

Cingulate Cortex in Schizophrenia: its relation with negative symptoms and psychotic onset. A review study

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Abstract. – OBJECTIVE: The cingulate cortex is a functionally heterogeneous region involved in diverse cognitive and emotional processes. It is a region of special interest to investigate the neurological substrate of schizophrenia. The aim of this paper is to review all the studies that investigated the relation between the cingulate cortex and two of the most important and little known areas of this disease: the psychotic onset and the negative symptoms.

MATERIALS AND METHODS: Relevant literature was identified through a search in PubMed, Web of Science, and Cochrane database. Search terms included negative symptoms, cingulate cortex, cingulate gyrus, schizophrenia, PET, SPECT, MRI, fMRI, BOLD, deficit schizophrenia, early-onset schizophrenia, psychotic onset, psychosis.

RESULTS: 9 studies evidenced a link between negative symptoms and hypoactivity of cingulate cortex, whereas 7 studies did not. A positive relationship between anterior cingulate cortex gray matter thinning and high risk for schizophrenia is well characterized in literature.

CONCLUSIONS: In a large portion of patients hypoactivity of cingulate cortex underlie the presence of negative symptoms. In particular, ACC (anterior cingulate cortex) thinning seems to be related to the increasing social withdrawal that is characteristic of the psychosis prodrome. New therapies focused on the brain stimulation of the cingulate cortex could represent an important aid for patients with this kind of symptoms.

Key Words:

Negative symptoms, Psychotic onset, Schizophrenia, Cingulate cortex.

Introduction

The cingulate cortex is part of the limbic system and has extensive reciprocal connections with cortical and sub-cortical structures. It is a functionally heterogeneous region involved in di-

verse cognitive and emotional processes that support goal-directed behaviour and it is involved in motivation, memory and attention¹. The cingulate cortex has, therefore, come under scrutiny as a region of special interest to those investigating the neurological substrate of schizophrenia.

It is anatomically divided into anterior and posterior portions; the anterior cingulate cortex (ACC) seems to be involved in the pathogenesis of negative-type processes both in neuropsychiatric patients² and in healthy populations³. Located bilaterally in the medial frontal lobes, the ACC comprises the cytoarchitectonic areas 24/24' and 32/32', with area 25, commonly called the subgenual cingulate⁴, located posterior to the subcallosal extension of area 24, ventral to the genu. Areas 24'/32' are located dorsal to the corpus callosum, while areas 24/32 occupy a pregenual position⁵. Areas 32 and 32' have been termed transition cortex because they possess cytoarchitectonic features common to areas 24/24' and adjacent frontal regions⁵. Other authors have labeled areas 32/32' as paralimbic, or paracingulate, cortex and areas 24/24' as limbic ACC due to the latter's denser connections with emotional centres^{6,7}.

Given the possible complex involvement of the cingulate cortex in the pathogenesis of schizophrenia, the aim of this paper is to review all the studies that investigated the relation between the cingulate cortex and two of the most important and little known areas of this disease: the psychotic onset and the negative symptoms.

Negative symptoms are a cluster of symptoms generally characterized by the absence of normal levels of activation, initiative, and affect⁸. The negative symptom constellation in schizophrenia includes psychomotor retardation, avolition, bi-rhythm disturbances, apathy, neurological soft signs, anhedonia, attention impairment and de-

creased emotional expression⁹⁻¹². These symptoms are associated with poor premorbid function, the male sex and a low IQ¹³ and are correlated with poor outcome¹⁴. Controversy surrounds whether second generation antipsychotics are more effective than first generation antipsychotics in the treatment of negative symptoms; undisputed, however, is that negative symptoms persist in many cases despite pharmacological treatment¹⁵⁻¹⁹. Moreover, it has become clear that it is the negative symptoms (more than the positive symptoms) that account for much of the functional disability of schizophrenia^{20,21}. Accordingly, the development of effective treatments for this kind of symptoms has the potential to remediate the often substantial functional disability associated with schizophrenia. Because of the importance of negative symptoms in schizophrenia, deficit schizophrenia (DS) has been proposed as a putative disease subtype defined by prominent, primary negative symptoms that endure as trait-like features during periods of clinical stability²². Although negative symptoms are considered an important feature of schizophrenia, they are not pathognomic of it. Negative symptoms of schizophrenia have generally been found in association with organic lesions and altered functioning in several cerebral regions, such as ventricles, prefrontal cortex and cingulate cortex²³⁻²⁸ and they often represent one of the most characterizing symptom of the first phases of schizophrenia.

