NEUROBIOLOGY OF PSYCHOSIS. CLINICAL AND PSYCHOSOCIAL IMPLICATIONS

This is a Section of *Epidemiologia e Psichiatria Sociale*, called *Neurobiology of Psychosis, Clinical and Psychosocial Implications*, that regularly appears in each issue of this Journal to describe relevant neuroscience topics. In particular, studies investigating the relationship between neurobiology and psychosocial psychiatry in major psychoses will be debated. The aim of these short articles is to provide a better understanding of the neural basis of psychopathology and clinical features of these disorders in order to raise new perspective in every-day clinical practice.

Paolo Brambilla, *Section Editor* and Michele Tansella, *Editor* EPS

Interhemispheric communication in schizophrenia

MARCELLA BELLANI,[1, 2] CARLO ALBERTO MARZI,[3] PAOLO BRAMBILLA[2, 4, 5, 6]

[1]*Department of Medicine and Public Health, Section of Psychiatry and Clinical Psychology, University of Verona, Verona (Italy)*
[2]*Inter-University Centre of Behavioural Neurosciences (ICBN), University of Verona, Verona and University of Udine, Udine (Italy)*
[3]*Department of Neurological and Visual Sciences, University of Verona and National Institute of Neuroscience, Verona (Italy)*
[4]*Section of Psychiatry, Department of Pathology and Experimental & Clinical Medicine, University of Udine, Udine (Italy)*
[5]*Scientific Institute 'E. Medea', Udine (Italy)*
[6]*CERT-BD, Department of Psychiatry, University of North Carolina (USA)*

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The corpus callosum (CC) is the brain's largest white matter tract, mostly composed by both myelinated and unmyelinated fibres, connecting the two cerebral hemispheres. The CC can be divided into different sections: rostrum, genu, body, isthmus and splenium (Aboitiz *et al.*, 1992). Myelinated fibres predominate in the midbody and the splenium while unmyelinated fibres are more numerous in the rostrum and the genu. The callosal fiber disposition approximately reflects brain topography: the anterior sections connect the frontal lobes, the median sections connect temporal and parietal regions, and the posterior sections link occipital areas (Pandya *et al.*, 1971). This traditional picture, however, which has been obtained mainly through studies in non-human primates has been partly modified by modern diffusion tensor imaging studies in humans (Hofer & Frahm, 2006). The CC matures after birth through adolescence and into early adulthood and is involved in different cognitive processes such as sensory-motor integration, attention, language, arousal and memory. Its size has been shown to be associated with handedness, sex (i.e., greater splenium in females and greater genu in males, Dubb *et al.*, 2003) and cerebral laterality (i.e., inverse correlation between callosal connectivity and brain lateralization in males; Luders *et al.*, 2003), and age (Ota *et al.*, 2006) Specifically, age-related callosal degeneration has been detected by a diffusion tensor imaging (DTI) study (Ota *et al.*, 2006) in the sub-regions that connect areas which are thought to be vulnerable to normal aging: the genu, rostral body, and isthmus. This result replicated post mortem findings of callosal degeneration in rostral body, anterior midbody and isthmus (Aboitiz *et al.*, 1996).

In particular, the CC has been shown to be crucial in determining inter-hemispheric transfer time (IHTT) of visuomotor information. IHTT can be assessed with the Poffenberger paradigm (Poffenberger, 1912; Marzi, 1999) or by using cortical evoked potentials (EPs). Both techniques are based on the callosal crossing of visual information which is required when simple visual stimuli are presented extra-foveally to the hemifield contralateral to the responding hand in a visuomotor reaction time task. The crossed hemifield-hand conditions produce longer RTs than the uncrossed conditions (for a review, see Marzi *et al.*, 1991). The crossed-uncrossed difference (CUD) mea-

Address for correspondence: Dr. M. Bellani, Department of Medicine and Public Health, Section of Psychiatry and Clinical Psychology, University of Verona, Piazzale L.A. Scuro 10, 37134 Verona (Italy).
Fax: +39-045-8027498
E-mail: marcella.bellani@univr.it

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sures IHTT, because in the crossed conditions the hemisphere of stimulus entry is different from the hemisphere controlling the motor response and an interhemispheric transfer is needed. In contrast, when stimuli and response are ipsilateral, hence processed by the same hemisphere, transfer is unnecessary. Therefore, by subtracting the mean RT of the two uncrossed combinations from the mean RT of the two crossed combinations, one can infer IHTT from the CUD. In normal subjects the IHTT is around 4 msec (Marzi *et al.*, 1991), but it shows a considerable lengthening when the CC is sectioned (i.e., the so called "split brain", IHTT about 30-60 ms) or absent (i.e., callosal agenesis, IHTT about 15-20ms). EPs can also provide information about IHTT by subtracting the latency of EP components recorded in the hemisphere contralateral to the hemifield of stimulation (direct pathway) from that recorded from the ipsilateral hemisphere (callosal pathway). EPs do not provide information about the motor response and normal IHTT is between 10 and 15 ms (Westerhausen *et al.*, 2006). Recent studies suggest that IHTT can be influenced by CC anatomy, i.e. shorter IHTT is related with larger midsagittal cross sectional area and higher microstructural integrity (Schulte *et al.*, 2005). In contrast, Westerhausen and collegues (2006) did not find significant correlations between IHTT and mid-sagittal areas of CC, except for electrophysiologic measures. The authors concluded that the detected association demonstrates that IHTT of visual information is directly related to the functional integrity of at least the posterior callosal third.

