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Sex differences in the absence of massa intermedia in patients with schizophrenia versus healthy controls

Peg C. Nopoulos*, David Rideout, Benedicto Crespo-Facorro, Nancy C. Andreasen

Mental Health Clinical Research Center, University of Iowa College of Medicine, Iowa City, IA 52242, USA

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Abstract

Objective. To evaluate sexual dimorphism and incidence of absent massa intermedia (MI), a midline thalamic structure, in patients with schizophrenia and healthy controls.

Methods. Thin slice magnetic resonance images of the brain were obtained. The presence of MI was determined by viewing sagittal, coronal, and axial planes.

Results. In healthy controls, females had a significantly lower incidence of absent MI (13.56%) compared with males (32.08%). In patients with schizophrenia, there was a sex by diagnosis interaction. Female patients had significantly higher incidence of absent MI (32.76%) compared with their healthy controls (13.56%), whereas the male patients showed no difference in incidence of absent MI compared with their controls.

Conclusion. The MI, a sexually dimorphic midline structure, is more commonly absent in female patients with schizophrenia. These results support the growing literature reporting structural aberration of the thalamus, as well as other midline structures in the brains of patients with schizophrenia.

Keywords: Massa intermedia; Magnetic resonance imaging; Schizophrenia; Sex differences

1. Introduction

Many of the structural brain abnormalities reported in patients with schizophrenia have been located in the midline or medial region of the brain. In particular, midline abnormalities have been consistently identified in the corpus callosum (Woodruff et al., 1995; Tibbo et al., 1998), septum pellucidum (Nopoulos et al., 1997a; Kwon et al., 1998), and cerebellar vermis (Weinberger et al., 1979; Lippman et al., 1982; Sandyk et al., 1991; Rossi et al., 1993; Nopoulos et al., 1999). Median structures would include the ventricular system and the thalamus. In particular, the thalamus has become a region that has been identified as having a central role in the pathophysiology of the illness. Neuroimaging (Andreasen et al., 1994; Flaum et al., 1995; Buchsbaum et al., 1996; Gur et al., 1998; Staal et al., 1998) and neuropathologic (Baumer, 1954; Treff and Hempel, 1958; Pakkenberg, 1990, 1992) studies have found morphologic abnormalities of the thalamus in patients with schizophrenia.

The massa intermedia (MI) is a midline thalamic structure, connecting the two thalami through somewhat loosely organized axons. In mammals this region is composed of several nuclei; however, in humans it

* Corresponding author. Present address: University of Iowa College of Medicine, Department of Psychiatry, 1–180 Medical Education Building, Iowa City, IA 52242-1000, USA. Tel.: +1-319-353-4233; fax: +1-319-353-3003.

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Table 1
Patient and control group demographics

	Patients ($n = 114$) mean (SD)		Controls ($n = 112$) mean (SD)	
	Male ($n = 56$)	Female ($n = 58$)	Male ($n = 53$)	Females ($n = 59$)
Age (years)	28.6 (8.83)	31.2 (11.9)	27.6 (7.87)	29.4 (12.2)
Parental SES[a]	3.01 (0.92)	3.01 (0.69)	2.84 (0.49)	2.89 (0.51)
Age at onset (years)	22.1 (6.24)	23.0 (6.8)		

[a] Parental socioeconomic status based on a modified Hollingshead scale (1–5); the lower the number, the higher the social class.

is much smaller and quite variable in its size. In fact, in post-mortem studies, the MI has been documented to be altogether absent in 20–30% of normal human brains (Barr and Kiernan, 1988; Carpenter, 1991). Furthermore, the variability in presence and size of MI is sexually dimorphic, with the MI being present more often in females compared with males (Morel, 1948; Rabl, 1958; Davie and Baldwin, 1967; Samra and Cooper, 1968; Allen and Gorski, 1991). In addition, the study by Allen and Gorski (1991) showed that, of those brains with an MI, the size of the MI was substantially larger in the women compared with men.