In addition to negative symptoms, we found that a consistent feature of psychosis prodromes is the presence of 'attenuated' or 'subthreshold' psychotic features. These differ from frank psychotic symptoms in their intensity, frequency and/or duration. It is likely that not all people with subthreshold forms of psychotic symptoms and syndromes will develop a full-blown psychotic disorder. However, a combination of these subthreshold syndromes with other risk factors for psychotic disorder may increase the likelihood of imminent onset of psychotic disorder in an individual. Many authors recently used such an approach for identifying a group said to be at ultra high risk (UHR) for psychotic disorder (i.e. putatively prodromal)²⁹⁻³¹.

Materials and Methods

We searched PubMed, Web of Science, and the Cochrane database of systematic reviews. We used the following keywords: cingulate cortex, cingu-

late gyrus, negative symptoms, schizophrenia, PET, SPECT, MRI, fMRI, BOLD, deficit schizophrenia, early-onset schizophrenia, psychotic onset, psychosis. We searched the references of all included articles. This strategy yielded more than 200 studies. Two independent reviewers extracted data and assessed the quality of methodological reporting of selected studies using data extractions forms. We considered only those studies investigating in several different ways the relation of cingulate cortex with negative symptoms and psychotic onset. Only clinical trials were included in this review. We excluded single case reports, dissertations, and meeting abstracts. In section 3 and section 4 of this paper we summarize the most important outcomes achieved.

Anterior Cingulate Cortex Abnormalities and Psychotic Onset

Mounting neuropathologic and magnetic resonance imaging (MRI) evidences support a primary role for abnormalities of the ACC in the pathogenesis of psychotic disorders³², but it remains unclear whether these abnormalities precede or follow psychosis onset. Establishing the timing of such neuroanatomic changes is critical to determine whether they represent a risk marker for illness onset or a secondary manifestation of the disease process. To determine whether neuroanatomic differences represent risk markers, it is necessary to identify and follow-up individuals at elevated risk for psychosis to characterize diagnostic outcomes. In recent years operationalised criteria have been developed that identify individuals in the prodrome to the first psychotic episode. These criteria require the recent onset of specific symptoms or clinical features, termed an 'at risk mental state' (ARMS), and are associated with functional impairment. Individuals with an ARMS display a need for care³³ and have an ultra high risk of developing a psychotic disorder, predominantly schizophrenia, within two years. Diffusion Tensor Imaging (DTI) studies have provided evidence of disruption in white matter tracts in first-episode psychosis patients in comparison to age matched controls, which indicates that abnormalities in structural connectivity are present at illness onset and are not a secondary consequence of medication, or illness duration³⁴. Similar abnormalities have also been reported in ARMS subjects³⁵.

In a study conducted by Lord et al³⁶, functional MRI and graph theoretical analysis were used to characterize the organization of a functional

brain network in at-risk mental state patients with varying symptoms assessed with the Positive and Negative Syndrome Scale (PANSS) and healthy volunteers during performance of a verbal fluency task known to recruit frontal lobe networks and to be impaired in psychosis. They first examined between-groups differences in total network connectivity and global network compactness/efficiency and then addressed the role of specific brain regions in the network organization by calculating the node-specific “betweenness centrality”, “degree centrality” and “local average path length” metrics; different ways of assessing a region’s importance in a network. They focused their analysis on the ACC. Although global network connectivity and efficiency were maintained in at-risk patients relative to the controls, they reported a significant decrease in the contribution of the ACC to task-relevant network organization in at risk subjects with elevated symptoms (PANSS ≥ 45) relative to both the controls and the less symptomatic at-risk subjects, as reflected by a reduction in the topological centrality of the ACC.

Two studies³⁷⁻³⁸ have investigated individuals at UHR for psychosis identified using state and trait criteria. Both the studies reported reduced ACC gray matter in UHR individuals who subsequently developed psychosis (UHR-P) compared with those who did not (UHR-NP).

Job et al³⁹⁻⁴⁰ found reduced ACC gray matter in individuals at genetic high risk for schizophrenia compared with healthy control subjects, but these reductions were no more severe in those high-risk individuals who eventually developed schizophrenia or subthreshold psychotic symptoms.

In a study of Fornito et al⁴¹, using the Comprehensive Assessment of At-Risk Mental States (CAARMS)⁴², a structured clinical interview designed to assess prodromal symptomatology and risk for psychosis, were recruited 103 participants. The UHR cohort was regularly monitored over a minimum 12-month period (mean=13; maximum=44 months). Participants were then divided into UHR-P and UHR-NP groups using operational criteria for determining psychosis onset⁴³. Baseline ACC morphometry was then compared between UHR individuals who developed psychosis (UHR-P; n=35), those who did not (UHR-NP; n = 35), and healthy control subjects (n = 33). Relative to control subjects, UHR-P individuals displayed bilateral thinning of a rostral paralimbic ACC region that was negatively correlated with negative symptoms, whereas UHR-

