

Volumetric investigation of brain regions in patients with conversion disorder

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Abstract

Preliminary evidence revealed a decrease of regional cerebral blood flow in the thalamus and basal ganglia contralateral to the deficit and suggested that hysterical conversion deficits might entail a functional disorder in striatothalamocortical circuits. However, there is no systematic structural magnetic resonance imaging (MRI) study in the literature in patients with conversion disorder (CD). Therefore, we aimed to perform structural MRI to evaluate the brain regions of interest in first applying patients with CD. Morphometric MRI was used to compare regional brain volumes in ten women with CD and same number of healthy comparison subjects. Intracranial volume (ICV), whole brain volume, gray and white matter volumes did not differ between the patient and control groups. Patients with CD had significantly smaller mean volumes of the left caudate nucleus, lentiform nucleus ($p < 0.01$ for caudate nucleus and $p < 0.05$ for lentiform nucleus) and right caudate nucleus and lentiform nucleus ($p < 0.05$ for both structures). In patients, the right thalamus was significantly smaller, and the left thalamus rendered to be smaller compared to healthy controls. Age at onset showed a significant relation with left caudate, and a near-significant trend with right thalamus volumes. In conclusion, our findings suggest that patients with CD have significantly smaller mean volumes of the left and right basal ganglia and smaller right thalamus, with a trend toward to smaller left thalamus compared to healthy controls and that these findings provide novel constraints for a modern psychobiological theory of hysteria.

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1. Introduction

Conversion disorder (CD) is defined as loss or distortion of neurological function that cannot be fully explained by a known organic neurological disease (American Psychiatric Association, 1994). Yet, their symptoms are not intentionally feigned, not adequately explained by malingering, and may result in significant distress and handicap (Merskey, 1995). In clinical neurological practice, conversion symptoms represent a common disorder, accounting for 1–3% of diagnoses in general hospitals (Marsden, 1986), or even more in some neurological settings (Binzer and Kullgren, 1998; Ron, 1994). Though CD is not very frequent in western societies, it is very common in eastern

societies (Pierloot and Ngoma, 1988; Chandrasekaran et al., 1994). The region differs from Western societies and even from Western Turkey in terms of more frequently encountered CD which constitutes an important psychiatric disorder in the region.

Hysterical symptoms long raised questions about mind–body relationships. Described in early medical writings as psychic disorders caused by bodily disturbances, they were later regarded as the physical effect of violent impressions or passions (Merskey, 1995). A role of neurobiological factors is suggested by the fact that symptoms are more frequent on left-side limbs, pointing to possible right-hemisphere involvement (Stern, 1983), and seem occasionally facilitated by a real coexisting brain disease (Eames, 1992). However, specific functional brain correlates of conversion symptoms have not been demonstrated, except for a few recent pioneering studies (Spence et al., 2000). Physicians, like philosophers, still often call upon a ‘disease of the will’ or ‘of the imagination’ (Merskey, 1995), yet little is known about the neural functioning of motor will or imagination, and how it may be affected in hysterical patients (Marshall et al., 1997; Spence et al.,

Abbreviations: CD, conversion disorder; ICV, intracranial volume; MRI, magnetic resonance imaging.

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2000). Demonstrating objective brain correlates of hysterical symptoms may therefore help to understand the mechanisms that underlie a subjective experience of abnormal neurological function in these patients. Also, it may provide unique insights into mechanisms that subservise normal conscious experience of sensation and volition. A variety of neuropsychological findings (Flor-Henry et al., 1981) and neurophysiological abnormalities (Tiihonen et al., 1995; Lorenz et al., 1998; Spence et al., 2000) have been reported in patients with hysterical conversion. However, many of these studies included only a few or single patients, and provided relatively conflicting or inconclusive results overall. Vuilleumier et al. (2001) evaluated seven patients with conversion disorder using by single photon emission computerized tomography using ^{99m}Tc -ECD and revealed a decrease of regional cerebral blood flow in the thalamus and basal ganglia contralateral to the deficit and suggested that hysterical conversion deficits might entail a functional disorder in striathalamocortical circuits controlling sensorimotor function and voluntary motor behaviour. However, there is no systematic structural magnetic resonance imaging (MRI) study in the literature. Therefore, taken together, we aimed to use structural MRI to evaluate the brain regions of interest in first applying patients with CD.

