magnetic resonance imaging scan was graded on a scale of 0 to 4 based on presence and size of the cavum septi pellucidi (CSP). A rating of grade 0 was assigned if there was an intact septum pellucidum, grade 1 = questionable CSP, grade 2 = mild CSP, grade 3 = medium CSP, grade 4 = large CSP.

Inter-rater agreement of two raters was therefore assessed using a weighted κ statistic and found to be moderate (weighted κ = 0.56). The superior reliability of CSP grade (above) motivated its preferential use in hypothesis testing.

**Statistical Analyses**

All statistical procedures were performed using SPSS for Windows version 10.0 (Statistical Product and Service Solutions, Chicago, IL). All p values were of the two-sided type.

**Ratings of CSP Size.** We tested our primary null hypothesis (that CSP size was not associated with the diagnosis of TS) using ordinal logistic regression with a logit link. Hypothesis testing was performed using the CSP grade primarily, although confirmatory secondary analyses were conducted using CSP length. Regression analyses were performed first in children (<18 years) and then in an independent sample of adults (18–64 years) in an attempt to replicate findings from the children.

Ordinal ratings of CSP grade were the dependent measure in ordinal regression analyses. Ordinal regression was selected for these analyses so as to maintain the quantitative, ordinal ranking of CSP ratings, as well as to permit the use of statistical covariates in the analyses. The diagnosis of TS was included as the between-subjects factor, and lifetime diagnoses of OCD or ADHD, age, gender, SES, and whole brain volume (WBV) measurements were included as covariates. Whole brain volume measurements were included to control for generalized scaling effects within the brain (Peterson et al 2001b). Although handedness and minority status were initially included as possible confounding factors, they were found to have negligible effects on the parameter estimates. Consequently, neither was included in the final models. The same set of regression analyses was then performed entering CSP length as the ordinal dependent measure.

In addition to the above covariates, two- and three-way interactions between diagnosis and covariates were considered for inclusion in the models. Terms that were not significant were eliminated via backward stepwise regression, with the constraint that the model at each step was hierarchically well formulated (i.e., all possible lower-order terms must be included in the model regardless of their significance) (Kleinbaum 1994; Morrell et al 1997). Two-way interactions between TS and medication use were also entered into the regression model to assess possible medication effects. No interactions were found to be significant, so none were included in the final models.

For each of the continuous covariates (age, SES, WBV), the proportional odds assumption was checked graphically by plotting the cumulative logs of dichotomized ordinal ratings against each covariate (Bender and Grouven 1997). Each plot confirmed that the dichotomized responses were linearly related to the covariates, validating use of the ordinal regression modeling for the analyses.

**Associations of CSP Grade with Symptom Severity.** Symptom severity ratings were available for the majority of TS subjects. Children and adults with TS were combined for these analyses. The associations of CSP grade with the severity of current and worst-ever tic and OCD symptoms, premedicated and current ADHD symptoms, Conners parent and teacher scores, and CBCL scores were explored. Correlations of symptom severity with CSP grade were performed using ordinal regression analysis, with CSP grade as the dependent variable, gender as a between-subjects factor, and symptom severity as a continuous covariate. Age and WBV were also entered as covariates.

**Results**

**Subjects**

High-resolution anatomic brain MRI scans were acquired in 161 children (97 TS subjects and 64 normal control subjects) and 107 adults (43 TS subjects and 64 normal control subjects). Among the children with TS, 30 (31%) of these subjects also carried lifetime diagnoses of OCD, and 29 (30%) had diagnoses of ADHD. In the TS adults, 23 subjects (53%) also had lifetime diagnoses of OCD, and 7 (16%) had ADHD.