NP individuals displayed a relative thickening of dorsal and rostral limbic areas that was correlated with anxiety ratings. An intriguing possibility arising from these data is that abnormal thickening in the UHR-NP group confers increased resilience against transition to psychosis, although the positive correlation observed between thickness and anxiety levels suggest that it predisposes to other psychopathology. Comparison between UHR-P and UHR-NP individuals indicated that changes in the rostral limbic-ACC and, to a lesser extent, the rostral paralimbic and limbic and paralimbic subcallosal regions, differentiated between the two groups. These thickness differences predicted time to psychosis onset independently of any correlations with baseline symptom ratings. With their findings Fornito et al⁴¹ demonstrated that anatomic changes in the ACC are apparent before the onset of frank psychosis, distinguish between UHR individuals who subsequently do and do not develop a psychotic episode and are relatively specific to individuals who develop a schizophrenia spectrum disorder. The differences between the UHR-P and UHR-NP groups are unlikely to be due to variations in their baseline clinical characteristics, given that ACC measures predicted time to psychosis onset independently of any shared variance with symptom measures. The two groups were well-matched demographically, and while a small proportion of UHR individuals were also enrolled in an intervention trial, the relative proportions in each group receiving each intervention type were similar. Moreover, the dissociation observed with respect to correlations between regional ACC abnormalities and symptom measures in the two groups suggests that the anatomic changes are related to distinct pathophysiologic processes related to their divergent psychiatric outcomes.

The localization of changes individuated by Fornito et al is interesting in light of a recent work demonstrating bilateral thinning of the paralimbic region in first episode schizophrenia, and longitudinal research in childhood-onset schizophrenia suggesting the earliest post-onset changes appear in paralimbic regions and spread to engulf the limbic ACC over a 5-year period.

A longitudinal gray matter reduction in dorsal paralimbic regions of ACC (ACCp) during the transition to psychosis was also demonstrated. Together these findings suggest a timetable for the progression of ACC abnormalities in schizophrenia, whereby the earliest reductions emerge in the rostral paralimbic region during the pro-

drome, extend across the dorsal and subcallosal paralimbic regions following psychosis onset, and spread to encompass limbic regions with continued illness duration.

Evidence that the rostral-ACCp plays an important role in social cognitive processing, particularly mentalizing others' intentions⁴⁴, suggests abnormalities in the area lead to difficulties interacting with others. This may underlie the increasing social withdrawal that is characteristic of the psychosis prodrome⁴⁵.

Recent data suggest⁴⁶ that high-risk relatives of individuals with schizophrenia displaying sub-threshold psychotic symptoms show poorer performances on theory of mind (ToM) tasks than those without such symptoms. This finding was confirmed by a neuroimaging study⁴⁷ of the same research team.

In a parallel study, Fornito et al⁴⁸ used a novel surface-based protocol for parcellating the ACC into functionally relevant regions, while accounting for individual variations in sulcal anatomy. The approach enabled calculation of multiple indices of anatomical change, including regional grey matter volume, surface area, cortical thickness, and sulcal depth and curvature with submillimeter precision. By focusing on a sample of patients experiencing their first episode of schizophrenia, they minimized the potential confounding influences associated with prolonged illness and treatment effects⁴⁹. Importantly, they individually matched patients and healthy controls for age, sex, and paracingulate sulcus (PCS) morphology to ensure that any identified changes could not be attributed to group differences in cortical folding patterns. In this study they applied a surface-based protocol to T1-weighted scans acquired from 40 first episode schizophrenia patients and 40 healthy controls individually matched for age, sex, and morphology of the PCS, a major anatomical variation that has been shown to affect morphometric estimates in the region. The surface-based approach enabled calculation of regional grey matter volume, surface area and curvature, cortical thickness, and depth of the cingulate sulcus, with sub-millimeter precision. Relative to controls, schizophrenia patients displayed a bilateral reduction in thickness of paralimbic regions of the ACC, along with a concomitant increase in surface area of both the limbic and paralimbic ACC. No differences were identified for regional grey matter volume, surface curvature, or CS depth. These findings indicate that the early stages of schizophrenia are as-

sociated with a specific pattern of ACC abnormalities that cannot be attributed to variations in sulcal and gyral morphology. The absence of grey matter volume differences described is likely explained by the fact that patients showed a simultaneous decrease in thickness and increase in surface area; that is, the different direction of these changes are likely to have cancelled each other out when combined in the summary volumetric measure⁴¹.