2. Methods

2.1. Subjects and clinical evaluation

Twelve female patients with unilateral motor symptoms meeting DSM-IV criteria for CD, as determined by the Structured Clinical Interview for DSM-IV (SCID; Spitzer et al., 1997) who consecutively applied to the Firat University School of Medicine Emergency Unit or to directly Department of Psychiatry and 12 healthy female controls were studied. The mean (\pm S.D.) age of the CD patients was 28.1 (5.1) years and the mean age of the normal subject group was 29.2 (5.6) years. All subjects were right-handed. Local Ethic Committee approved the study. Written informed consents for voluntary participation in this research were obtained.

Patients with any comorbid psychiatric disorder, current or lifetime neurologic, current medical problems, alcohol/substance abuse within the 6 months preceding the study and any use of psychoactive medication within 2 weeks of the study were excluded. Healthy control subjects had no DSM-IV Axis I disorders in self or in a first-degree relative, as determined by the SCID non-patient version, no current medical problems, neurologic or psychiatric histories, and no use of psychoactive medication within 2 weeks of the study.

2.2. MRI procedure

MRI was obtained on a 1.5-T GE Excite high speed signal scanner (Milwaukee, USA). Spiral pulse sequences were employed because of insensitivity to subject motion. A high-resolution structural image of the entire brain was obtained using sagittally acquired 3D spiral fast spin echo high-resolution images (repetition time [TR]=2000 ms, echo time [TE]=15.6 ms, field of view [FOV]=240 mm, flip angle=20°, bandwidth=20.8,

slice thickness=2.4 mm, echo spacing=15.6 ms, 8 echoes, resolution=0.9375×0.9375×1.328 mm).

Anatomic measurements were conducted on a computer workstation with the GE Volume Viewer voxtool 3.0 64q program. Tracing was performed by one researcher (KP) blind to subject diagnosis, and independently verified by a second (AM) blinded investigator. The boundaries of structures evaluated were delineated on the coronal MRIs according to standard brain atlases (Yuh et al., 1994; Jackson and Duncan, 1996; Patel and Friedman, 1997) and were adapted from Lacerda et al. (2003) and Zhou et al. (2003). For the tracing of caudate nucleus, in the slice where the anterior commissure was most visible, a horizontal line underlying the lateral ventricles was drawn. The software automatically drew horizontal lines at the same level in all slices in order to exclude the nucleus accumbens. The posterior landmark was represented by the pontine cistern; tracings were performed on all slices moving anteriorly when the nucleus caudatus disappeared. The lateral ventricle and the internal capsule represented the medial and lateral boundaries. The demarcation of the lentiform nucleus was performed primarily on the basis of segmented gray matter, but it was necessary to delineate the dorsomedial and ventral boundaries manually to separate it from the internal capsule and from the substantia innominata and/or the anterior commissure. The definitions of the landmarks used for the thalamus were according to the detailed description of Portas et al. (1998). The most anterior boundary was identified using the mammillary bodies of the hypothalamus as a landmark. The ventralis anterior nucleus is just dorsal to the hypothalamus, bounded laterally by the third ventricle. The posterior boundary was defined when the thalamus merged under the crus fornix. The medial boundary was defined using the third ventricle. The inferior border was defined when the thalamus merged with the brain stem and the superior border, by the main body of the lateral ventricle. Examples of the structures of coronal slices are presented in Fig. 1. All volumes were reported in cubic centimeters.

2.3. Statistical analysis

Analysis of covariance (ANCOVA), *t* test and partial correlation analyses were conducted using SPSS for Windows software, version 10.0 (SPSS, Chicago, IL).

3. Results

3.1. Demographic variables

There were no significant differences in demographic variables of age, gender composition, educational level, and handedness between patients with CD and healthy controls ($p>0.05$).

3.2. Interrater reliability measurements

All interrater and intrarater reliability scores were equal to or above 0.82, demonstrating sufficient inter- and intra-reliability.