Only one other study has evaluated the presence or absence of the MI in patients with schizophrenia. In a magnetic resonance imaging (MRI) and post-mortem study of first-episode patients, Snyder et al. (1998) found that patients with schizophrenia were more likely to have an absent MI compared with healthy controls. However this study did not examine the sexual dimorphism of the MI either in the controls or the patients.

Gender differences in the severity of morphologic brain changes within schizophrenia have been well documented. Although male and female patients tend to have the same pattern of abnormal brain morphology, most of the studies indicate that male patients tend to have more severe brain changes [for review see Nopoulos et al. (1997a)]. The current study was designed to evaluate the frequency in which the MI appears in a large sample of patients with schizophrenia and a comparison group of healthy controls using state of the art MRI. In addition, the sexual dimorphism of this structure, both among the controls and the patient population, was evaluated.

2. Methods

2.1. Subjects

Patients were consecutive admissions to the University of Iowa Mental Health Clinical Research Center (MH-CRC) and participated in a brain imaging protocol. As our male to female ratio of admissions is roughly 2.5:1, the male sample ($n = 56$) was acquired considerably quicker than the female sample ($n = 58$). Each patient was diagnosed as having schizophrenia using either DSM-III-R or DSM-IV criteria and based on data obtained using the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al., 1992a). Of the 114 patients, 43 were considered first episode (defined by first psychiatric hospitalization) and the remaining 71 were chronic. Of the 43 that were first episode, seven were not given the diagnosis of schizophrenia at intake, but, through their participation in our prospective longitudinal study, the diagnosis of schizophrenia was confirmed on their 2 year follow-up evaluation.

Symptom data were obtained from the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983) and Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) within the CASH. Summary scores for three dimensions of symptoms (positive, negative, and disorganized) were calculated using sums of global scores from the SANS/SAPS. The positive symptom dimension was the sum of global scores for hallucinations and delusions. The negative symptom dimension score was the sum of global scores for alogia, affective flattening, avolition-apathy, and anhedonia-asociality. The disorganized symptom dimension was comprised of the global scores of positive formal thought