The combined decrease in ACC cortical thickness and increase in surface area provides some clues regarding the underlying pathophysiology causing the change. Similar changes are also seen during normal adolescent (and early adult) brain maturation, to the extent that continued brain growth is accompanied by a reduction in cortical grey matter, the changes being particularly protracted in frontal regions⁵⁰. In this regard, decreased thickness coupled with increased surface area may reflect an exaggeration of normal neurodevelopmental processes. The specificity of the thickness reduction to paralimbic, but not limbic, areas in their sample (which contrasts the surface area expansion of both) may reflect a regionally specific pathology that spreads from the paralimbic ACC to the limbic ACC with illness progression.

Kuperberg et al⁵¹ have reported thickness reductions in both the limbic and paralimbic ACC of patients with established schizophrenia, but with more prominent differences occurring in the latter. By way of speculation, the gradual progression of anatomical abnormalities from paralimbic to limbic regions may represent a pathophysiological basis for the increasing prominence of negative symptoms in the clinical presentation of patients with prolonged illness, consistent with reports of limbic ACC involvement in motivational function³ and evidence that lesions in the area can lead to apathy and/or akinetic mutism⁵².

The earlier involvement of paralimbic regions may be associated with the deficits in executive function and social cognition known to occur from the outset of the illness and even prior to psychosis onset⁵³, consistent with evidence that the ACCp is critically involved in these functions⁴⁴, and functional imaging studies demonstrating abnormal ACCp activation in schizophrenia patients performing such tasks⁵⁴. The cortical grey matter reduction seen in MRI studies of normal adolescent development is thought to reflect partial volume effects caused

by ongoing myelination of fibers penetrating the cortical mantle, rather than overt neuronal loss³.

Postmortem studies have found increased axonal input into the limbic ACC of patients with schizophrenia⁵⁵, suggesting that myelination of these excess fibers in early illness stages may contribute to a thinning of the cortical ribbon (Table I).

Von Economo Neurons, Anterior Cingulate Cortex and Early-Onset Schizophrenia

The human ACC comprises an extraordinary spindle-shaped bipolar neuron in layer V, first discovered by Betz, later studied in detail by von Economo and Koskinas, and hence referred to as von Economo neurons (VENs), a label that is less ambiguous than the wide-spread use of the term “spindle cells”. The density of VENs in humans reaches the adult figure around 4 years of age, suggesting a role in functional domains that mature slowly, such as emotion regulation, motor control⁵⁶, and economic decision-making⁵⁷. In support of this assumption, VENs have been found to be rich in vasopressin, dopamine, and serotonin receptors. These neurotransmitters are known to be critically involved in the regulation of reward and complex social behaviours.

With regard to pathological conditions, VENs contain a high amount of neurofilament, which is why they are assumed to be affected in

Alzheimer’s disease⁵⁸. Moreover, VENs have been found to be selectively reduced in frontotemporal dementia⁵⁹, in cases with agenesis of the corpus callosum⁶⁰, and it has also been speculated that VENs may play a role in the pathophysiology of autism. VENs comprise an interesting population of neurons that could be affected in complex diseases, such as schizophrenia in which both neurodevelopmental and neurodegenerative alterations occur^{12,61}.

Brune et al⁶² tested the hypothesis that the density of VENs is reduced in a neurodevelopmental subtype of schizophrenia, defined by an early onset of the disorder. The density of VENs was estimated in layer V of Brodmann’s area 24 in 20 subjects diagnosed with schizophrenia. The results were compared with 19 specimens from patients with bipolar disorder as a clinical control and 22 non-psychiatric samples. The density of VENs did not differ between the three groups. However, the VEN density in the right ACC correlated with the age at onset, and inversely with the duration of the illness in schizophrenia, but not in bipolar disorder. Thus, patients with early onset schizophrenia (and longer duration of illness) had a reduced VEN density. Age, sex, postmortem interval, brain weight, and cortical thickness had no significant impact on the results. These findings suggest that VENs in the ACC are involved in neurodevelopmental and perhaps neurodegenerative processes specific to schizophrenia.

Table I. Resume of the studies investigating the ACC abnormalities in relation with the psychotic onset.

| Study | Acc abnormalities and psychotic onset |
|---|--|
| Gasparotti et al, 2009; Bloemen et al, 2009 | Disruption in white matter tracts in first-episode psychosis patients in comparison to age matched controls |
| Pantelis et al, 2003; Borgwardt et al, 2007 | Reduced ACC gray matter in UHR individuals who subsequently developed psychosis compared with those who did not |
| Job et al, 2003; Job et al, 2005 | Reduced ACC gray matter in individuals at genetic high risk for schizophrenia compared with healthy control subjects |
| Fornito et al, 2008 | ACC thickness differences predicted time to psychosis onset independently of any correlations with baseline symptom ratings, also these differences are relatively specific to individuals who develop a schizophrenia spectrum disorder |
| Fornito et al, 2008 | Bilateral thinning of the ACC paralimbic region in first episode schizophrenia |
| Fornito et al, 2008 | The early stages of schizophrenia are associated with a specific pattern of ACC abnormalities: combined decrease in ACC cortical thickness and increase in surface area. |
| Lord et al, 2011 | Significant decrease in the contribution of the ACC to task-relevant network organization in at risk subjects with elevated symptoms relative to both the controls and the less symptomatic at-risk subjects |