Amongst the children, the patient group was slightly older than the control group [11.2 ± 2.3 vs. 10.1 ± 2.2 (mean ± SD) years, t(159) = 2.76, p = .006] and had a higher proportion of boys (79.4% vs. 54.7%, χ^2 = 11.1, p < .001), but both groups were comparable in terms of SES (p = .38). In the adult population, the control group had a higher SES [48.5 ± 9.8 vs. 43.6 ± 11.1, t(105) = −2.40, p = .02] than the TS group, but they were similarly aged (p = .16) and had similar proportions of men (p = .96).
In an analysis of the children only, a diagnosis of TS was a significant predictor of CSP grade in children ($p < .03$, see Table 1), allowing rejection of our null hypothesis that CSP size was unrelated to diagnosis of TS. The parameter estimate for a diagnosis of TS ($PE = -.77$) indicated that these subjects had smaller CSPs than did the control group (see Figure 2A). The covariates of OCD and ADHD were not found to be significant, suggesting that the association of TS with CSP grade was not caused by the presence of comorbid OCD or ADHD. Whole brain volume was included as a covariate to account for scaling effects, and it was associated with CSP grade only at a trend level of significance ($PE = 2.71E^{-06}$, $p = .07$). Socioeconomic status at birth, age, and gender were not associated with CSP grade, and they did not interact significantly with a diagnosis of TS. Interactions between TS diagnosis and psychotropic medication use, specifically neuroleptic use, were not significant (TS $\times$ any medication: $PE = .02$, $p = .98$; TS $\times$ neuroleptic: $PE = .17$, $p = .73$), indicating that medication use did not significantly contribute to our finding of smaller CSPs in the patient group.

Findings were similar when CSP length was entered as the ordinal dependent measure in our regression analyses (see Table 1). Cavum septi pellucidi length tended to be shorter in the TS children ($PE = -.64$, $p = .06$) compared with healthy subjects. No covariates or interactions were associated significantly with CSP length.

### Hypothesis Testing

In adults, a diagnosis of TS was found to be a significant predictor of CSP grade ($p < .05$) and CSP length ($p < .01$) (Table 1). As in the child population, the CSPs in TS adults were smaller than in control adults (Figure 2B) (CSP grade: $PE = -.105$; CSP length: $PE = -.140$). Interactions between diagnoses and covariates were not significant and therefore were not included in the final model. Whole brain volume was the only significant covariate in the CSP grade regression model ($PE = 2.71E^{-06}$, $p < .01$), confirming the presence of scaling effects. Age was a significant covariate in the CSP length regression model ($PE = .04$, $p < .04$). No significant interactions of TS with neuroleptic or other medication use were detected.

### Associations with Symptom Severity

In TS children and adults, CSP grade was significantly associated with the premadedicated severity scores for ADHD inattention and combined-type symptoms (inattention: $PE = -.12$, $p < .002$, $n = 64$; combined-type: $PE = -.06$, $p < .003$, $n = 64$). For subjects with TS, including those with comorbid OCD or ADHD, having a smaller CSP was associated with more severe premadicated ADHD symptoms. Cavum septi pellucidi grade was not significantly associated with the severities of current ADHD symptoms, nor with tic or OCD symptoms.
Additional Characterization of the CSP and CV

In the children, 30 patients (31%) and 10 normal control subjects (16%) had no CSP (i.e., Grade 0), whereas 44 patients (51%) and 43 normal control subjects (67%) had mild, moderate, or large CSPs (i.e., grades 2–4). One child with TS and ADHD had a CSP of grade 4 with a CV. In the adult population, 9 TS (21%) and 10 normal control subjects (16%) had no CSP, whereas 16 TS subjects (37%) and 38 normal control subjects (59%) had CSPs of grade 2–4. Two of the adult normal control subjects and one TS subject with OCD had a CSP of grade 4 with a CV. The presence of a CV was not significantly associated with a diagnosis of TS (Fisher’s p = 1.0 for children and adults).

