Neurobiology of Psychosis. Clinical and Psychosocial Implications

This is a Section of *Epidemiologia e Psichiatria Sociale*, 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.

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Longitudinal imaging studies in schizophrenia: the relationship between brain morphology and outcome measures

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Abstract. Imaging studies have tried to identify morphological outcome measures of schizophrenia in the last two decades. In particular, longitudinal studies have reported a correlation between larger ventricles, decreased prefrontal volumes and worse outcome. This would potentially allow to isolate subtypes of schizophrenia patients with a worse prognosis and more evident biological impairments, ultimately helping in designing specific rehabilitation interventions.

KEY WORDS: outcome assessment, schizophrenia, longitudinal studies, magnetic resonance.

Schizophrenia is a heterogeneous syndrome including patients with a relatively positive course of illness and others with a much worse long term prognosis (Carpenter & Kirkpatrick, 1988; Shenton *et al*., 2001). One strategy for a better understanding of the disease would be the identification of homogenous subtypes of patients, according to some clinical, cognitive and morphofunctional descriptors (Roy *et al*., 2001; Bellani *et al*., 2009). In this regard, Keefe and colleagues first differentiated patients with *krapelinian* and *non-krapelinian* schizophrenia, according to the worse long term clinical outcome of the first group. Kraepelinian patients had to be continuously hospitalized for the previous five years or, living outside the hospital, needed continuous assistance, didn't have an employment and didn't have remission of symptoms (Keefe *et al*., 1987). Different outcome measures have been used so far, such as duration and severity of positive symptoms (Ho *et al*., 2003), recovery from the first episode (Lieberman *et al*., 1996), or psychopathological indicators of the Brief Psychiatric Rating Scale (BPRS) and the Global Assessment of Functioning (GAF) (Delisi *et al*., 1998; van Haren *et al*., 2008).

Cross-sectional imaging studies have explored the relationship between brain structure and outcome. Interestingly, poor outcome patients (defined as hospitalized for more than 50% of their total duration of illness)

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Table I – *Longitudinal imaging studies on outcome measures and brain morphology among patients with schizophrenia.*

Study	Subjects (n)	Follow up (years)	Outcome measures	Method and brain structure	Findings in schizophrenia
Vita *et al.*, 1991	18	2	Score on intimacy of interpersonal contacts scale, Strauss-Carpenter scale	CT Ventricles and cortical atrophy	↑ ventricles and cortical atrophy associated with poor outcome
DeLisi *et al.*, 1992	30	2	Admission rate, BPRS, GAF, hospitalization lenght, Strauss Carpenter scale	MR Ventricles and temporal lobe	↑ ventricles associated with ↑ hospitalization rate and ↑ BPRS
Lieberman *et al.*, 1996	62	1,5	CGI, GAF, SANS, SADS, Strauss Carpenter scale	MR 3rd and lateral ventricles, frontal/parietal cortex, medial temporal cortex	↑ ventricles associated with poorer treatment outcome
Davis *et al.*, 1998	55	5	kraepelinian and non kraepelinian patients, SANS	CT Ventricles	No difference at baseline ↑ left ventricles in kraepelinians at follow up
DeLisi *et al.*, 1998	50	5	BPRS, Cannon and Spoor pre-morbid social adjustment scale, GAF, SADS	MR Left and right ventricles, hemispheres	No correlation
Gur *et al.*,	40	2,5	SANS, SAPS, neurocognitive battery	MR Whole brain, CSF, frontal and temporal lobes	↓ whole brain and ↑ CSF predictors of cognitive deterioration
Lieberman *et al.*, 2001	51	1	CGI, SAEPS, SADS, SANS, treatment response	MR Ventricles, cortex, caudate nucleus, hippocampus	↑ ventricles in poor outcome patients
Mathalon *et al.*, 2001	24	4	Admission rate, BPRS, hospitalization length	MR CSF, prefrontal, frontal, temporal lobes and lateral ventricles	Frontal and prefrontal ↓ GM ↓ CSF associated with worse BPRS and longer hospitalization length
Cahn *et al.*, 2002	34	1	CAN	MR Cranium, total brain, cerebellum, ventricles	↓ GM associated with poor outcome
Van Haren *et al.*, 2003	109	2	CAN, GSDS, MADRS, PANSS	MR Cranium, total brain, cerebellum, ventricles	No correlation
Ho *et al.*, 2003	73	3	SANS, SAPS, Shipley Institute of Living Scale, WAIS, WCST	MR TBV, lateral ventricles, cerebellum frontal, temporal and parietal lobes and CSF	Poor outcome associated with ↑ lateral ventricles; frontal lobes and CSF and ↓ frontal lobe WM and GM
DeLisi *et al.*, 2004	26	10	Admission rate, BPRS, GAF, SANS, SAPS, Strauss Carpenter outcome scale, Tsuang and Winokur scale	MR Ventricles	↑ ventricles associated with ↑ admission rate
Van Haren *et al.*, 2007	96	5	Admission rate, PANSS	MR VBM	↓ superior frontal GM associated with ↑ admission rate
Van Haren *et al.*, 2008	96	5	CAN, GAF	MR Cranium, total brain, cerebellum, lateral and 3rd ventricles	↑ lateral ventricles and ↓ cerebral volumes in poor outcome patients
Mitelman *et al.*, 2009	49	4	Poor and good outcome	MR Caudate nucleus and putamen	↓ putamen in poor outcome patients