Cingulate Cortex Abnormalities and Negative Symptoms

Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET) Studies

Since 1981, more than 100 articles on functional brain imaging in schizophrenia have been published. PET and SPECT, which measure regional cerebral blood flow (rCBF) and or metabolism, reveal a number of abnormalities and deficiencies in people with schizophrenia compared with healthy subjects⁶³.

Sabri et al in 1997⁶⁴ performed a study in which 24 drug-naive acute patients with a first manifestation of schizophrenia and 20 control subjects were examined with technetium-99m-labeled hexamethylpropyleneamine oxime (99mTc-HMPAO) brain SPECT. The patients with schizophrenia were also assessed according to PANSS. The results of this study showed that all negative symptoms had a negative correlation to bifrontal, bitemporal, cingulate, basal ganglia and thalamic rCBF.

Ashton et al in 2000⁶⁵ presented a SPECT study involving 39 exclusively neuroleptic naive schizophrenic patients and a tightly selected control group (n=39). Imaging was performed on a high resolution SPECT scanner with the perfusion tracer 99mTc-HMPAO and the PANSS was used for the psychopathological assessment. A verbal fluency task⁶⁶ was used to produce a degree of standardisation of the cognitive state of subjects during the period of fixation of the tracer and to accentuate task related group differences. They found an association between negative PANSS scores and decreased rCBF in the cingulate gyrus.

Potkin et al in 2002⁶³ used PET to compare cerebral metabolic patterns in schizophrenic subjects with predominantly negative or positive symptoms. 14 right-handed male subjects with DSM-IV schizophrenia were assigned to groups with predominantly negative or predominantly positive symptoms on the basis of their post-drug-washout scores on the PANSS. The patients were compared to 7 age- and gender-matched normal volunteers. PET scans with 18-F-fluorodeoxyglucose were obtained during a degraded Continuous Performance Task to measure absolute glucose metabolic rates. The results showed that negative symptom subjects had a lower glucose metabolic rate in several sections of the right hemisphere including posterior cingulate cortex.

Galeno et al in 2004⁶⁷ performed a study to compare the cerebral regions that are involved in

mild and severe negative symptoms, and to determine whether the degree of severity can be related to specific dysfunctional areas of the brain. The PANSS was used to form two groups of patients (n=14) with prevalence of negative symptoms: Mildly Affected (MA), and Severely Affected (SA). Brain PETs were obtained in resting conditions and Statistical Parametric Mapping was used to perform statistical comparisons. It was not highlighted any correlation between negative symptoms and ACC both in MA and in SA group; on the other hand, the MA-group showed increased activity in posterior cingulate gyrus.

Lahti et al in 2006⁶⁸ reported the correlations between whole brain rCBF and the positive and negative symptoms of schizophrenia in two cohorts of patients who were scanned while free of antipsychotic medication. Both cohorts of patients with schizophrenia (Cohort 1: n=32; Cohort 2: n=23) were scanned using PET with H₂(15)O while free of antipsychotic medication for an average of 21 and 15 days, respectively. Both groups were scanned during a resting state. Negative symptoms correlated inversely with rCBF in frontal and parietal regions, but not in cingulate cortex (Table II).

Magnetic Resonance Spectroscopy (H-MRS) Studies

Magnetic resonance spectroscopy (H-MRS) allows in vivo measurement of several metabolites critically important for brain function, including N-acetylaspartate (NAA), an amino acid considered a marker of neuronal integrity⁶⁹⁻⁷¹, glutamate (Glu), an amino acid involved in excitatory neurotransmission⁷² and metabolism^{73,74}, and choline-containing compounds (Cho), that reflect primarily the constituents of cell membranes, phosphocholine and lycerophosphocholine, that increase with accelerated turnover or loss of membrane phospholipids⁷⁵.

In the study performed by Yamasue et al in 2002⁷⁶ schizophrenic (n=15) and normal control (n=13) subjects were examined using both H-magnetic resonance spectroscopy (MRS) and MRI, in order to accurately assess the partial volume within the spectroscopic volume of interest (VOI) in the anterior cingulate cortex. The gray matter volume within VOI correlated positively with the NAA to Cho ratio in patients with schizophrenia only, not in controls. The results of the study showed that there was a significant negative correlation between the NAA/Cho ratio and the severity of blunted affect symptom in patients with schizophrenia.

