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Differential relationship of frontal pole and whole brain volumetric measures with age in neuroleptic-naïve schizophrenia and healthy subjects

John P. John [a,*], Paul W. Burgess [b], B.S. Yashavantha [a], Mohammed K. Shakeel [a], Harsha N. Halahalli [a], Sanjeev Jain [a]

[a] Department of Psychiatry, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India
[b] Executive Functions Group, Institute of Cognitive Neurosciences (ICN), Alexandra House, University College London (UCL), 17 Queen Square, London, WCIN 3AR, United Kingdom

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ABSTRACT

Brodmann's area (BA) 10, which occupies the frontal pole (FP) of the human brain, has been proven to play a central role in the executive control of cognitive operations. Previous *in vivo* morphometric studies of the FP have been limited by the lack of an accepted boundary of its posterior limit. We studied the FP gray matter volume in 23 healthy subjects who were age-, sex-, and education-matched to 23 neuroleptic-naïve recent-onset schizophrenia subjects in the age span 20–40 years, using a cytoarchitectonically and functionally valid landmark-based definition of its posterior boundary that we proposed recently (John, J.P., Yashavantha, B.S., Gado, M., Veena, R., Jain, S., Ravishankar, S., Csernansky, J.G., 2007. A proposal for MRI-based parcellation of the frontal pole. Brain Struct. Funct. 212, 245–253. 2007). Additionally, we examined the relationship between FP volume and age in both healthy and schizophrenia subjects to examine evidence for a possible differential relationship between these variables across the samples. A major finding of the study was the absence of a group-level difference in frontal pole gray volumes between the healthy and schizophrenia participants. However, a more complex finding emerged in relation to age effects. The healthy participants showed an inverse relationship of FP gray volume with age, even after taking total brain volume differences into account. But this age effect was completely absent in the schizophrenia group. Moreover, all the volumetric measures in schizophrenia subjects showed substantially higher range, variance, skewness and kurtosis when compared to those of healthy subjects. These findings have implications in understanding the possible role of FP in the pathophysiology of schizophrenia.

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1. Introduction

Brodmann's area (BA) 10, which occupies the rostral-most part of the human brain, i.e., the frontal pole (FP), is probably the single largest cytoarchitectonic area of the human prefrontal cortex (PFC) (Ramnani and Owen, 2004). It has an unusually protracted course of development (review, Dumontheil et al., 2008), and has been shown to play a critical role in many aspects of complex human cognition (meta-analysis, Gilbert et al., 2006; review, Burgess et al., 2006). These include multi-tasking (Burgess et al., 2006; Koechlin et al., 1999), processing of 'cognitive branching' based on reward expectations (Koechlin and Hyafil, 2007), time- and event-based prospective memory (Okuda et al., 2007), conflict resolution (Posner et al., 2006) and selection of processes or sub-goals (Fletcher and Henson, 2001). The functional relevance of this important brain region is further exemplified by its suggested role as a "gateway" which biases the priority of information from among stimulus-oriented and stimulus-independent cognitive operations (Burgess et al., 2007a; 2006).

The FP exerts its influence probably through three important connections which link it to the superior temporal

* Corresponding author. National Institute of Mental Health and Neurosciences (NIMHANS), P.B. No. 2900, Dharmaram P.O., Hosur Road, Bangalore,560 029, Karnataka, India. Tel.: +91 80 26995349, +91 80 26995306; fax: +91 80 26564822.
E-mail addresses: jpjnimhans@gmail.coms, jpjinc@yahoo.com (J.P. John).

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gyrus (STG) via the extreme capsule, the amygdala via the uncinate fasciculus, and the anterior cingulate gyrus (aCiG) through the cingulate fasciculus (Petrides and Pandya, 2007). These three brain regions (Sigmundsson et al., 2001; Shenton et al., 2001) and their white matter connections to the FP (Rosenberger et al., 2008; Burns et al., 2003) have been shown to be crucially involved in the pathophysiology of schizophrenia. The study of the FP therefore, is important not only for unraveling the neurobiological substrate of executive control of human cognitive operations, but also for examining the role that it plays in the pathophysiology of neuropsychiatric disorders such as schizophrenia.

During the past decade, there has been a plethora of functional imaging studies that have examined the role of FP in complex cognitive operations (Burgess et al., 2007b), and a number that have made links between schizophrenia and FP dysfunction (see e.g. Simons et al., 2006; MacDonald et al., 2005; Copolov et al., 2003; Buchsbaum et al., 2002). Moreover activation of the rostral PFC has been suggested to correlate with clinical improvement following drug treatment (Stip et al., 2005). Evidence for structural abnormalities of the FP emanates primarily from post-mortem studies, which have revealed increased neuronal density in the PFC of those who had schizophrenia (Selemon et al., 1995, 1998; Pakkenberg, 1993). Moreover, there is evidence for specific changes in BA 10 in schizophrenia (Benes et al., 1991; Beasley and Reynolds, 1997; Vogeley et al., 2003).

