Title

Cognitive and Clinical Predictors of Prefrontal Cortical Thickness Change Following First-Episode of Psychosis

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Abstract

The association of neuroanatomical progression with cognitive and clinical deterioration after first-episode of psychosis remains uncertain. This longitudinal study aims to assess whether i)impaired executive functioning and emotional intelligence at first presentation are associated with progressive prefrontal and orbitofrontal cortical thinning ii)negative symptom severity is linked to progressive prefrontal cortical thinning. 1.5T MRI images were acquired at baseline and after 3.5 years for 20 individuals with first-episode psychosis and 18 controls. The longitudinal pipeline of Freesurfer was employed to parcellate prefrontal cortex at two time points. Baseline cognitive performance was compared between diagnostic groups using MANCOVA. Partial correlations investigated relationships between cognition and negative symptoms at baseline and cortical thickness change over time. Patients displayed poorer performance than controls at baseline in working memory, reasoning/problem solving and emotional intelligence. In patients, loss of prefrontal and orbitofrontal thickness over time was predicted by impaired working memory and emotional intelligence respectively at baseline. Moreover, exploratory analyses revealed that the worsening of negative symptoms over time was significantly related to prefrontal cortical thinning. Results indicate that specific cognitive deficits at the onset of psychotic illness are markers of progressive neuroanatomical deficits and that worsening of negative symptoms occurs with prefrontal thickness reduction as the illness progresses.

Keywords

First-episode psychosis, Cognitive impairment, Magnetic resonance imaging, Cortical thickness, Longitudinal study, Negative symptoms

1. Introduction

Patients experiencing their first-episode of psychosis display cognitive impairments compared with healthy controls across different domains, such as verbal learning, executive functions, general intelligence, social cognition, attention and working memory (Aas et al., 2014; Kenney et al., 2015). Recent findings have identified executive impairments as one of the most central deficits in patients with schizophrenia (Chan et al., 2006a, 2006b; Orellana and Slachevsky, 2013). In neuropsychology, the term executive function is used to indicate higher-order cognitive processes, which enable people to control and plan their behaviours. This set of cognitive abilities includes planning, working memory, attention, problem solving, verbal reasoning, inhibition, mental flexibility and monitoring of actions (Chan et al., 2008). Neuroimaging, neuropsychological and lesion studies have shown that optimal executive functioning depends on healthy prefrontal cortex (Gazzaniga, 2004).

In this study, we focused our analyses on cortical thickness, given that it is highly heritable and driven by specific cellular mechanisms (Panizzon et al., 2009). It therefore represents an important measure for the identification of prognostically meaningful biological markers in patients experiencing their first-episode of psychosis. Longitudinal studies of patients following their first-episode of psychosis have reported progressive cortical changes, including cortical volume loss in frontal regions (Arango et al., 2012; Pina-Camacho et al., 2016; Roiz-Santiáñez et al., 2014), which may be attributable to reduced cortical thickness. Cortical thinning over time in frontal and prefrontal regions has been widely reported in patients with established schizophrenia and first-episode of psychosis compared with controls (Gutiérrez-Galve et al., 2015; Nesvåg et al., 2008). Janssen et al's study identified bilateral cortical thinning in the superior prefrontal cortex in patients with early-onset first-episode psychosis (Janssen et al., 2009).

The relationship between cortical thickness and cognition has been explored in some longitudinal studies. Specifically, reductions of cortical thickness in patients with schizophrenia have been shown to relate to executive functioning (Ehrlich et al., 2012; Geisler et al., 2015). Less improvement over time in general cognitive performance has been demonstrated to correlate with a greater longitudinal volume loss in frontal regions, particularly medial frontal gyrus and inferior frontal gyrus, in patients with first-episode of schizophrenia (Asami et al., 2012). Another longitudinal study, based on 20 patients

experiencing their first-episode of psychosis and 25 healthy controls, found that low working memory at baseline predicts frontal and parietal cortical thinning 2 years later (Gutiérrez-Galve et al., 2015).