Table II. Studies investigating the relation between negative symptoms and hypoactivity of cingulate cortex.

| Study | Neuroimaging technique | Patients | Relation between negative symptoms and hypoactivity of cingulate cortex |
|------------------------|-----------------------------|---|---|
| Sabri et al 1997 | SPECT/99mTc-HMPAO | 24 drug-naive first-episode schizophrenia patients. | Yes |
| Ashton et al 2000 | SPECT/99mTc-HMPAO | 20 healthy control subjects. 39 drug-naïve patients with schizophrenia | Yes |
| Sigmundsson et al 2001 | MRI | 39 healthy control subjects 27 patients with schizophrenia and predominant negative symptoms | Yes |
| Potkin et al 2002 | PET/18-F-fluorodeoxyglucose | 27 healthy control subjects 14 patients with schizophrenia | Yes |
| Yamasue et al 2002 | H-MRS/ NAA, Cho, Cr | 7 healthy control subjects 15 patients with schizophrenia | Yes |
| Galeno et al 2004 | PET/18-F-fluorodeoxyglucose | 13 healthy control subjects 10 patients with schizophrenia and low negative symptoms | No |
| | | 4 patients with schizophrenia and high negative symptoms | |
| Lahti et al 2006 | PET/H2(15)O | 6 healthy control subjects 55 patients with schizophrenia | No |
| Wood et al 2007 | H-MRS/NAA, Glx | 15 patients with schizophrenia | No |
| Calabrese et al 2008 | MRI | 14 healthy control subjects 28 patients with schizophrenia and their non-psychotic siblings. | Yes |
| | | 38 healthy control subjects and their siblings. | |
| Galderisi et al 2008 | MRI | 34 patients with schizophrenia and predominant negative symptoms | No |
| | | 32 patients with schizophrenia | |
| | | 31 healthy control subjects | |
| Lui et al 2009 | MRI | 68 antipsychotic-naive first-episode schizophrenia patients | No |
| | | 68 healthy control subjects | |
| Preuss et al 2010 | MRI | 50 patients with schizophrenia. | Yes |
| | | 50 healthy control subjects. | |
| Makris et al 2010 | MRI | 88 patients with schizophrenia and predominant negative symptoms | No |
| | | 40 healthy control subjects | |
| Cascella et al 2010 | MRI | 19 patients with schizophrenia and predominant negative symptoms. | Yes |
| | | 31 patients with schizophrenia. | |
| | | 90 healthy control subjects | |
| Berge et al 2010 | MRI | 21 drug-naive first-episode schizophrenia patients | No |
| | | 20 healthy control subjects | |
| Reid et al 2010 | H-MRS/ NAA, Cho, Cr, Glx | 26 patients with schizophrenia | Yes |
| | | 23 healthy control subjects | |

In the study performed by Wood et al in 2007⁷⁷ 15 male patients with schizophrenia and 14 male controls were assessed using H-MRS, with regions of interest placed in the right and left dorsal and rostral cingulate. The metabolites of interest were NAA and glutamate + glutamine (Glx). Schizophrenia patients had lower NAA

concentrations throughout the dorsal and rostral portions of the anterior cingulate and in both hemispheres, but showed no changes in Glx. Patients were administered the PANSS to assess general psychopathology. A significant positive correlations was found between right rostral NAA and the Negative Syndrome factor.

In 2010 Reid et al⁷⁸ used H-MRS acquired in the dorsal anterior cingulate cortex and fMRI during performance of a Stroop color-naming task⁷⁹ to investigate the neurochemistry and functional response of the anterior cingulate cortex/medial frontal cortex in 26 stable, medicated subjects with schizophrenia and 23 matched healthy control subjects. They observed a significant negative correlation between Glx (glutamate+glutamine)/Cr levels and negative symptoms in the group of medicated subjects. Because of this correlation, this study assessed the relation between the deficit of integrity of ACC and negative symptoms in patients with schizophrenia (Table II).

MRI Studies

Structural MRI studies have used 2 approaches to investigating neuroanatomical changes in patients with schizophrenia. One, the region-of-interest (ROI) method, involves manual delineation of the ACC on each scan, with morphometric parameters such as gray matter volume calculated secondarily. The second, commonly termed voxel-based morphometry (VBM), is an automated technique that involves spatial normalization of each participant's scan to a common stereotactic space, followed by voxelwise statistical comparison of group differences in gray matter measures. This has provided an attractive alternative to the ROI methodology because it affords a relatively unbiased assessment of gray matter changes across the entire brain, although errors in spatial normalization, particularly in morphologically variable regions such as the ACC, can complicate interpretation of findings⁷.

