Frontal cortical thickness correlates positively with impulsivity in early psychosis male patients

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ABSTRACT

Aim: Impulsive behaviors, which are frequent in young people suffering from psychosis have been linked to risky and violent behaviors and participate to the burden of psychotic illness. Given that morphological brain correlates of impulsivity in schizophrenia have been poorly investigated especially in young adults, the aim of this study was to investigate the relationship between impulsivity and cortical thickness in early psychosis patients.

Method: 17 male subjects in the early phase of psychosis were recruited. Impulsivity was assessed with the Lecrubier Impulsivity Rating Scale. Mean cortical thickness was extracted from magnetic resonance imaging brain scans, using surface-based methods.

Results: Mean cortical thickness in the frontal lobe correlated positively with mean impulsivity in early psychosis male patients.

Conclusion: Our results suggest that psychotic subjects exhibiting higher impulsivity have larger frontal cortical thickness, which may pave the way towards the identification of patients with a higher risk to display impulsive behaviors.

KEY WORDS (3): Magnetic resonance imaging, violence, impulsivity, cortical thickness, early psychosis

Introduction

Impulsivity is a multidimensional construct that is often defined as “a tendency to respond quickly to a given stimulus, without deliberation and evaluation of consequences”(Buss & Plomin, 1975; Lecrubier, Braconnier, Said, & Payan, 1995; Ouzir, 2013). Impulsive behaviors are present not only in patients with schizophrenia but across the psychosis spectrum(Nanda et al., 2016) and have been linked to increased risky behaviors including violence, substance abuse and suicide(Gut-Fayand et al., 2001; Nanda et al., 2016; Ouzir, 2013).

Impulsivity is thought to be related to dysfunction in a brain circuit comprising cortico-subcortical regions, including the frontal cortex, pallidum, striatum and thalamus (Abdel-Baki, Turgeon, Chalfoun, & Nguyen, 2013; Aron, Behrens, Smith, Frank, & Poldrack, 2007; Hoptman, 2015), which results in a failure to inhibit inappropriate behavior(Hoptman, Antonius, Mauro, Parker, & Javitt, 2014). Although the understanding of how impulsivity may emerge during adolescence in relation to specific brain circuits and their maturation is of considerable interest(Whelan et al., 2012), it as received little attention in the field of early psychosis (EP)(Nielssen, Malhi, McGorry, & Large, 2012). The relation between impulsivity and brain maturation is of particular interest with respect to early psychosis. Psychotic disorders have typical onset during adolescence and early adulthood and are associated with a high incidence of impulsive behaviors(Nielssen et al., 2012). To the best of our knowledge, there is no study that examined the brain structure correlates of impulsivity in early psychosis although better understanding of the genesis of impulsivity may pave the way towards the development of treatment and preventive strategies in early psychosis. In the current study we focus on a group of early psychosis patients who underwent brain magnetic resonance imaging (MRI) and explore the relationship between impulsivity and cortical thickness.

Materials and Methods

Participants and clinical assessments

EP within the first 3 years of treatment for a psychotic disorder and having met psychosis threshold according to the Comprehensive Assessment of At Risk Mental States criteria (CAARMS)(Yung et al., 2005) were selected from a large study on impulsivity in Early Psychosis including 265 patients (Moulin, Palix, et al., 2017). Seventeen male patients (age 24.5 ± 4.8 yo) who had an available brain MRI scan and an assessment of impulsivity (Impulsivity Rating Scale), and satisfied the criteria listed above, were included in the current study. All patients were part of the TIPP (Treatment and Early Intervention in Psychosis Program), an integrated EP program(Baumann et al., 2013).

Impulsivity was assessed with the Impulsivity Rating Scale (IRS)(Lecrubier et al., 1995). Overall impulsivity of patients was rated at the end of the 3-year follow-up period. The IRS is a 7-item hetero-evaluation of impulsivity, ranging from 0 to 21 (dimensions include irritability, aggressiveness, impatience, time needed for decision, capacity to pursue an activity, ability to delay and control of response).

Diagnosis was based on an expert consensus based on Diagnostic and Statistical Manual of Mental Disorders (fourth Edition; DSM-IV criteria). Symptom severity at the time of scanning was assessed with the Positive and Negative Syndrome Scale (PANSS)(Kay, Fiszbein, & Opler, 1987) and substance use (Cannabis, alcohol and other) with the Case Manager Rating Scale (CMRS; adapted from(Drake et al., 1990)). Violent behaviors defined as « serious violence », i.e. « an assault causing any degree of injury, any use of weapon and any sexual assault»(Large & Nielssen, 2011), were identified by case-managers during follow-up. Dosages of antipsychotic medication were converted to chlorpromazine equivalents (CPZ eq.)(Andreasen, Pressler, Nopoulos, Miller, & Ho, 2010).

Informed written consent in accordance with institutional guidelines (protocol approved by the Ethic Committee of Lausanne University) was obtained for all the subjects.