Discussion

The aims of this study were to characterize the CSP in TS subjects and to assess whether symptom severity was related to CSP size. We found that the CSP in TS children was smaller than in normal control children, using both CSP grade and estimated CSP length as indicators of CSP size. We then replicated these findings in an independent sample of TS and normal adult subjects. CSP grade and length were not significantly associated with gender, SES, or a lifetime diagnosis of comorbid OCD or ADHD. The absence of an association with ADHD is consistent with a prior study of ADHD children (Nopoulos et al 2000). Age was significantly associated with CSP length only in the adult group. Neuroleptic or other psychotropic medication use did not seem to contribute to the finding of smaller CSPs in TS subjects. CSP grade was also significantly related to the severity of inattention and combined-type ADHD symptoms in the TS subjects before beginning medications. CSP grade was not associated, however, with the severity of current ADHD, tic, or OCD symptoms.

In addition to the findings in TS subjects, this study provides normative data on CSP size in a large, community-based sample of healthy children and adults. Previous prevalence estimates for the presence of a CSP in normal adults has ranged widely, from 2% to 85% (Degreffe et al 1992; Hughes et al 1955; Nopoulos et al 1997; Schwidde 1952; Van Wagenen and Aird 1934). This variability in previous prevalence estimates has several likely sources. First, most prior studies regarded the CSP dichotomously, as either “enlarged” (and pathologic) or “within normal limits,” and the criteria for this rating varied considerably across studies. Second, most prior studies have been either postmortem investigations, in which fixation procedures can alter CSP morphology, or lower-resolution imaging studies that could underestimate the prevalence of small CSPs. Third, prior studies have drawn subjects from heterogeneous clinical populations, where CSPs tend to be larger and more variable (Bruyn 1977). In contrast, the present study employed measures from high-resolution scans obtained in a large, community-based sample of healthy subjects.

These methodological advantages probably account for the ability of these data to suggest that CSP size in the general population is a continuous and normally distributed variable (Figure 2). The underlying normal distribution of CSP size in healthy individuals is presumably a direct consequence of normal variability in CSP closure during early development. It also clearly suggests that the “normal” CSP is not one that is entirely closed, but one that instead ranges around a size that is reasonably small (i.e., averaging a Grade 2 in our scheme). In addition, our data suggest that the distribution of CSP sizes is similar in children and adults (Nopoulos 1999; Pauling et al 1998), consistent with the determination of CSP size early in development.

Embryology of the Septal Region

The embryology of the CSP and the associated septal region is relevant to understanding the significance of these findings within the context of the pathophysiology of
TS. The CSP first appears in week 12 of gestation. It begins as a hollowing of the solid lamina terminalis beneath primordial hippocampal tissue. Initially, differential growth of the neighboring corpus callosum is thought to stretch and progressively thin the lamina terminals to form a clear membrane, the septum pellucidum. Continued growth of the corpus callosum further stretches the septum pellucidum to produce a midline cleavage (Bruyn 1977; Hughes et al 1955; Rakic and Yakovlev 1968; Swenson 1944) (see Figure 3A, B). Invasion of circulating phagocytic monocytes may help to cavitate the septum to create the CSP (Tseng et al 1982; Valentino and Jones 1982). At this point in development, the leaves of the septum pellucidum laterally bound the CSP on each side.

At approximately the 20th week of gestation, the leaves of the septum pellucidum fuse in the posterior to anterior direction, probably as a consequence of continued growth of the anterior portion of the corpus callosum and hippocampal alvei (Sarwar 1989; Schwidde 1952). Growth of the rostrum of the corpus callosum apposes the inferior aspect of two leaves of the septum pellucidum and subsequently seals the CSP inferiorly. Cells migrating inward from the lateral septal nuclei then populate the CSP (Tseng et al 1982; Valentino and Jones 1982). CSP closure reaches its adult state in the majority of children by 6 months of age (Shaw and Alvord 1969). Whether structural plasticity in the surrounding septal tissue can alter CSP morphology subsequently in development is unknown.