Although executive dysfunction reflects a cognitive impairment and negative symptoms are a characteristic of schizophrenic illness, these two indices of dysfunction tend to overlap and are associated with similar behaviours, such as incongruous emotional responses, reductions in speech, impaired attention and loss of spontaneity (Orellana and Slachevsky, 2013). Cross-sectional studies tend to report a significant correlation between executive impairment and negative symptoms in schizophrenia (Bagney et al., 2013; Nieuwenstein et al., 2001) and first-episode of psychosis (Faerden et al., 2009). The large ENIGMA cross-sectional meta-analysis reported a significant association between prefrontal thinning and negative symptom severity in schizophrenia, specifically in the left medial orbitofrontal cortex, left lateral orbifrontal gyrus and left pars opercularis (Walton et al., 2018). This relationship has also been explored using a longitudinal design, with reports that less improvement in negative symptoms was significantly correlated with volume loss in middle and inferior frontal gyrus over time (Asami et al., 2012). These studies emphasise how both negative symptoms and executive dysfunction can occur with abnormalities in prefrontal regions.

Emotional intelligence, a domain of social cognition, has also been reported to be impaired in patients experiencing their first-episode of psychosis compared with healthy volunteers (Healey et al., 2016; Kenney et al., 2015). Emotional intelligence is a subset of social intelligence described by Salovey and Mayer (1990) as the ability to monitor one's own and others' feelings and emotions, to discriminate among them and to use this information to guide one's thinking and actions' (Salovey and Mayer, 1990). The prefrontal cortex plays an important role in the regulation of emotional processing (Forbes and Grafman, 2010); in particular the orbitofrontal cortex is implicated in emotional and social cognition (Beer et al., 2006; Nestor et al., 2013), while emotional intelligence is reduced in those with lesions in the right orbitofrontal cortex (Barbey et al., 2014).

Although several studies have investigated the cross-sectional relationship between cognition, cortical thickness and clinical symptoms in first-episode psychosis, few have carried out longitudinal analyses to clarify such associations over time. The present study, with its

longitudinal design offers an excellent opportunity to explore whether impaired executive functioning and negative symptom severity at the onset of psychosis (markers of a potentially more severe illness process) are predictors of prefrontal cortex thinning in subsequent years; and also to clarify whether impaired emotional intelligence at onset of psychosis is associated with loss of orbitofrontal cortical thickness over time. We considered that more severe executive dysfunction and negative symptoms at baseline would be associated with more progressive neuroanatomical changes and hypothesize three associations: (1) that performance in those executive functions tests showing an impairment in patients at baseline compared to healthy controls will be significantly associated with loss of thickness in total prefrontal cortex in patients over time; (2) impaired emotional intelligence at baseline will be associated with orbitofrontal cortex thinning in patients as the illness progresses; and (3) severity of negative symptoms at baseline will be associated with prefrontal cortical thinning in patients over time. Additionally, through exploratory analyses, we investigated the relationship of cognitive and clinical change over time with prefrontal cortical thickness change.

2. Methods and materials

2.1 Participants

As reported in our previous study (Kenney et al., 2015), 23 individuals in their first-episode of psychotic illness and 21 healthy controls participated at both baseline and follow-up in clinical and cognitive assessments. Of these, 20 patients and 18 healthy controls also participated in MRI scanning and were included in the present study. The recruitment and clinical assessment of participants was previously described in detail (Kenney et al., 2015; McFarland et al., 2013; Scanlon et al., 2014). Exclusion criteria for all participants included neurological disorders, learning disability, life-time substance dependence, a history of head injury resulting in loss of consciousness for over 5 minutes, oral steroid use in the previous 3 months and general MRI contraindications. Exclusion criteria for controls included also a personal or family history of psychosis or affective disorder. The study was approved by the Research Ethics Committees of the National University of Ireland Galway and Galway University Hospital. Fully informed written consent was obtained for all participants.

2.2 Neuropsychological assessment

The MATRICS Consensus Cognitive Battery (MCCB) (Nuechterlein et al., 2008) was used to assess patients and controls at baseline and follow-up. MCCB was chosen for its excellent test-retest reliability and minimal practice effects (Nuechterlein et al., 2008). Within the MCCB, only the tests assessing specific domains of executive functions were utilised in the analyses. Following the definition of executive functioning as set of abilities, presented by Chan et al., (2008), we were able to cover the following domains: working memory (Wechsler Memory Scale (WMS®-III): Spatial Span forward and backward and Letter Number Span); attention (Continuous Performance Test (CPT): Identical Pairs); fluency (Category fluency: Animal Fluency) and reasoning & problem solving (Neuropsychological Assessment Battery (NAB): Mazes). Emotional intelligence was measured using the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT): Managing Emotions. A detailed description of the neuropsychological tests has been outlined previously (Kenney et al., 2015).