MRI acquisitions and analysis

MRI sessions were performed on a 3 Tesla scanner (Magnetom TrioTim, Siemens Medical Solutions), equipped with a 32-channel head coil. Each scanning session included a magnetization-prepared rapid acquisition gradient echo (MPRAGE) T1-weighted sequence with 1mm in-plane resolution and 1.2 mm slice thickness, covering 240x257x160 voxels. The TR, TE and TI were respectively 2300, 2.98 and 900 ms. Each scan was visually inspected for quality check. Surface-based morphometry (FreeSurfer software, version 5.0.0) allowed the estimation of cortical thickness from the T1-weighted images(Fischl & Dale, 2000). The pial surface and the gray-white matter interface of each subject were visually inspected and checked for errors, blind to diagnosis. Average cortical thickness values were computed for each of the 4 lobes, and for each of the 68 cortical regions depending on the Desikan-Killiany atlas. White matter volume per lobe and subcortical volumes for the thalamus, pallidum and striatum, automatically generated by FreeSurfer were also extracted and used in a secondary analysis.

Statistical analysis

We initially focused on the mean cortical thickness of each of the 4 lobes. Pearson's correlation coefficient and partial correlation were used to assess the relationship between frontal, temporal, occipital, parietal cortical thicknesses and IRS impulsivity score while controlling for possible confounding factors (age, substance use, CPZ equivalents, and positive symptoms). The p-values were adjusted for multiple comparisons (i.e., 4 comparisons) using the Bonferroni correction. Post-hoc analysis was only performed on lobe(s) surviving correction for multiple comparisons to identify which cortical regions (of a lobe) contributed the most to the correlation with IRS impulsivity scores (Pearson's correlation coefficient; p-value < .05). To investigate more deeply the underlying network, white matter volume was computed for the lobe(s) surviving correction for multiple comparisons in a secondary analysis. In addition, subcortical volumes were also calculated for total thalamus (left + right), striatum (left and right caudate + left and right putamen) and pallidum. The p-values were adjusted for multiple comparisons (i.e., 3 comparisons) using the Bonferroni correction. In the IRS score, impulsivity is assessed with a very diverse set of dimensions. This is why we tested first the global score (i.e., all items together). In a second

step, individual IRS items were correlated with the mean cortical thickness of surviving lobe(s) to identify which items contributed the most to the correlation (Pearson's correlation coefficient; p-value < .05).

Results

76.5% of patients fulfilled criteria for schizophrenia or schizoaffective disorder (n = 13) and 4 patients for another psychotic disorder (major depression with psychotic features, brief psychotic disorder, psychotic disorder not otherwise specified). Subject's characteristics can be found in table 1.

Mean cortical thicknesses were the following for each lobe: frontal (2.52 ± 0.1 mm), parietal (2.44 ± 0.09 mm), occipital (2.03 ± 0.09 mm), temporal (2.92 ± 0.12 mm). Among the 4 lobes, after correction for multiple comparisons, only mean frontal cortical thickness correlated positively at a significant level with IRS impulsivity score (frontal: r = .651, adj. p = .02; parietal: r = .444, adj. p = 0.296; occipital: r = .115, adj. p =1.00; temporal: r = .430, adj. p = .34) (Fig 1), which remained significant when controlling for possible confounding factors (age, CPZ eq., substance use, positive symptoms) (frontal: r = .902, adj. p < .001). The implicated frontal regions in the left hemisphere were the superior frontal gyrus (r = .567, p = .018), the rostral part of the middle frontal gyrus (r = .541, p = .025), the pars opercularis (r = .500, p = .041) and pars triangularis (r = .580, p = .015) of the inferior frontal gyrus and rostral part of the anterior cingulate (r = 0.679, p = .003). In the right hemisphere, the superior frontal gyrus (r = .487, p = .048), the rostral part of the middle frontal gyrus (r = .595, p =.012), the medial (r = .531, p = .028) and lateral (r = .486, p = .048) parts of the orbitofrontal gyri and the precentral gyrus (r = .24, p = .024) were correlated (p < .05) with the IRS impulsivity score. IRS items 'aggressiveness' (#5)(r = .515, p = .034) and 'lack of control of response' (#6) (r = .642, p = .005) were the most strongly associated (p < .05) with mean frontal cortical thickness. Although, when entered simultaneously into a stepwise multiple linear regression model, only 'lack of control of response' (#6) showed to be independently related to mean frontal cortical thickness (β = .642, p = .005). In a secondary analysis, we also found that IRS impulsivity score correlated negatively with mean frontal white matter volume (r = -.582, p =.014). IRS impulsivity score did not correlate with subcortical volumes of the thalamus (r =- .545, adj. p = .072), striatum (r = -.108, adj. p = 1.00) or pallidum (r = -.130, adj. p = 1.00).

Violent behavior had occurred in 41.2 % of the group (n = 7). Impulsivity ratings were significantly higher in violent patients (8.29 ± 2.5) compared to non-violent patients (4.9 ± 3.5) (p = .046).