IHTT speed can give information about CC integrity and Iacoboni & Zaidel (2004) analyzed inter-hemispheric visuomotor integration in right-handed normal volunteers combining event related functional magnetic resonance imaging (fMRI) and a simple visuomotor behavioural task. This study showed a greater activity in crossed conditions in bilateral frontal, bilateral dorsal premotor and right superior parietal areas inferring a role of superior parietal cortex in visuo motor integration. In a previous fMRI study, Tettamanti and collegues (2001) found an activation of the genu of CC during the Poffenberger task in the crossed condition that was confirmed by using a different version of the Poffenberger paradigm (Omura *et al.*, 2004; Weber *et al.*, 2005). Therefore the role of the CC in sustaining inter-hemispheric connectivity is well documented in humans both for simple and more cognitively demanding tasks.

In contrast to simple visuomotor information which can still transfer, although at a slower velocity, between hemispheres despite callosal section, the CC is exclusively responsible for the transfer of cognitive information between the two hemispheres (Gazzaniga, 2000). Therefore, if hemispheres are disconnected (i.e. split brain patients) percepts and memories generated in one hemisphere are excluded from the conscious awareness of the other one. Alterations in inter-hemispheric communication have also been shown in schizophrenia subjects (Mohr *et al.*, 2000). Specifically, two different mechanisms causing abnormal connectivity have been proposed, the hyper-connectivity hypothesis, in which synapses are supposed not to be eliminated in development (Feinberg, 1982), and the hypo-connectivity hypothesis in which too many synapses are eliminated because of abnormal interactions between neurons (Friston, 1995). The latter seems to be compatible with some neurobiological features which have consistently been shown in schizophrenia such as ventricular enlargement. A post mortem study reported density reduction of myelinated fibers and glial cells in all regions of the CC, except for the rostrum, in female patients with schizophrenia (Highley *et al.*, 1999) but these findings were not confirmed by other studies. Also, size reduction and microstructural disruption of the CC in schizophrenia have been demonstrated in several imaging studies (Diwadkar *et al.*, 2004). Interestingly, in a prospective study of childhood-onset schizophrenia an abnormal developmental trajectory for the splenium was shown in patients with schizophrenia during adolescence and early adulthood (Keller *et al.*, 2003). Only few studies have investigated inter-hemispheric information exchange in schizophrenia using behavioural tasks. Shelton & Knight (1984) found no difference in CUD between individuals with schizophrenia and normal controls. Florio and collegues (2002) using the Poffenberger paradigm found a CUD=0 in schizophrenia patients. The authors explained this result with the presence of excessively slow responses involving the left hemisphere (both crossed and uncrossed). IHTT seems to be impaired also in alexithymia patients (Parker *et al.*, 1999), in psychopathic offenders (Hyatt & Neumann 2007) and in alcoholics (Schulte *et al.*, 2005). In this regard, David *et al.* (1993) proposed abnormal inter-hemispheric integration as a "*plausible model for a range of psychiatric phenomena from alexithymia to delusions and hallucinations*".

Taken together these findings strongly suggest that basic visuomotor processes are affected in schizophrenia and that the CC is involved in the pathophysiology of the illness. Future fMRI studies should further investigate the role of the CC in regulating functional communication between the hemispheres in schizophrenia, particularly in subjects at the early phases of the illness, in order to better delineate the contribute of inter-hemispheric connectivity to the clinical course of the disease (Killackey *et al.*, 2007; Ruggeri *et al.*, 2007).

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Table I – *Behavioural and magnetic resonance imaging studies investigating inter-hemispheric communication in humans and psychiatric patients.*

Study	Subjects (males/females)	Age (years)	Task	Type of study	Findings
Shelton & Knight 1984	12 right handed schizophrenia patients 12 right handed patients with personality disorder or episodic alcohol abuse	35.75 36.25	Simple visual reaction time paradigm	Behavioural	No evidence of IHTT difference between the two groups
Tettamanti *et al.* (2001)	8 right handed healthy subjects	24.5 (21-28)	Poffenberger Paradigm	fMRI	Activation of frontal, parietal, and temporal cortical areas and genu of corpus callosum
Florio *et al.* (2002)	27 right handed schizophrenia patients (14 males) 20 right handed healthy controls (10 males)	45 (23-62) 45 (24-65)	Poffenberger Paradigm	Behavioural	CUD = 0 Abnormal reaction time latency in the left hemisphere of schizophrenics
Iacoboni & Zaidel (2004)	5 right handed subjects (3 males)	23.6±2.5	Poffenberger Paradigm	fMRI	Strong correlation between CUD and signal intensity in the right superior parietal cortex
Omura *et al.* (2004)	21 right handed subjects (9 males)	24.7±5.4	Modified Poffenberger paradigm	fMRI	Activation of the genu of the genu of the corpus callosum
Weber *et al.* (2005)	10 right handed healthy subjects (6 males)	24.9±2.0	Modified Poffenberger paradigm	fMRI	Activation of the right genu of the corpus callosum (in the crossed minus uncrossed condition)
Schulte *et al.* (2005)	11 alcoholics (7 males) 13 controls (8 males)	52.6±11.0 51.6±12.9	Poffenberger paradigm	DTI	Lower FA and higher D in alcoholics than in controls. In controls large CUDs correlated with low FA and high D in total corpus callosum and regionally in the genu and splenium

CUD = crossed-uncrossed difference, IHTT = interhemispheric transfer time, FA = fractional anisotropy, a measure of orientation of water diffusion usually in white matter fibers; D = diffusivity a measure of the intracellular and extracellular fluid diffusion.

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