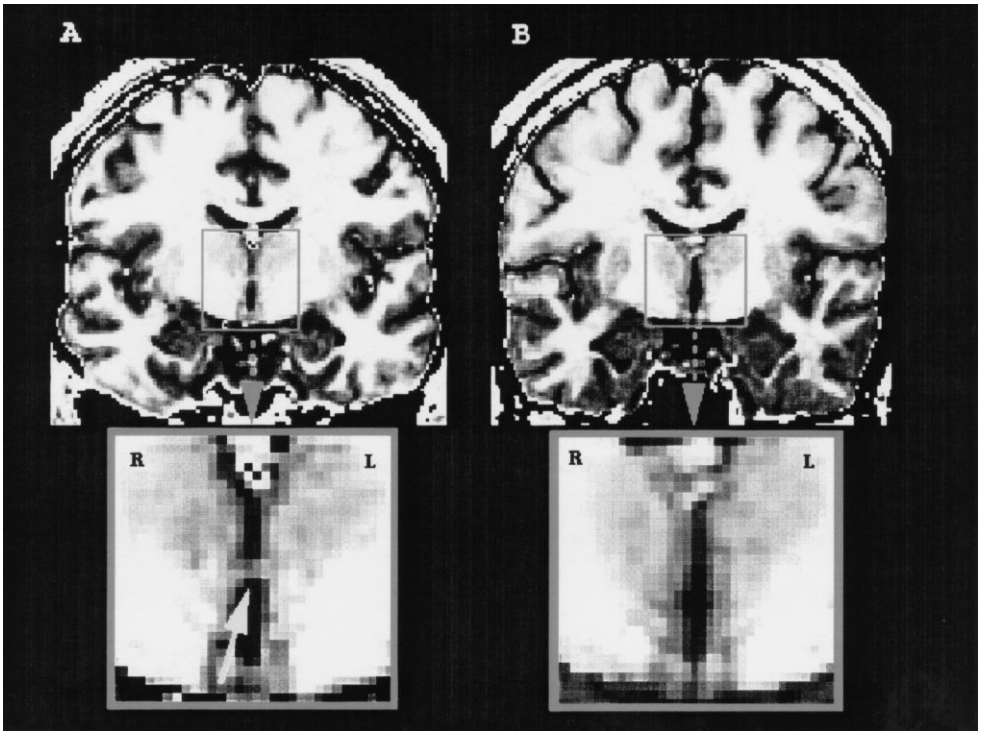

Fig. 1. Coronal sections of two brains, one with (A) a present MI (arrow) and one with (B) an absent MI.

disorder, disorganized/bizarre behavior, and inappropriate affect.

The control group consisted of healthy volunteers who were recruited from the community through newspaper advertising. Each control subject was evaluated using an abbreviated version of the CASH and was excluded if there was any history of psychiatric illness. They were also excluded if they had a family history of schizophrenia. Patients and/or controls were excluded if they had a lifetime history of serious (requiring medical treatment) head trauma, neurological illness, medical or surgical illness, or recent (within the last 6 months) heavy psychoactive drug use or abuse. After complete description of the study to the subjects, written informed consent was obtained.

Demographic data, broken down by gender, for the patient and control groups are shown in Table 1. As a group, the patients had an average age of 29.9 years (SD 10.5), which was not different from the average age of the controls at 28.5 years (SD 10.4). There was no significant difference between the ages of the male and female patients or in parental socioeconomic status between patients and controls.

2.2. MR acquisition and analysis

MR scans were obtained with a T1-weighted three-dimensional SPGR sequence on a 1.5 T GE Signa Scanner (TE = 5, TR = 24, flip angle = 40, NEX = 2, FOV = 26, matrix = 256 × 192) using the coronal plane, yielding 124 contiguous slices, 1.5 mm thick.

Processing of the images after acquisition was done using a locally developed family of software programs called BRAINS (acronym for Brain Research: Analysis of Images, Networks, and Systems). Details of the image analysis are published elsewhere (Andreasen et al., 1992b; Andreasen et al., 1993; Harris et al., 1999). Briefly, a three-dimensional data set is created and the images are realigned and resampled to a 1 mm thickness.