Discussion

The main finding in this study is that mean cortical thickness in the frontal lobe was positively correlated with impulsivity score, suggesting an implication of frontal structures in the development of impulsivity in early psychosis. Accordingly, frontal white matter volume was negatively correlated with IRS impulsivity score. To the best of our knowledge, this is the first study investigating cortical thickness in relation to impulsivity in early phase psychosis. Comparison with other studies is difficult because they vary in terms of phases of the illness, conceptualization of impulsivity and brain imaging parameters (Lee et al., 2013; Ouzir, 2013). Our brain imaging results are in line with some previous findings showing that orbito-frontal volume relates positively to aggression in schizophrenia (Hoptman et al., 2005), orbito-frontal cortex volume relates positively to motor impulsivity in a non-psychotic psychiatric population (Antonucci et al., 2006), and gray matter volume of superior and middle frontal regions correlates positively with impulsiveness score in healthy controls (Gardini, Cloninger, & Venneri, 2009). The finding of a positive association between impulsivity and frontal cortical thickness may seem rather counterintuitive and is in contrast with studies where impulsive behavior is linked to reduced gray matter volume in healthy controls (Korponay et al., 2017) or reduced cortical thickness in schizophrenia (Hoptman et al., 2014); for review see (Ouzir, 2013). The normal process of brain development and maturation involves a phase of cortical thickness increase during childhood, followed by cortical thinning during adolescence and adulthood, which plays an important role in the refinement of neural circuits (Giedd et al., 1999; Shaw et al., 2008). In parallel, white matter volume expands throughout adolescence (Paus, 2005). In this regard, it is noteworthy that in the current study, frontal white matter correlated negatively with IRS impulsivity score. It is thus tempting to suggest that psychotic subjects exhibiting higher impulsivity may experience a delayed maturational process in frontal areas implicated in the control of emotions and impulsivity, similarly to what has been described for patients with attention deficit hyperactivity disorder (ADHD)(Rubia, 2007), who interestingly may as well develop violent behaviors as adults(Mckay & Halperin, 2006). Nonetheless, this hypothesis remains speculative and a longitudinal design is needed to investigate this theory.

In the current study, impulsivity ratings were higher in violent patients. Given that Impulsivity is a risk factor for violence in early psychosis (Moulin, Golay, et al., 2017), brain correlates of impulsivity may also help to identify individuals at risk for violence although this would need to be confirmed in another study.

Of note, the current sample is rather young (mean age 24.8 ± 4.8 yo) and in the early phase of psychosis, compared to the chronic sample studied by (Hoptman et al., 2014)(mean age of 38.2 ± 10.4).

Frontal cortex thickness is the only cortical brain region, which correlated with impulsivity after correction for multiple comparisons. When the correlations of individual items were examined, results suggested that the strongest correlation was with "lack of control of response". It is worth mentioning that correlations coefficients for other lobes were not small (e.g. parietal lobe, r = .444; temporal lobe, r = .430) and correlation with thalamus was close to significant (r =- .545, adj. p = .072). A lack of power due to the current small sample size is a possible factor explaining these negative findings.

'Lack of control of response' (item 6 of the Lecrubier IRS) reflects the capacity of inhibiting a behavioral response and is then under the influence of inhibitory control. The implicated brain circuit (Chambers, Garavan, & Bellgrove, 2009)includes the pars opercularis of the right inferior frontal gyrus, supplementary motor area and preSMA, the globus pallidus, the striatum, the thalamus, and the subthalamic nucleus which overlaps partially with the brain regions identified in the current study.

General limitations for the current study include the presence of antipsychotic medication and a sample with males only. Given that males are more impulsive than females, it was an obvious sample to investigate first. Further studies will however be needed to confirm the current findings and investigate if they are also valid in a female population.

If replicated, these results may pave the way to further exploration of the mechanisms of the genesis of impulsivity in EP. Ultimately, this may lead to the identification of patients with a higher risk to display impulsive behaviors and to the development of preventive interventions in this domain.

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Table 1. Early psychosis patients characteristics	
Age, mean ± SD	24.8 ± 4.8
Gender (male)	100%
Impulsivity Rating Scale, mean score ± SD	6.29 ± 3.5
Education of parents (years) ± SD	13.8 ± 4.2
Duration of illness (days) ± SD	1021.5 ± 827.7
Duration of untreated psychosis (days) ± SD	104.0 ± 309.6
Mean CPZ eq. ± SD	336.7 ± 235.6
PANSS positive, mean ± SD	14.1 ± 5.3
PANSS negative, mean ± SD	15.3 ± 4.7
PANSS general, mean ± SD	32.9 ± 8.7
History of violent behavior	41.2%
Substance use	
All substances	82.4%
Cannabis	52.9%
Alcohol	82.4
Other substances (opioids, cocaïne, hallucinogens, volatile solvents)	5.9%

Age in years; CPZ eq., chlorpromazine equivalent (antipsychotic medication converted to chlorpromazine equivalent, in mg); PANSS, Positive and Negative Syndrome Scale: positive symptom score, negative symptom score, general symptom score; SD, standard deviation

Figure 1. Correlation of impulsivity and frontal cortical thickness.

Impulsivity Rating Scale (IRS)(mean score) and frontal cortical thickness (mean in mm). Linear trend line was added. Larger frontal cortical thicknesses are associated with higher levels of impulsivity (tested with Pearson's correlation coefficient).