2.3 Clinical assessment

Patients were diagnosed using the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders IV text revision version at both timepoints. The antipsychotic medication taken by patients was recorded and the total dose converted to chlorpromazine (CPZ) equivalents (Lehman and Steinwachs, 1998; Woods, 2003). The severity of negative and positive symptoms was assessed at both timepoints using the 0-6 point Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Our interest was specifically directed to negative symptoms. The original PANSS negative symptom subscale contains two items better considered to be part of the cognitive domains: "Stereotyped Thinking" and "Difficulty in Abstract Thinking" (Daniel, 2013; Emsley et al., 2003). We therefore organised the Negative Subscale according to the Five-Factor solution where Blunted Affect, Emotional Withdrawal, Poor Rapport, Passive Withdrawal, Lack of Spontaneity, Motor Retardation and Active Social Avoidance were the included items (Lehoux et al., 2009). Social, occupational and psychological functioning of patients was assessed using a Global Assessment Functioning score (Hall, 1995) at both time points.

2.4 MRI data acquisition

MRI images were acquired for all participants at baseline and follow-up at University Hospital Galway in a 1.5 Tesla Siemens Magnetom Symphony scanner (Erlangen, Germany) equipped with a 4-channel head coil. A magnetisation prepared rapid gradient echo sequence was used to generate high-resolution volumetric T1-weighted images with the following parameters: repetition time=1140 ms, echo time=4.38 ms, inversion time=600 ms, flip angle=15°, matrix size=256 x 256: slice thickness=0.9 mm and in plane resolution=0.9 mm x 0.9 mm.

2.5 MRI processing

Volumetric T1-weighted images were intensity inhomogeneity corrected using non-parametric, non-uniform intensity normalisation (N3) (Sled et al., 1998) as previously described (Ahmed et al., 2015; Scanlon et al., 2014). The longitudinal stream (Reuter et al., 2012) of Freesurfer v.5.3.0 ("FreeSurfer," 2013) was employed to parcellate prefrontal cortical regions at two time points. This technique has sufficient sensitivity and reliability for small sample sizes and uses a robust and inverse consistent registration method to create an unbiased within-subject anatomical template, overcoming the risk of underestimating change and avoiding over-regularization or temporal smoothness constraints (Reuter et al., 2012,

2010). The processing pipeline included skull-stripping (Ségonne et al., 2004), Talairach transformation, subcortical gray/white matter segmentation according to the Desikan-Killiany atlas (Desikan et al., 2006; Fischl et al., 2002), intensity normalization (Sled et al., 1998), tessellation of the gray/white matter boundaries, automated topological correction (Fischl et al., 2001; Ségonne et al., 2007) and surface deformation following intensity gradients in the subject template (Dale et al., 1999). At each step, the output was visually inspected, and if necessary corrected according the protocol ("FreeSurfer Quality Control Guide," 2013). The selection of subregions of the prefrontal cortex (Carlen, 2017) included the following bilaterally: superior frontal gyrus; middle frontal gyrus subdivided into rostral and caudal division; inferior frontal gyrus subdivided into pars opercularis, triangularis and orbitalis; orbito frontal subdivided into lateral and medial division and frontal pole. These regions were all added to create a total prefrontal cortical region of interest (ROI) (Figure 1A). The orbitofrontal ROI was created by adding the lateral and medial orbitofrontal subregions (Figure 1A). Lastly, the thickness, defined as the average distance between the gray-white boundary and the pial surface within each ROI, was extracted at baseline and follow-up for all the regions of interest for all the patients.

2.6 Statistical analysis

2.6.1 Clinical and demographics

All analyses were carried out with the Statistical Package for the Social Sciences version 23 for Windows. Shapiro-Wilk Test was used to test for normal distribution of each cognitive, clinical and neuroimaging variable. Outliers were defined as greater or less than 3 by standard deviation from the mean. Age, years of education, gender, time between scanning and cognitive testing were compared between groups using t-test, chi-square and Mann-Whitney Test. Differences between baseline and follow-up on clinical variables were tested using Wilcoxon Signed-ranks Test and Paired-Sample T-test. Raw scores of the cognitive tests for both patients and controls were age and gender corrected using normative data previously collected (Kern et al., 2008).