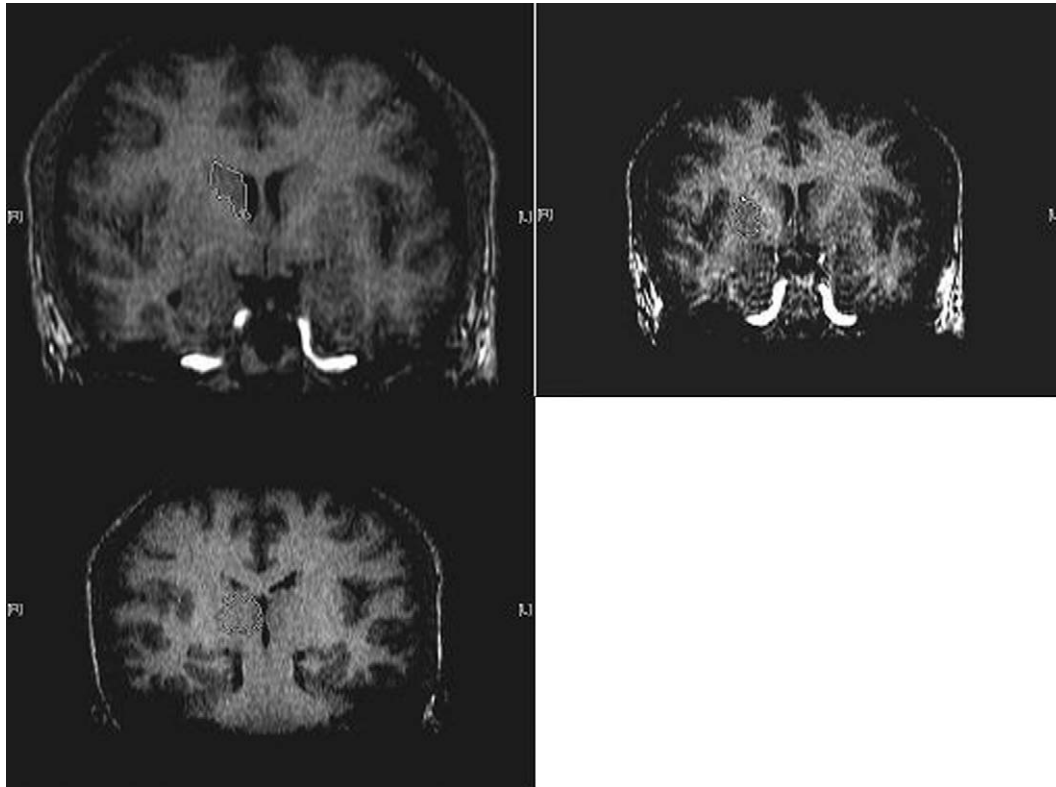


Fig. 1. Anatomic landmarks for the tracing of the structures evaluated.

3.3. Unadjusted whole brain and regional brain volumes

Table 1 presents the unadjusted volumes of the structures evaluated. ICV, whole brain volume, gray and white matter volumes did not differ between the patient and control groups ($p > 0.05$). Patients with CD had significantly smaller mean volumes of the left ($p < 0.01$ for caudate nucleus and $p < 0.05$ for nucleus lentiformis) and right caudate nucleus and lentiform nucleus ($p < 0.05$ for both structures) using independent t test. In patients, the right thalamus was significantly smaller ($p < 0.001$), and the left thalamus rendered to be smaller compared to healthy controls ($p = 0.07$).

3.4. Adjusted regional brain volumes

ICV, whole brain volume, gray and white matter volumes still remained statistically insignificant in patients with CD after covarying for age. But left caudate nucleus volumes remained significantly smaller after covarying for age and whole brain volume, and lentiform nucleus volumes tended to be significant in patients with CD after covarying for age and remained significantly smaller after whole brain volume as a covariate. Specifically, the repeated measures ANCOVA predicting left caudate and lentiform nucleus volumes detected a significant main effect of diagnostic group [$F = 5.12$, $p < 0.05$ for left caudate and $F = 4.26$, $p < 0.05$ for lentiform nuclei]. Right caudate nucleus and lentiform nucleus volumes remained significant smaller [$F = 5.47$, $p < 0.05$ for caudate nucleus; and $F = 4.56$, $p < 0.05$ for lentiform nucleus] in

patients with CD after covarying for age. While right caudate nucleus maintained significance after covarying for whole brain volume [$F = 6.89$, $p < 0.01$], lentiform nucleus volumes tended to be significantly smaller in patients with CD after covarying for whole brain volume [$F = 3.23$, $p = 0.08$]. In the repeated measures ANCOVA predicting right caudate and lentiform nuclei volumes, the main effect of diagnostic group