In vivo morphometric studies of the FP in the normal brain have been limited by the lack of a consistent definition of its posterior boundary having cytoarchitectonic and or functional validity (John et al., 2006). Consequently, those that have reported FP volume findings in schizophrenia (Mitelman et al., 2007; Goldstein et al., 1999; Wible et al., 1997) have used varying definitions of its posterior boundary, rather limiting the significance of the findings.

In a recently published paper (John et al., 2007), we proposed the coronal plane containing the anterior termination of the olfactory sulcus (ATOS) as a cytoarchitectonically meaningful and a potentially functionally valid landmark for demarcating the posterior boundary of the FP on MR images. This landmark corresponds to +49 to +50 in the coronal/verticofrontal axis in the standard Co-Planar Stereotaxic Atlas of the Human Brain by Talairach and Tournoux (1988). Independent functional validation of this structural MRI-based definition was provided by Smith et al. (2007), who, using a task to functionally localize the rostrolateral prefrontal cortex, reported predominant activation foci with posterior limit overlapping with the above-mentioned Talairach *y*-co-ordinate.

We used this cytoarchitectonically and functionally valid landmark-based definition to study the FP gray matter volume in a sample of healthy subjects who were age-, sex- and education-matched to neuroleptic-naïve, recent-onset schizophrenia subjects. Functional abnormalities in anterior PFC have been demonstrated by fMRI in schizophrenia patients (Simons et al., 2006; Whalley et al., 2004; Callicott et al., 2003). However structural MRI studies in neuroleptic-naïve schizophrenia patients have failed to report consistent reductions of the prefrontal sub-regions (review, Torrey, 2002). Considering that ours is the first *in vivo* structural MRI study of its kind, and additionally since the schizophrenia sample constituted of recent-onset, neuroleptic-naïve subjects, we hypothesized that there will be no significant group reductions in the FP gray volumes in the schizophrenia sample compared to healthy subjects. However, a further possibility exists. There is evidence for disproportionate tissue loss in the frontal cortex underlying normal aging process (Jernigan et al., 2001; Raz et al., 1997; West, 1996; Moscovitch and Winocur, 1995). Accordingly, we also set out to study the relationship between age and FP gray volume in healthy subjects in comparison to that of schizophrenia. Since schizophrenia is conceptualized as a disorder of aberrant/deviant neurodevelopment (Weinberger, 1987; Murray et al., 2002) with associated cellular abnormalities of the FP as mentioned earlier, we hypothesized that there might be differences in the age-related changes in FP volume between healthy subjects and schizophrenia subjects.

2. Methods

The study was carried out at the National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore India, with due approval from the NIMHANS Ethics Committee, thus conforming to the ethical standards laid down in the 1964 Declaration of Helskinki. Written informed consent was obtained from all the subjects (and their legally qualified representatives in case of patients) prior to enrollment into the study.

2.1. Subjects

2.1.1. Patients

The patient sample constituted of 23-right-handed, neuroleptic-naïve schizophrenia subjects, recruited into the study by purposive sampling from those who attended the outpatient services of NIMHANS. The inclusion criteria were: a DSM-IV diagnosis of schizophrenia or schizophreniform disorder, right-handedness [as assessed by modified Annett's (1976) inventory], duration from onset of illness $\leq$5 years, age between 17 and 50 years and an MMSE score of $\geq$22. The diagnosis of schizophrenia or schizophreniform disorder was arrived at using criteria from the Diagnostic and Statistical Manual for Mental Disorders-Fourth edition (DSM-IV) based on the consensus of a research psychiatrist who conducted a semi-structured interview and a trained research assistant who used the Mini International Neuropsychiatric Interview (MINI) Plus (Sheehan et al., 1998). The exclusion criteria included previous exposure to psychotropic drugs; significant suicidal or homicidal risk or other disruptive behaviour which warranted immediate interventions and history of ECT within the previous 6 months. The baseline severity of schizophrenia psychopathology was evaluated using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) for all subjects by one trained rater (V.A.) who had established good inter-rater reliability with another trained rater (B.R.), as reported previously (John et al., 2008). Overall clinical status was assessed using Clinical Global Impression-Severity (CGI-S) (Guy, 1976).

2.1.2. Healthy subjects

Twenty three right-handed healthy subjects individually matched with the schizophrenia subjects for age, sex and education, with MMSE score of $\geq$22, constituted the control sample. These subjects, predominantly consisting of hospital

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