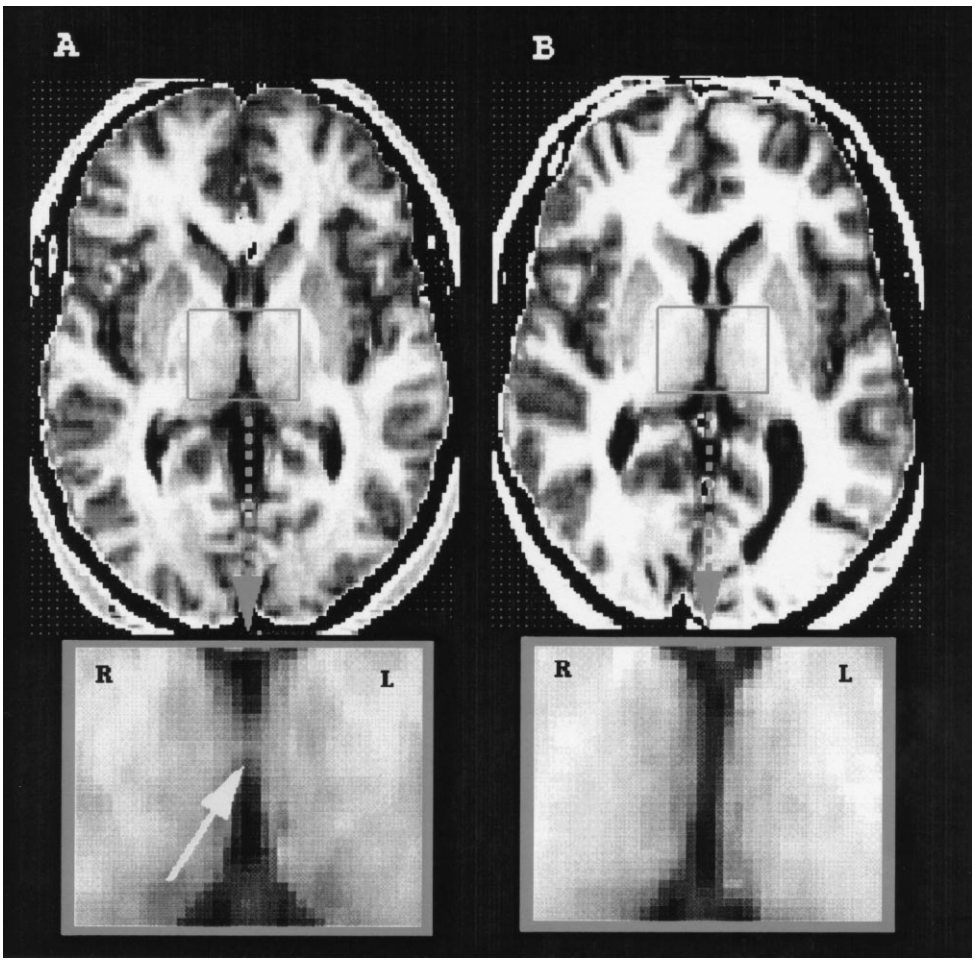

Fig. 2. Axial views of the same two brains in Fig. 1, one with (A) a present MI (arrow) and one with (B) and absent MI.

2.3. Determination of presence of absence of massa intermedia

The realignment of all images corrects for any head position variation in the scanner. All scans are identified only by number and the rater is blind to all demographic information about the scan. The realigned and resampled images are viewed in three orthogonal views simultaneously: axial, coronal, and sagittal. The MI was defined as an interthalamic adhesion located between the two adjacent thalami in the anterior–posterior midline. Initially, images were displayed in three orthogonal views simultaneously to determine general location of MI. A full-screen sagittal view was used to place a 'landmark' on the defined anterior–posterior position of the thalami. A coronal view was used at high magnification to determine the presence or absence of the MI. When present in at least two coronal sections (to allow for partial voluming), confirmation was performed by reviewing its presence and location in both the axial and sagittal views. If not present, confirmation of its absence was also performed by viewing both the axial and sagittal cuts (see Figs. 1 and 2 for examples).

MI was rated as present, absent or indeterminate. Indeterminate MI was often due to motion artifact creating poor visibility. For reliability, a sample of 100 brains was independently rated by D.R. and B.F. Of this sample of 100, the percent agreement was high at 98%. The remaining sample was rated

by D.R. All indeterminate MI ratings were dropped from analysis (seven patients and seven controls), leaving a total sample of 112 controls and 114 patients.

2.4. Statistical analysis

Logistic regression analysis was used, with the dependent variable predicting the presence/absence of MI and independent variables of diagnosis, sex, and the interaction of the two. In addition, χ^2 was used to asses the presence versus absence of MI in four separate analyses: all patients versus all controls; control males versus control females; female patients versus female controls; male patients versus male controls.

3. Results

Results of the logistic regression analysis showed a significant sex effect (Wald $\chi^2 = 5.25$, df = 1, $P = 0.02$). There was no significant effect of diagnosis (Wald $\chi^2 = 1.88$, df = 1, $P = 0.17$). However, there was a significant sex by diagnosis interaction (Wald $\chi^2 = 3.73$, df = 1, $P = 0.05$). The results of the χ^2 analysis documenting the frequency of absent/present MI in each group are shown in Table 2 and presented as indicated below.