The formation and resolution of the CSP is therefore intimately linked with concurrent development of the corpus callosum, hippocampus, amygdala, and septal nuclei, and disturbances of CSP anatomy in children and adults could reflect embryological abnormalities in the development of these neighboring structures. Given the possible relevance of these multiple neighboring regions in determining CSP morphology, focusing solely on either the CSP in the coronal view or on its anteroposterior length (as many previous studies have done) may offer an incomplete view of CSP pathology. The degree of non-closure of the CSP in the lateral and superior–inferior dimensions (i.e., the width or height of the cavity) along with its anteroposterior length may jointly provide important clues to altered central nervous system development.

**Septal Anatomy and Function**

The septal region is an important component of the limbic system that has widespread connections to other regulatory centers in the brain (see Figure 4). It serves as a key relay station between the hypothalamus, hippocampus, amygdala, and brainstem (Cavazos et al 1997). These septal circuits are thought to play an important role in numerous biological and behavioral systems, including self-maintenance, sensory processing, attention and activity, memory and learning, sexuality, aggression, homeostasis, emotionality, and maternal behavior (Fried 1972; Luban and Numan 1973; Sarwar 1989; Sheehan et al 2000). Abnormal development of the septal region therefore may disrupt one or more of these functions.

The septal nuclei and related limbic system circuits are interconnected with many of the brain regions implicated in the pathophysiology of TS-related disorders (Peterson et al 1999). The sexual and aggressive content of many tics, obsessions, and compulsions, for example, suggests involvement of these systems in TS and OCD. The septal nuclei are thought to help filter sensory input, and lesions in this region have resulted in increased motoric activity and hyperreactivity to stimuli (Carey 1982; Douglas and Raphelson 1966; Luban and Numan 1973). Related limbic circuits could thereby contribute to the attentional and motor abnormalities in TS and ADHD. The regions with the strongest anatomic connections to the septal nuclei, such as the cingulate cortex, temporal lobe, hypothalamus, and periaqueductal gray, are limbic system components that have previously been hypothesized to contribute to the appearance and modulation of TS-related symptoms (Braun et al 1993; Lakke and Wilmink 1985; Leckman et al 1994; Peterson et al 1998; Robertson et al 1990).

**Pathophysiology**

The finding of smaller CSPs in a patient population has not been reported previously. It highlights the importance of considering the role of the developing CSP and associated septal nuclei in the pathogenesis of TS. A smaller CSP in TS patients could arise from disturbances in the formation of the CSP, from excessive or premature closure of the CSP, or as a consequence of potential postnatal plastic changes in septal tissue surrounding the CSP. The timing of these developmental abnormalities, whether early or late in life, are key to determining what role the altered CSP morphology might play in the pathophysiology of TS.

The embryological origins of the CSP suggest that smaller CSPs could be a consequence of an initial failure of the corpus callosum to develop properly during gestation. It may therefore be relevant that abnormalities in corpus callosum morphology have been reported in both TS children and adults (Baumgardner et al 1996; Peterson et al 1994). Alternatively, smaller CSPs could arise secondary to a genetic or environmental event during the pre- or perinatal period that exaggerates CSP closure. Peri- or postnatal plastic changes in the septal area that preferentially affect TS subjects could also produce localized septal hypertrophy and therefore smaller CSPs (Peterson et al 2001b). Similarly, hypertrophy of neighboring structures potentially involved in TS pathophysiology (such as the thalamus or hypothalamus) could contribute to in-
creased closure rates for the CSP. Finally, postnatal fibrosis and gliosis in the septal region, perhaps a consequence of autoimmune processes that have been suspected in some cases of TS (Kiessling et al 1993; Swedo et al 1998), could produce CSP narrowing.

The pathophysiological relevance of the association of CSP grade with the severity of premedicated ADHD symptoms in TS subjects is unclear. CSP size may reflect alterations in septal tissue or related brain regions that help to modulate the severity of ADHD symptoms. The association therefore suggests that early developmental events may contribute to ADHD comorbidity in TS subjects. Because ADHD (unlike OCD) is unlikely to be a variant expression of an underlying TS genetic diathesis (Pauls et al 1986; Peterson et al 2001a), these early developmental events that influence ADHD comorbidity in TS seem likely to be of a nongenetic origin. Cavum septi pellucidi size may also be associated nonspecifically with ADHD symptom severity (i.e., regardless of the presence of tics). The group specificity of these associations therefore requires further study in larger samples of OCD and ADHD subjects.