Table 1
Basal ganglia and thalamus volumes in patients with CD versus control subjects (mean \pm standard deviation)

	CD patients ($n = 12$)	Comparison subjects ($n = 12$)	p
ICV	1490.55 \pm 141.12	1481.32 \pm 124.28	>0.05
Whole brain volume	1267.22 \pm 110.11	1255.01 \pm 126.42	>0.05
Gray matter volume	828.46 \pm 78.44	809.34 \pm 83.76	>0.05
White matter volume	438.75 \pm 27.12	445.67 \pm 26.42	>0.05
Caudate volumes			
Left	3.23 \pm 0.26	3.82 \pm 0.34	<0.01
Right	3.19 \pm 0.16	3.61 \pm 0.20	<0.05
Lentiform volumes			
Left	4.14 \pm 0.59	4.89 \pm 0.67	<0.05
Right	3.95 \pm 0.43	4.44 \pm 0.38	<0.05
Thalamus volumes			
Left	5.17 \pm 0.48	5.46 \pm 0.56	=0.07
Right	4.58 \pm 0.69	5.47 \pm 0.64	<0.001

Volumes presented are in cubic centimeters (cm^3).

was significant [$F=6.32$, $p<0.01$ for caudate and $F=4.37$, $p<0.05$ for lentiform nuclei]. Right thalamus volumes still remained statistically significant in patients with CD after covarying for age [$F=8.24$, $p<0.001$]. Likewise, the volumes of thalamus were still considerable smaller after covarying for whole brain volume [$F=9.72$, $p<0.001$ for right thalamus], with a trend toward reduced left thalamic volumes [$F=3.09$, $p=0.09$]. The repeated measures ANCOVA predicting left and right thalamus volumes detected a significant main effect of diagnostic group [$F=8.78$, $p<0.001$]. The effect of hemisphere was also significant [$F=4.12$, $p<0.05$].

3.5. Clinical correlates

Duration of illness also did not predict basal ganglia structures ($r=0.25$, $p>0.05$ for caudate and $r=0.34$, $p>0.05$ for lentiform nucleus) or thalamus volumes (left: $r=0.13$, $p=0.58$; right: $r=-0.30$, $p=0.21$). Age at onset showed a significant relation with left caudate ($r=0.61$, $p<0.01$), and a near-significant trend with right thalamus volumes ($r=0.45$, $p=0.06$). In a secondary analysis, we examined subgroups of patients that were similar with regard to family history. Neither the basal ganglia structures nor thalamus results were changed by restricting the patient group to family history positive patients ($n=7$).

4. Discussion

The father of modern psychology, William James remarked long ago (James, 1986): ‘Poor hysterics. First they were treated as victims of sexual trouble...then of moral perversity and mediocrity...then of imagination. Among the various rehabilitation which our age has seen, none are more deserving or humane. It is a real disease, but a mental disease.’ As mentioned in Williams James saying, CD is a real disease but a mental disorder seems to involve some brain volumetric differences when compared to healthy controls. To the best of our knowledge, this is the first report of structural investigation using MRI on patients with CD without comorbidity. In the present study we found that there were no significant differences in regard to whole brain volume, gray and white matter volumes. However, we found significant smaller mean volumes of the left caudate and lentiform nuclei, right caudate and lentiform nuclei, and right thalamus. Vuilleumier et al. (2001) first demonstrated a systematic neural correlate of CD, involving the basal ganglia and thalamus and provided the first direct evidence of functional abnormalities in sensorimotor pathways specifically related to the presence of subjective neurological symptoms. They reported that transient unilateral sensorimotor loss of hysterical origin was associated with a relative hypoactivation of contralateral thalamus and basal ganglia circuits and concluded that this would be consistent with an abnormal modulation from subcortical circuits in the thalamus and basal ganglia (Rossini et al., 1998), and possibly some secondary interhemispheric imbalance (Seyal et al., 1995). Our findings, from structural point of view, support their study demonstrat-

