Schizophrenia Research 106 (2008) 164–171

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Evidence for reduced neuronal somal size within the insular cortex in schizophrenia, but not in affective disorders

K. Pennington [a,b,*], P. Dicker [c], L. Hudson [a], D.R. Cotter [a,*]

[a] Department of Psychiatry, Royal College of Surgeons in Ireland, Dublin, Ireland
[b] Proteome Research Centre, UCD Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Ireland
[c] Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin, Ireland

ARTICLE INFO

Article history:
Received 15 April 2008
Received in revised form 11 August 2008
Accepted 12 August 2008
Available online 21 September 2008

Keywords:
Schizophrenia
Insular cortex
Layer 2
Neuronal somal size

ABSTRACT

The insular cortex is a paralimbic area of the brain thought to have important roles in sensory integration, auditory hallucinations and language. Both structural and functional MRI studies have revealed that this brain area is abnormal in both size and activity in schizophrenia. Further investigation of this region at the cellular level in schizophrenia has not been carried out. In the current study, we conducted a stereological examination of neuronal and glial size and density in layers 2 and 3 of the dorso-caudal region of the insular cortex in 15 schizophrenic, 15 bipolar, 15 unipolar and 15 control patients. These cortical layers are candidate layers based on previous cytoarchitectual investigations. Statistical analysis (ANCOVA, correcting for pH, post-mortem interval and age) showed decreased neuronal volume in layer 2 in schizophrenia ($p=0.0008$, 16.2% mean reduction). No other significant changes were observed. This study thus provides the first evidence of cytoarchitectural abnormality of the insular cortex in the pathophysiology of schizophrenia but not mood disorders. Further work is needed to investigate the molecular basis for this neuronal abnormality in schizophrenia in order to elucidate its role in the pathophysiology of schizophrenia.

© 2008 Elsevier B.V. All rights reserved.

1. Introduction

Over the last ten years evidence has been accumulating for the involvement of the insular cortex (IC) in schizophrenia. Structural MRI studies have repeatedly shown a reduction in size of the IC in these patients (Wright et al., 1999; Crespo-Facorro et al., 2000; Paillere-Martinot et al., 2001; Sigmundsson et al., 2001; Bagary et al., 2003; Yamasue et al., 2004; Ardekani et al., 2005), and these studies collectively indicate that this abnormality is present in first episode drug-naïve patients (Crespo-Facorro et al., 2000; Yamasue et al., 2004), in early onset schizophrenia (Paillere-Martinot et al., 2001) and in patients with negative symptoms (Sigmundsson et al., 2001). Studies investigating the IC in schizophrenia in comparison with schizotypal disorder (Takahashi et al., 2005), obsessive compulsive disorder (Kim et al., 2003) and affective psychosis (Kasai et al., 2003) found changes only in schizophrenia. In bipolar disorder a significant increase in the IC volume compared to controls (Lochhead et al., 2004) has been observed.

The insular cortex (Brodmanns' area 13–16), which has been termed the 'fifth lobe' of the cortex (Augustine, 1996) is a paralimbic brain region which is generally larger in the left hemisphere than the right. Structurally, it is separated by a central sulcus in 90% of all hemispheres (Ture et al., 1999) which divides the insular into the anterior and posterior areas, both significantly reduced in size in schizophrenic patients (Takahashi et al., 2005). The anterior, more agranular region is thought to have a main role in olfaction, gustation, and autonomic responses (Mesulam and Mufson, 1982b) while the posterior granular region is thought to be more involved in auditory, somesthetic and skeletomotor functioning (Mesulam and Mufson, 1982b). Reciprocal projections

* Corresponding authors. Cotter is to be contacted at Department of Psychiatry, Royal College of Surgeons in Ireland, Dublin, Ireland. Tel.: +353 1 809 3862. Pennington, Section of Opthalmology and Neuroscience Institute of Molecular Medicine, Leeds University, Leeds, LS9 7TF. Tel.: +44 113 3438444.
E-mail addresses: k.pennington@leeds.ac.uk (K. Pennington), drcotter@rcsi.ie (D.R. Cotter).

0920-9964/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.schres.2008.08.022

from the insular cortex to areas of the limbic system such as the amygdala, hippocampus and entorhinal cortex (Augustine, 1996) suggest the posterior region may also function as a limbic association area.

To date, there has been no post-mortem studies investigating the basis of the abnormalities observed in schizophrenia within the insular cortex. However, the relevance of this brain region in Alzheimer's disease (Augustine, 1996) and frontotemporal dementia, a neurodegenerative disease involving loss of social and emotional functioning, have been reported previously (Seeley et al., 2006), More generally, cytoarchitectual studies of the cortex in schizophrenia have identified a variety of abnormalities of neuronal and glial density and size across multiple cortical regions (Harrison, 1999; Todtenkopf et al., 2005; Kolluri et al., 2005). Prominent among these changes are reductions in neuronal somal size in layers 3 and/or 5 of the dorsolateral prefrontal cortex (Rajkowska et al., 1998; Cotter et al., 2001; Pierri et al., 2001; Cotter et al., 2002b; Pierri et al., 2003; Sweet et al., 2003) and reduced density of presumed GABAergic neurons in layer 2 (Benes, 1999; Lewis, 2000; Benes et al., 2001; Reynolds et al., 2001; Beasley et al., 2002; Cotter et al., 2002a; Todtenkopf et al., 2005; Chance et al., 2005), These, and other studies (e.g. O'Connor and Hemby, 2007) provide evidence implicating layers 2 and 3 in schizophrenia. Consequently, the aim of this study was to evaluate neuronal and glial size and density in layers 2 and 3 of the granular (posterior) region of the IC in schizophrenia, bipolar disorder and major depression. We hypothesised that changes in the cellular architecture are present in the IC in schizophrenia in comparison to non-psychiatric controls. In addition, cortical lamina widths were measured and compared between disease and control groups in order to identify any gross alterations in all cortical layers in this brain region.