**Limitations and Future Directions**

This study points to the likely importance of early developmental events in the pathophysiology of TS. Future studies will need to focus on these early events to determine which pre- and perinatal complications might affect both the size of the CSP and the course of illness. Our findings suggest that the limbic system may be an increasingly important, though heretofore relatively neglected, area of TS research. The CSP, however, offers only an indirect assessment of the development of the septal region and its associated limbic structures. More detailed morphometric, functional imaging, and postmortem studies are needed to define better the sequelae of disturbances in septal and limbic system development in TS. Studies of the nucleus accumbens, hippocampus, amygdala, cingulate, hypothalamus, and brain stem nuclei may therefore be informative in TS research, as they all have strong connections to the septal nuclei. They would complement the current findings and further elucidate the role of the limbic system in the pathophysiology of TS.

**Figure 3.** (A) Development of the corpus callosum (CC) and cavum septum pellucidum (CSP) (coronal view). (i) Juxtaposition of the banks of the median sulcus, and formation of the massa commissuralis (MC) in the region of the primordial hippocampus (PriHp) in the floor of the interhemispheric fissure. (ii) The commissuration of the hemispheres by fibers of the CC and rostral extension of the massa commissuralis (MC) over the median sulcus. (iii) Separation of the banks of the median sulcus forming the leaves of the septum pellucidum (SP). The CSP is sealed inferiorly by the rostrum of the CC (Rakic and Yakovlev 1968). (B) Phylogenetic development of the septal region (sagittal view). Development of the CSP in humans roughly recapitulates phylogenetic development. (i) Marsupials: the hippocampus (Hp) and subiculum (su) are dorsal to the lamina terminalis (LT). (ii) Intermediate stage: the hippocampus begins to infold. (iii) Hedgehog and bat: the corpus callosum (CC) and fornix (Fo) have broken through the subiculum. (iv and v) Rat: the intercommissural hippocampus has been obliterated, leaving only the pre- and postcommisural parts. (vi) Humans: the CC grows lengthwise in the direction of the arrows, and the septum pellucidum (SP) stretches anteriorly. Iso, isocortex; SA, septal area; GE, ganglionic eminence; PHp, precommissural hippocampus; AC, anterior commissure; Rcc, rostrum of CC; Scc, splenium of CC; Gcc, genu of CC (Bruyn 1977).
Figure 4. Anatomy of the septal region. The septal nuclei are located inferolateral to the septum pellucidum. These nuclei, part of the limbic system, relay fibers between the brain stem, hippocampus, amygdala, habenula, hypothalamus, mammillary bodies, substantia nigra, cingulate gyrus, forebrain, and cortex. The medial septal nuclei are primarily output nuclei and include the nucleus of the diagonal band of Broca, the bed nucleus of the stria terminalis, the bed nucleus of the anterior commissure, and the septofimbrial nuclei. The lateral septal nuclei are primarily input nuclei and include the nucleus basalis of Meynert and the nucleus accumbens. These nuclei, part of the limbic system, include the bed nucleus of the stria terminalis, the basal nucleus of Meynert, and the bed nucleus of the stria terminalis. The lateral septal nuclei are primarily input nuclei and include the nucleus basalis of Meynert and the nucleus accumbens (Cavazos et al 1997). The brain is represented here in a coronal view. CA, caudate nucleus; PU, putamen; SP, septum pellucidum; SN, septal nuclei; NDB, nucleus of the diagonal band of Broca; CC, body of the corpus callosum; NA, nucleus accumbens; SI, substantia innominata; AON, anterior olfactory nucleus; SG, subcallosal gyrus; IC, internal capsule; LV, lateral ventricle, frontal horn (Nieuwenhuys et al 1988).

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