3.1. Sexual dimorphism

For the control group there was a significant difference between the sexes: females had an MI absent only 13.56% of the time compared with males, where it was absent 32.08% of the time ($\chi^2 = 5.51$, $P = 0.019$).

Table 2
Percentage present and absence of MI

	MI present (%)	MI absent (%)	χ^2	P
Male controls	67.92	32.08		
Female controls	86.44	13.56		
			5.51	0.019
All patients	68.42	31.58		
All controls	77.68	22.32		
			2.45	0.117
Female patients	67.24	32.76		
Female controls	86.44	13.56		
			6.07	0.014
Male patients	69.64	30.36		
Male controls	67.92	32.08		
			0.03	0.847

3.2. Effect of diagnosis

In the evaluation of the entire patient sample compared with the entire control sample, results indicate that patients with schizophrenia are more likely to have an absent MI compared with controls (31.58% absent in patients, 22.32% absent in controls). However, this was not statistically significant.

3.3. Interaction of sex and diagnosis

When the patient and control samples were broken down by sex and evaluated separately, results show that there is no difference at all in the percentage absent MI between male patients and male controls (MI present in 32.08% of male controls, present in 30.36% of male patients). However, there was a significant difference between female patients and female controls in the percentage of absent MI. The female patients had an absent MI 32.76% of the time, which was substantially higher than the percentage absent MI in the comparison group of female controls (MI absent only 13.56% of the time).

3.4. Relationship to total brain volume

Even after controlling for overall body size, males have significantly larger brain volumes than females (Nopoulos et al., 2000). To assess for the possibility that the sexual dimorphism in the frequency of absent MI was related to difference in total brain volume between the sexes, an additional logistic regression analysis was performed using the same variables as before, but adding total brain volume as an independent variable. The results indicate that there was no effect of total brain volume on the frequency of absent MI (Wald $\chi^2 = 0.07$, df = 1, $P = 0.78$).

3.5. Relationship to clinical variables

To assess any possible clinical relevance of an absence of an MI in female patients with schizophrenia, several clinical variables were compared between the female patient group with absent MI ($n = 17$) and those without an MI ($n = 39$). Variables assessed included age of onset, and summary scores for positive, negative, and

disorganized symptoms. Paired *t*-tests were calculated. There were no significant differences between the two groups for any of these clinical variables.

4. Discussion

4.1. Sexual dimorphism

This is the first modern neuroimaging study to evaluate the Massa Intermedia with regard to sex differences in a normal population. Like the few previous pathologic studies (Morel, 1948; Rabl, 1958; Allen and Gorski, 1991) or ventriculography studies (Davie and Baldwin, 1967; Samra and Cooper, 1968), we have found this structure to be present more commonly in the female brain than in the male brain. Although the functional significance of this is uncertain, some have hypothesized that the female brain is more functionally symmetrical compared with the male brain, especially with regard to language function. This theory is supported by studies performed in stroke patients, which show that, after a left-hemisphere stroke, men are more likely than women to have a pervasive and lasting language disorder, suggesting that women have more bilateral function for language than men (McGlone, 1980). In addition, functional imaging studies using functional MRI have shown that brain activation in males during a language task was shown to be lateralized to the left frontal regions, but in females the pattern of activation was *bilateral* in the frontal regions (Shaywitz et al., 1995). Although the functional significance of the MI in humans is still unclear, several studies have shown that there is thalamic lateralization of language function (Ojemann, 1977, 1982, 1984; Ricklan and Cooper, 1977; Reynolds et al., 1978; Reynolds et al., 1979). Since the MI, when present, would serve to connect the two thalami functionally, the finding that it is more often present in women could be related to the more bilateral organization of language function in women compared with men.