2.6.2 Cognitive impairment at baseline & prefrontal cortical thickness change over time

One-way MANCOVA was used to compare executive functioning and emotional intelligence performance at baseline between patient and control groups, covarying for years of education. Partial correlation, covarying for age, gender and intracranial volume (ICV), was used to assess associations between the tests showing impairment in executive functioning and emotional intelligence in patients at baseline and total prefrontal and orbitofrontal thickness change respectively. Change in neuroanatomical measures was expressed using the following formula: $\frac{Follow-up\ -\ Baseline}{Baseline} \times 100$. In the case of statistically significant correlation with total prefrontal cortex, post-hoc analysis assessed whether cognitive impairment at baseline significantly correlated with specific subregions.

2.6.3 Negative symptoms severity at baseline & prefrontal cortical thickness change over time

Partial correlation was used to assess association between negative symptoms severity at baseline and total prefrontal cortical thickness in patients. Age, gender and ICV were added as confounding variables. Change in neuroanatomical measures was expressed using the following formula: $\frac{Follow-up\ -Baseline}{Baseline} \times 100$.

2.6.4 Cognitive and clinical change & prefrontal cortical thickness change

Partial correlation was used to explore the relationship between cognitive and clinical change (*Follow-up–Baseline)* with prefrontal cortical thickness progression over time ($\frac{Follow-up\ -\ Baseline}{Baseline} \times 100$) in patients. Post-hoc analysis was carried out to clarify which specific prefrontal cortical subregions were involved. Given the exploratory nature of the analyses, all the results were corrected for multiple comparisons, using the Benjamini-Hochberg procedure with α= 0.05, which decreases the false discovery rate (Benjamini and Hochberg, 1995; Chen et al., 2017).

3. Results

Patient and control groups were matched for gender, age, time between scans and predicted IQ, measured using the national adult reading test (Table 1). Years of education was significantly different between patients and controls and was included as a covariate in all analyses. Patients significantly improved over time in positive, general and total score in the PANSS scale (Table 2). Global assessment of functioning strongly improved 3.5 years following the first-episode of psychosis. At the follow-up time point, patients were diagnosed with schizophrenia (n=5), schizoaffective disorder (n=3), delusional disorder (n=1), psychotic disorder not otherwise specified (n=3), bipolar type I (n=6) and psychotic depression (n=2).

3.1 Groups Differences at Baseline in Cognition

There was a significant difference between patients and controls at baseline when considering jointly the six cognitive measures Wilk's Λ $F(6,30)= 4.823$, $p= <.001$. For executive functioning patients scored significantly worse than controls in Category Fluency: Animal fluency, CPT: Identical Pairs, WMS: Spatial Span and NAB: Mazes and not WMS: Letter Number Span. Patients' performance in MSCEIT: Managing Emotions was significantly worse compared with controls (Figure 1B, table 3).

3.2 Executive Impairment & Prefrontal Cortical Thickness

In the patient group, change in total prefrontal cortical thickness, specifically loss of thickness over time, was significantly associated with impaired working memory: spatial span at baseline (r=0.517; p=0.040, Figure 1C). Post-hoc analysis conducted to determine the prefrontal subregions involved in the patient group revealed a significant involvement of rostral middle frontal cortex (r=0.546; p=0.029) and the frontal pole (r=0.507; p=0.045). However, this association lost significance after correcting for multiple comparisons [rostral middle frontal & frontal pole (p=0.245; p=0.245)]. No significant correlation was found between total prefrontal cortical thickness change and the remaining impaired executive functioning tests (*r-range*=-0.064 – 0.458; *p-range*=0.075 – 0.814). In the control group, none of the executive function measures at baseline (working memory, attention, fluency and reasoning & problem solving) were significantly correlated with total prefrontal thickness change over time (*r-range*=-0.362–0.325; *p-range*=0.185–0.759). Additionally, the relationship between spatial working memory and total prefrontal cortical thickness change

was significantly different (z=2.28; p=0.02) in patients compared to controls. Exploratory analyses investigating the relationship between change in cognitive performance and change in total prefrontal thickness did not reveal any significant associations (r=-0.273–0.327; p= 0.216–0.959).

3.3 Emotional Intelligence Impairment & Orbitofrontal Thickness

When investigating the relationship between emotional intelligence at baseline and orbitofrontal thickness change, we found that impaired emotional intelligence in the patient group was a significant predictor of loss of orbitofrontal thickness 3.5 years following the first-episode of psychosis (r=0.512; p=0.042, Figure 1D). Although this significant relationship was not present in the control group (r=0.178; p=0.542), the difference between the relationships in patients and controls was not statistically significant (z=1.09; p=0.138).