Sigmundsson et al in 2001⁸⁰ performed a study involving 27 right-handed patients who met DSM-IV criteria for schizophrenia with enduring negative symptoms and 27 healthy comparison subjects. All these patients received dual echo MRI. Significant deficits of gray and white matter volume in the patient group were found at the ACC and medial frontal gyri.

To investigate whether the decrease in the gray matter volume of the cingulate gyrus in subjects with schizophrenia might be related to heritable influences Calabrese et al in 2008⁸¹ used high-resolution MRI and labeled cortical mantle distance mapping to measure gray matter volume, as well as thickness and the area of the gray/white interface, in the anterior and posterior segments of the cingulate gyrus in 28 subjects with schizophrenia and their non-psychotic siblings, and in 38 healthy control subjects and their siblings. The results of the

study showed that subjects with schizophrenia and their non-psychotic siblings had similar reductions of gray matter volume (approximately 10%) in the posterior cingulate cortex (PCC) compared to healthy control subjects and their siblings; in the combined group of schizophrenia subjects and their siblings, an inverse correlation between left PCC volume and negative symptoms, such that a larger left PCC volume was associated with fewer negative symptoms, was found; there was no significant effect of group on ACC volume, thickness, or area.

Galderisi et al in 2008⁸² performed a study including 34 patients with Deficit Schizophrenia (DS), 32 with nondeficit schizophrenia (NDS), and 31 healthy comparison subjects. The schedule for the Deficit Syndrome was used to categorize patients as DS or NDS patients. The 2 patient groups were matched on age and gender and did not differ on clinical variables, except for higher scores on the negative dimension and more impaired interpersonal relationships in DS than in NDS subjects. This study found that the cingulate gyri volume was smaller in NDS but not in DS patients as compared with healthy subjects.

Lui et al in 2009⁸³ used MRI optimized voxel-based morphometry and resting state functional connectivity analysis to characterize the association between clinical symptoms and anatomical cerebral deficits in a large sample of antipsychotic-naive first-episode schizophrenia patients. The participants of the study were 68 antipsychotic-naive first-episode schizophrenia patients and 68 matched healthy comparison subjects. Both patients and healthy comparison subjects were scanned using a volumetric three-dimensional spoiled gradient recall sequence and a gradient-echo echo-planar imaging sequence. They used the PANSS⁸⁴ to assess the psychopathological status. Optimized voxel-based morphometry was used to characterize gray matter deficits in schizophrenia patients. The clinical significance of regional volume reduction was investigated by examining its association with symptoms in patients with first-episode schizophrenia and with alterations in resting state functional connectivity when brain regions with gray matter volume reduction were used as seed areas. Significantly decreased gray matter volume was observed in schizophrenia patients in the right anterior cingulate gyrus but not related with the severity of negative-type processes.

In the MRI study performed by Makris et al in 2010⁸⁵, the researchers compared the volume of all brain fiber systems between chronic patients

with DSM-III-R schizophrenia (n=88) and matched healthy community controls (n=40). They found that a set of a priori white matter regions of local and distal associative fiber systems was significantly different in patients with schizophrenia. They found a positive correlations between volumes (larger) in anterior callosal, cingulate and temporal deep WM regions.

Preuss et al in 2010⁸⁶ examined a large sample of schizophrenic inpatients and controls in order to assess the potential relationship between anterior cingulate cortex volumes and P300 characteristics in patients with more pronounced negative symptoms. They obtained auditory P300 and structural magnetic resonance imaging volume measurements of the ACC in 50 male schizophrenic patients and 50 matched controls. Patients' negative symptoms were assessed using the PANSS. The results of the study showed that volumetry of ACC subregions revealed a volume reduction in patients with schizophrenia compared with controls in right hemispheric rostral ACC subregions that were most pronounced in more negative schizophrenia patients.

In 2010, Cascella et al⁸⁷ performed a study where they acquired MRI of the whole brain in 19 outpatients with Deficit Schizophrenia, 31 with Non Deficit Schizophrenia, and 90 healthy adults. The results of the study showed that regions in which Gray Matter Volume reductions best distinguished negative symptoms patients from non negative symptoms patients included the left anterior cingulate cortex.

Berge et al in 2010⁸⁸ tried to determine brain areas reduced in first episode of psychotic subjects and its association with lack of insight and negative symptoms. In their study 21 drug naive first-episode subjects and 20 controls underwent a structural MRI scan and were clinically assessed. Optimized voxel-based-morphometry analysis was implemented to find between-group differences and correlations between GMV volume and lack of insight and negative symptoms. Negative symptoms correlated with decreased GMV volume at cerebellum and frontal inferior regions, but not at cingulate cortex (Table II).