ing that thalamus and basal ganglia may be involved in the pathogenesis of CD. The thalamus is also strategically placed to modulate sensory and motor signals as it is the main relay of afferents to the cortex, and it may control the selective engagement of cortical areas involved in motor and cognitive functions via the intralaminar and reticular nuclei systems (Strafella et al., 1997; Mogenson et al., 1980). Although we are still at an early stage of understanding the role of thalamus in motor control, important progress has been made in the past few years. The most anterior nuclei of the motor thalamus, the ventrolateral pars oralis and medialis and the ventroanterior proper along with its pars magnocellularis, receive afferents from the output nodes of the basal ganglia—the globus pallidus and the substantia nigra (Middleton and Strick, 2000) and project to the motor cortex with a bias towards the supplementary motor area (Sakai et al., 2002). Basal ganglia have been shown to play a major role in motor control (Kaji, 2001) as well as in cognitive and emotional functions, including language (Burgund et al., 2003), attention (Vallar, 2001; Karnath et al., 2002), working memory (Lewis et al., 2004), as well as emotion and motivation (Rolls, 1995; Cardinal et al., 2002). The basal ganglia consist of many nuclei which are involved in the control of movement, and the regulation and monitoring of ongoing movements (Wise et al., 1996). Decreased activity in basal ganglia–thalamic circuits might set the motor system in a functional state characterized by impaired motor readiness and initiation, resulting in abnormal voluntary behaviour. The dominant hypothesis as to the function of the basal ganglia pathway through the thalamus is that it helps to generate willful movements (Mushiake and Strick, 1995; Van Donkelaar et al., 2000; Hikosaka et al., 2000). The specific contribution of the basal ganglia pathway to voluntary movement generation remains controversial; a major hypothesis is that the pathway helps to select which movement to make when multiple alternatives are possible (Mink, 1996; Basso and Wurtz, 2002). Von Giesen et al. (1994) reported evidence suggesting that motor hemineglect is thought to reflect a dysfunction in striatotalamic circuits mediating motor preparation and intention, and if associated with real paralysis, such a loss of intention may impede awareness of motor function and contribute to anosognosia for hemiplegia (Vuilleumier, 2000). Striatotalamic premotor loops may contribute to the subjective sense of motor volition and effort (Gandevia, 1987). Neurological dysfunction in these circuits can cause a variety of motor and neuropsychiatric illnesses, such as Parkinsonism, chorea, or tics, all implicating abnormal control of cortical function by basal ganglia–thalamic systems (Rauch and Savage, 1997; Brown and Pluck, 2000). Taken together, our findings support previous theoretical proposals suggesting that motor and motivational mechanisms might operate at the level of thalamus or basal ganglia to influence motor processes in CD (Trimble, 1996).

Our patients were all selected on the basis of limited unilateral motor deficit. Therefore, our findings might reflect only motor but not sensory hysterical deficits in these patients. Further research is needed to determine whether sensory and motor symptoms may relate to distinct thalamic or basal ganglia abnormalities. Recent

studies have shown that both the thalamus (Tracey et al., 2000) and basal ganglia (Tracey et al., 2000) are emphasized in normal or abnormal sensory integration and pain processing.

A number of factors need to be considered when interpreting these results. First, the relatively small and homogeneous sample may limit the generalizability of our findings. Although significant differences were observed with this limited power, replication of the results with larger samples will be necessary to establish the reliability of these anatomical differences. Second, our samples were females. Despite known gender differences in the prevalence of CD and so, we were unable to examine the interactions of diagnosis and gender, and diagnosis and gender and age.

5. Conclusion

In conclusion, our findings suggest that patients with CD have significantly smaller mean volumes of the left and right basal ganglia and smaller right thalamus, with a trend toward to smaller left thalamus compared to healthy controls and that these findings provide novel constraints for a modern psychobiological theory of hysteria. Although this reduction may be important in understanding the pathophysiology of CD, its functional and psychopathologic consequences are still unclear. Future studies examining the relationship between relevant symptom dimensions of CD and basal ganglia and thalamus volumes and evaluating the effects of drugs or psychotherapeutic approaches could be especially informative.

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