4.2. Relevance to schizophrenia

The anatomic location of the MI may be important in the pathology of schizophrenia for two reasons. The first is that the MI is a midline structure. Several studies have documented that midline brain regions have abnormal morphology in patients with schizophrenia (Andreasen et al., 1995), including the corpus callosum (Woodruff et al., 1995; Tibbo et al., 1998), septum pellucidum (Nopoulos et al., 1997a,b; Kwon et al., 1998), and cerebellar vermis (Weinberger et al., 1979; Lippman et al., 1982; Sandyk et al., 1991; Rossi et al., 1993; Nopoulos et al., 1999). Moreover, the greater percentage of absent MI in patients with schizophrenia suggests developmental aberration. That is, the development of the MI occurs in early gestation, around weeks 15–16 (Rosales et al., 1968). The absence of an MI therefore suggests possible developmental problems during early gestation, a time when other developmental risk factors for schizophrenia, such as maternal viral infection (Wright and Murray, 1996) or malnutrition (Susser et al., 1998), reportedly have their effect.

The second reason for the importance of the anatomic location of the MI in relation to the pathology of schizophrenia is that the MI is a subregion of the thalamus. Many neuroimaging studies have indicated structural (Andreasen et al., 1994; Flaum et al., 1995; Buchsbaum et al., 1996; Gur et al., 1998; Staal et al., 1998) and functional (Silbersweig et al., 1995; Andreasen et al., 1996; Buchsbaum et al., 1996; Crespo-Facorro et al., 1999) abnormalities in the thalamus among patients with schizophrenia. In particular, our laboratory has identified the thalamus as an important node in a neural circuit (the cortico-cerebellar–thalamic–cortical circuit or CC–T–CC) that may underlie the pathology of the illness (Andreasen et al., 1998). The current data lend further support to the growing literature documenting structural aberration in this key structure in the brains of patients with schizophrenia.

4.3. Interaction of sex and diagnosis

The current findings show that abnormally elevated frequency of absent MI in patients with schizophrenia is exclusive to females. This is somewhat counterintuitive given the fact that many studies, including several from our laboratory, have documented that brain morphology in schizophrenia is typically more severely disturbed in males compared with females [for reviews see Nopoulos et al. (1997a,b)]. This appears particularly true for ventricular enlargement,

but may also be true for tissue decrement in frontal and temporal lobes.

Our findings are consistent, however, with some findings in another midline commissure — the corpus callosum. Hoff et al. (1994) found that, in first-episode patients, there was a significant sex by diagnosis interaction for the size of the CC, with females patients having the most pronounced decrement in volume. This finding was supported by a recent post-mortem study by Highly et al. (1999) evaluating the size and fiber composition of the CC in healthy controls and in patients with schizophrenia. They found that, amongst controls, females had a greater density of CC fibers compared with males. In patients with schizophrenia, this difference was reversed — decrement in CC fibers was seen only in female patients compared with their controls — a sex by diagnosis interaction. This is corollary to our findings, in that the MI was found in controls to be present more frequently in females, but in patients the difference was reversed — female patients were more likely to have an absent MI.

The literature on sexual dimorphism of the CC is large and somewhat convoluted. The vast majority of these studies are either MRI or post-mortem studies measuring length, width, and area of the CC. The findings are very mixed, with a recent meta-analysis by Bishop and Wahlsten (1997) showing no overall gender differences, but also with two recent reports showing significant sex differences (Davatzikos and Resnick, 1998; Oka et al., 1999). Although the sexual dimorphism of the gross morphology of the CC may be in question, the study by Highley et al. (1999) suggests that there may be important gender differences at the level of fiber composition of the CC. The findings of sex by diagnosis interactions in schizophrenia with regard to the CC and the MI (current study) suggest that commissures that are sexually dimorphic in the normal brain may somehow be more developmentally vulnerable, and to manifest abnormal morphology in the context of schizophrenia.

In sum, the current study found that the MI is sexually dimorphic in the healthy brain, being present more frequently in females than in males. In patients with schizophrenia, elevated frequency of absent MI is dependent on sex, with female patients having a significantly elevated frequency of absent MI compared with their controls, whereas no difference in frequency of absent MI was found between male patients and their controls.

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