2. Materials and methods

2.1. Subjects

Fixed human brain tissue was obtained from the Stanley Foundation Brain Consortium and comprised 60 samples (15 schizophrenia, 15 bipolar disorder, 15 major depression, 15 controls). This brain collection has been described in detail previously (Torrey et al., 2000). Diagnoses were made according to Diagnostic and Statistical Manual of Mental Disorders (DSM) IV criteria. For detailed case summaries see Table 1. Fixed tissue was available from one hemisphere of each brain and in total this sample consisted of 27 insular cortices taken from the left and 33 taken from the right hemispheres.

2.2. Identification of area of interest and tissue processing

In the insular cortex there is a rostral agranular cytoarchitecture changing to caudal granular cytoarchitecture (Mesulam and Mufson, 1982a). Preliminary work by us in which we sampled the subregions of the IC, revealed that the most dorso-caudal point next to the central sulcus is the most representative area of the granular IC with clear laminar boundaries characteristic of granulated tissue (Fig. 1 a and c). This region was sampled in the current investigation and, after dissection (see Fig. 1b), tissue blocks were serially sectioned in the coronal plane at 100 μm using a vibrotome (Intracel 1500). Systematic random sampling was carried out from the series of 100 μm sections with every 4th section being mounted onto a slide for analysis. After mounting, sections were stained with cresyl violet using standard methods.

2.3. 3D cell counting and cell size estimates

Stereological methods and standard criteria for the identification of Nissl-stained neurons and glia were carried out as described previously (Cotter et al., 2001). Specifically, neurons were distinguished by the presence of a nucleolus and some or all of the following; euchromatin, Nissl positive cytoplasm, Nissl positive dendritic processes and an ovoid or irregularly shaped nucleus. In contrast, glial cells were characterised by their lack of nucleolus, the presence of heterochromatin, a thicker nuclear membrane and a usually smaller shape and size.

In brief, all investigations used a Leica DMLB microscope (Leica Microsystems, UK), a Hitachi 3CCD colour camera (HVC20) (Hitachi, Japan), and a Marzhauser 100× *x*-, *y*-

Table 1
Summaries of the demographic, histological and clinical data for the Stanley Foundation Brain Consortium

Variable	Unaffected controls	Schizophrenic	Bipolar disorder	Major depression
Number of cases	15	15	15	15
Age at death in years	48.1 (10.7)	44.5 (13.1)	42.3 (11.7)	46.5 (9.3)
Gender (female, male)	6F, 9M	6F, 9M	6F, 9M	6F, 9M
Mean PMI and range (h)	23.7 (9.9)	33.7 (14.6)	32.5 (16.1)*	27.5 (10.7)
Mean pH and range	6.27 (.24)	6.16 (.26)	6.18 (.23)	6.18 (.22)
Side of brain (left, right)	8L,7R	9L, 6R	7L,8R	9 L,6R
Brain weight (g)	15.0 (164.1)	1471.7 (108.2)	1441.2 (171.5)	1462 (142.1)
Causes of death	13 cardiac	8 cardiac	4 cardiac	7 cardiac
	3 accident	2 accident	1 accident	0 accident
		4 suicide	9 suicide	7 suicide
		1 other	1 other	1 other
Treated with antipsychotics at time of death (no:yes)	15:0	3:12	7:8	15:0
Treated with antidepressants at time of death (no:yes)	15:0	10:5	7:8	3:12
Treated with mood stabilizers at time of death (no:yes)	15:0	12:3	5:10	13:2

Stars indicate results of independent *T*-test analysis between the disease group and control patients. $^{*}p<0.05$.

دریافت فوری ← متن کامل مقاله

ISIArticles
مرجع مقالات تخصصی ایران

✓ امکان دانلود نسخه تمام متن مقالات انگلیسی
✓ امکان دانلود نسخه ترجمه شده مقالات
✓ پذیرش سفارش ترجمه تخصصی
✓ امکان جستجو در آرشیو جامعی از صدها موضوع و هزاران مقاله
✓ امکان دانلود رایگان ۲ صفحه اول هر مقاله
✓ امکان پرداخت اینترنتی با کلیه کارت های عضو شتاب
✓ دانلود فوری مقاله پس از پرداخت آنلاین
✓ پشتیبانی کامل خرید با بهره مندی از سیستم هوشمند رهگیری سفارشات