3.4 Negative Symptoms & Prefrontal Cortical Thickness

The severity of negative symptoms at illness onset was not significantly related to total prefrontal thickness change over time (r= -0.095; p=0.717). However, our exploratory analysis after correcting for multiple comparison revealed that change in negative symptoms was strongly correlated with reduction of total prefrontal cortical thickness over time (r=-0.627; p=0.007, Figure 2A). This association remained significant after controlling for both positive symptoms change and total medication intake (r=-0.553; p=0.032). Specifically we found the involvement of medial orbitofrontal (r=-0.721; p=0.01, Figure 2B), caudal (r=-0.659; p=0.01) and rostral anterior cingulate (r=-0.604; p=0.02), and rostral middle frontal cortex (r=-0.695; p=0.01); with the exception of pars triangularis (r=-0.519; p= 0.07) which did not survive multiple comparison correction. When using the standard negative subscale of the PANSS, our results were very similar: correlation between change in negative symptoms and change in total prefrontal cortical thickness was significant (r=-0.644; p=0.005), with the involvement of medial orbitofrontal (r=-0.721; p=0.002), caudal (r=-0.659; p=0.002) and rostral anterior cingulate (r=-0.604; p=0.002), and rostral middle frontal (r=-0.695; p=0.035). These correlations were present even though the difference between negative symptoms at baseline and follow-up was not statistically significant (Table 2).

4. Discussion

In this study, consistent with the extant literature we found that patients in their first-episode of psychotic illness perform significantly worse on several tests assessing different aspects of executive functions compared to healthy controls, including category fluency, attention, working memory and reasoning & problem solving (Holmén et al., 2012; Leeson et al., 2010; Perez-Iglesias et al., 2010; Zabala et al., 2010). Of these executive functioning impairments and consistent with our first hypothesis, we found that poorer performance at baseline in spatial working memory was a significant predictor of loss of total prefrontal cortical thickness in the initial years after illness onset. Furthermore, this relationship between cognitive function and brain change was not found in the control group, consistent with a disorder-related pathological process marked by working memory dysfunction and underpinning cortical thinning over time. Working memory has been considered a central component of executive functioning since they share a large proportion of common variance (McCabe et al., 2010; Zillmer & Spiers, 2001) and the nature of executive functions in controlling and monitoring information is intertwined with the function expressed by working memory, understood as dynamic manipulation of contents (Miyake et al., 2000). Our finding is consistent with that of Gutierrez-Galve et al'(2015), which reported that poor working memory present at the time of the first assessment in first-episode of psychosis patients was associated with frontal cortical thinning after 2 years (Gutiérrez-Galve et al., 2015). In an 18 years longitudinal study on first-episode of schizophrenia patients, working memory was also found to be associated with frontal grey and white matter loss (Andreasen et al., 2011). In a healthy control study, low working memory performers showed significantly less surface area in the inferior, superior frontal gyrus and medial orbitofrontal gyrus compared to high working memory performers (Nissim et al., 2017).

Although post-hoc results did not survive multiple comparisons and require replication, we detected relationships between impaired working memory at baseline and thinning of the rostral middle frontal gyrus and frontal pole over time. The contribution of the dorsolateral prefrontal cortex to optimal functioning of spatial working memory has been extensively reported in both human and non-human primates (Goldman-rakic, 1996). The involvement of mid-dorsolateral frontal cortex has been demonstrated when the working memory task required active monitoring and manipulation of spatial information (Owen et al., 1996). In

patients with schizophrenia, greater dysfunction in the physiological activation of the dorsolateral prefrontal cortex has been linked to poorer working memory performance (Perlstein et al., 2001). Bertolino and colleagues reported that in schizophrenia the functional integrity of neurons within the dorsolateral prefrontal cortex has also predictable physiological impacts throughout the entire working memory cortical network (Bertolino et al., 2000). Our study additionally identified a significant relationship between impaired working memory at baseline and frontal pole thinning. The activation of the lateral frontopolar area during working memory tasks has been also reported in meta-analysis based on healthy controls (Bludau et al., 2014).