Discussion

The data we presented suggest that there is a large portion of patients where hypoactivity of cingulate cortex underlie the presence of negative symptoms. As negative symptoms tend to

be enduring and less reactive to medication, other concomitant therapies that are focused on the brain stimulation of the cingulate cortex could represent an important aid for patients with this kind of symptoms. In fact recent technologies as the H-coil for the Transcranial Magnetic Stimulation (deep TMS)⁸⁹ and the surgical Deep Brain Stimulation⁹⁰ offer the opportunity to stimulate specific brain regions⁹¹. In particular we think that deep TMS, as it is a totally non-invasive and well tolerated procedure, could easily be used in schizophrenic patients with pharmaco-resistant negative symptoms^{92,93} as well as in patients with other psychopathological problems⁹⁴⁻⁹⁶.

Over recent years, the concept of negative symptoms has also been described as a prominent feature in other neurological and psychiatric disorders including mood disorders⁹⁷⁻⁹⁸, Parkinson's disease⁹⁹⁻¹⁰⁰, Conversion disorder¹⁰¹, substance abuse¹⁰², Alzheimer's disease¹⁰³⁻¹⁰⁴ and Epilepsy¹⁰⁵. In particular, in patients with Alzheimer's disease negative symptoms were correlated with a significantly lower rCBF in cingulate cortex¹⁰⁶.

Some of the studies we reviewed used the PANSS to evaluate negative symptoms; this fact represent a limit of the specificity of the clinical evaluation of patients because the items of the PANSS for negative symptoms are also symptoms and signs sometimes found in MDD; blunted affect, emotional withdrawal, poor rapport, social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation and stereotyped thinking. This could mean that negative symptoms could just reflect depressed mood at the time of assessment¹⁰⁷.

The studies we reviewed also found that cingulate hypoactivity was often connected with hypo or hyper functionality of other brain regions such as dorsolateral prefrontal cortex, left anterior temporal cortex, posterior inferior frontal gyrus, transcortical speech area, retrosplenial cortex, lingual gyrus, occipitotemporal convergence, middle temporal gyrus, inferior temporal gyrus, superior temporal gyrus, premotor cortex and deep cerebellar nuclei. This point reflects that cingulate cortex has large anatomical connections and that negative symptoms are complex and cannot be associated with only one brain area, but rather with neuron networks that involve all the brain.

From a clinical point of view, this wide spread of connections could also explain the

role of the anterior cingulate in cognitive functions. In fact, studies using fMRI¹⁰⁸⁻¹⁰⁹ and PET¹¹⁰⁻¹¹¹ have shown that the anterior cingulate and/or the pre-motor areas are activated in normal control subjects when performing a verbal fluency test. In particular, three of these studies showed activation of both the anterior cingulate and premotor areas in normal subjects with verbal fluency tests, some of which involved a memory component in addition to free recall. Fletcher et al. extended their results using connectivity theory¹¹² to suggest that the anterior cingulate with the premotor areas form part of a network of interconnected regions involved in cognitive functions that may be disrupted in schizophrenia¹⁰⁷.

The data we presented also offer other suggestions: a change in cingulate function could be a useful objective biological marker in the assessment of neuroleptic medication on negative symptoms.

It is also true that recognizing the prodrome of a first psychotic episode prospectively creates the opportunity of intervention, which could delay, ameliorate or even prevent onset.

A positive relationship between ACC gray matter thinning and high risk for schizophrenia is well characterized in literature. Anatomic changes in the ACC are apparent before the onset of frank psychosis and are relatively specific to individuals who develop a schizophrenia spectrum disorder. In this context, the finding of an inverse correlation between rostral-ACCp thickness and negative symptoms in the UHR-P group suggests the functional consequences of these anatomic changes include a diminished engagement with the external world. This may underlie the increasing social withdrawal that is characteristic of the psychosis prodrome. However, determining whether the rostral-ACCp changes cause elevations in negative symptoms or whether both are manifestations of some other trait marker requires further longitudinal investigation.

By the way of speculation, the gradual progression of anatomical abnormalities from paralimbic to limbic regions may represent a pathophysiological basis for the increasing prominence of negative symptoms in the clinical presentation of patients with prolonged illness, consistent with reports of limbic ACC involvement in motivational function³ and evidence that lesions in the area can lead to apathy and/or akineti-
c mutism¹¹³.

Conclusions

Our review evidences that cingulate cortex dysfunction may underlie negative symptoms and that there is a relation between a gray matter thinning of ACC and high risk for schizophrenia. For these reasons, therapies focused on the stimulation of this area should be further investigated.

Conflict of Interest

All authors of this paper have no relevant affiliations or financial involvement with any organization or entity with a financial interest in, or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. All authors acknowledge that the conflict of interest disclosures are complete for both themselves and their co-authors, to the best of their knowledge.

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