BPRS= Brief Psychiatric Rating Scale; CAN= Camberwell Assessment of Need scale; CGI= Clinical Global Impression scale; CSF= cerebrospinal fluid; GAF= Global Assessment of Functioning scale; GM= gray matter; GSDS= Groningen Social Disabilities Schedule; MADRS= Montgomery Asberg Depression Rating Scale; MR= magnetic resonance; PANSS= Positive and Negative Symptoms Scale; SADS= Schedule for Affective Disorders and Schizophrenia; SAEPS= Simpson Angus Extrapyramidal Symptoms Scale; SANS= Scale for Assessment of Negative Symptoms; SAPS= Scale for Assessment of Positive Symptoms; TBV= total brain volume; CT= computerized tomography; VBM= Voxel Based Morphometry; WAIS= Wechsler Adult Intelligence Scale; WCST= Winsconsin Card Sorting Test; WM= white matter.

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have shown to have larger ventricles and smaller prefrontal, temporal, and putamen volumes than good outcome ones (Buchsbaum *et al*., 2003; Staal *et al*., 2001; Mitelman *et al*., 2003). Also, larger ventricular volumes were associated with poorer response to treatment (Weinbeger *et al*., 1980), with a larger incidence of negative symptoms and with a poorer premorbid social functioning (Williams *et al*., 1985). Moreover, longitudinal imaging studies have shown progressive enlargement in ventricles and decrease of whole brain and putamen volumes in both chronic (Vita *et al*., 1991; Davis *et al*., 1998; van Haren *et al*., 2008; Mitelman *et al*., 2009) and first-episode poor outcome patients (DeLisi *et al*., 1992; Gur *et al*., 1998; Lieberman *et al*., 2001; Cahn *et al*., 2002), defined as either continuously dependent on others' assistance, unremitting, or with a low GAF score. Furthermore, increase in frontal cerebrospinal fluid (CSF) and reduction in prefrontal white and gray matter volumes, over time, were associated with higher symptom severity, poor cognitive performances, poor treatment response, higher admissions rate and time spent in hospital (Gur *et al*., 1998; Mathalon *et al*., 2001; Ho *et al*., 2003; van Haren *et al*., 2007).

However, few negative results have also been reported. In particular, van Haren and colleagues in a multicenter study failed to demonstrate that volumes of total white and grey matter, cerebellum, and lateral and third ventricles predict clinical outcome in schizophrenia after a 2-year follow up (van Haren *et al*., 2003). In a 10-year follow-up study, ventricular enlargement was surprisingly associated with clinical improvement instead of poor outcome, even though enlargement of ventricles after ten years was correlated with the amount of time spent in hospital (DeLisi *et al*., 2004). The authors argued that these controversial results might be affected by insufficient statistical power or sampling bias, since only 50% of the population was studied after ten years.

In conclusion, there is evidence that larger lateral ventricles and decreased prefrontal volumes, even over time, are associated with worse outcome, potentially allowing to identify a subgroup of patients with schizophrenia with more evident biological alterations. Nonetheless, there is no concordance on the outcome measures, which assess different domains, such as social functioning, cognition, illness severity and treatment response. To further characterize schizophrenia, based on the outcome, future neuroimaging studies should longitudinally investigate chronic unremitting patients (Mitelman & Buchsbaum, 2007) and premorbid or first outbreak samples (Raune *et al*., 2009), correlating imaging markers with clinical, genetic, and neuropsychological assessment (Ruggeri & Tansella, 2009). This will also be crucial to guide innovative and specific rehabilitation interventions for particular subtypes of patients.

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