We also found impairment of emotional intelligence at baseline in individuals experiencing first-episode of psychosis compared to controls, as demonstrated by other studies focusing on schizophrenia (Dawson et al., 2012; Frajo-apor et al., 2017). Impaired emotional intelligence was significantly associated with a reduction of orbitofrontal thickness over time in patients after their first-episode of psychosis, supporting our second hypothesis. Orbitofrontal cortex is an area crucial for the generation of emotions that guide interpersonal behaviour (Beer et al., 2006) and critical for emotional processes, given its connection to the limbic system (Krueger et al., 2009; Nestor et al., 2013). Nestor and colleagues reported that subregions of orbitofrontal cortex were involved in performance on behavioural measures of various aspects of social cognition (Nestor et al., 2013). In schizophrenia middle prefrontal abnormality has been linked to emotional attribution deficit (Yamada et al., 2007).

The neurobiological mechanism that underlies the progressive loss of prefrontal thickness is still unknown, although some evidence suggests that neuropil pruning could be the cause of this progressive reduction of grey matter in schizophrenia (Selemon and Goldman-rakic, 1999). Reduced N-acetyl aspartate (NAA), which is an amino acid involved in the synthesis pathway of glutamate and used as a marker of neural viability, is reduced in prefrontal regions in schizophrenia (Abbott and Bustillo, 2006) and in the left frontal lobe of patients at risk of developing schizophrenia (Jessen et al., 2006). NAA reduction might be due to reduced neuropil, as indicated by post-mortem studies (Selemon and Goldman-rakic, 1999). Although the pathogenetic mechanisms underlying neuropil reduction requires further clarification, we speculate that cognitive deficits, such as spatial working memory and emotional intelligence impairments at presentation of psychotic illness, could represent biomarkers that signal a

391 neuroprogressive process culminating in loss of cortical thickness as the illness progresses.
392 Spatial working memory impairment has been also presented as an effective endophenotypic
393 marker for schizophrenia (Glahn et al., 2003) and significantly associated with a major
394 candidate gene: Disrupted in Schizophrenia-1 (DISC-1) (Carless et al., 2011). The variation in
395 DISC1 sequence seems to affect both neuroanatomy and cognition; Vázquez-bourgon et al.'s
396 study showed the potential role of this gene in modulating longitudinal cortical thinning in
397 patients suffering from a first-episode of non-affective psychosis, especially prominent in the
398 frontal cortex (Vázquez-bourgon et al., 2016).

399 Whilst on the one hand, our findings show that cognitive deficits at the onset of psychotic
400 illness are associated with progressive prefrontal cortical thickness reduction, our exploratory
401 analysis failed to find any association between change in cognitive performance and change
402 in total prefrontal thickness, as reported elsewhere (Gutiérrez-Galve et al., 2015). The
403 executive functioning and emotional intelligence impairment remain stable in patients,
404 without showing a significant worsening over time compared to controls (Table 2). These
405 findings suggest that cognitive impairment at onset of psychosis represents a trait marker and
406 that the progressive neuroanatomical thinning over time in the prefrontal cortex does not
407 mediate cognitive deterioration.

408 Our study failed to find any significant association between severity of negative symptoms
409 at illness onset and total prefrontal thickness change, thus rejecting our third hypothesis. In
410 contrast, our exploratory analysis revealed that the clinical observation of worsening negative
411 symptoms is indeed associated with total prefrontal thickness reduction over time. When
412 exploring which prefrontal subregions were involved, we found thickness reduction in caudal
413 and rostral anterior cingulate, medial orbitofrontal and rostral middle frontal cortex. A 4-year
414 longitudinal study based on 24 patients with chronic schizophrenia and 25 controls found that
415 greater negative symptoms severity was associated with faster rates of frontal and temporal
416 brain volume changes, indicators of faster deterioration (Mathalon et al., 2001). In a voxel-
417 based morphometry 1.5-year longitudinal study on first-episode schizophrenia, Asami et
418 colleagues reported that less improvement in negative symptoms, assessed with Brief
419 Psychiatric Rating Scale, was correlated with more longitudinal loss, in inferior and superior
420 frontal gyrus (Asami et al., 2012). Negative symptom severity in a large ENIGMA study was
421 found to be significant related to left lateral orbitofrontal cortical thickness (Walton et al.,

2018). Other longitudinal studies failed to find any association over time (Cobia et al., 2012; Gutiérrez-Galve et al., 2015). The observation from the current study that prefrontal neuroanatomical progression more closely aligned with progression of negative symptoms than of cognitive impairment suggests a progressive pathophysiological process plays an important role in the worsening of clinical symptoms.

Strengths and limitations

The main strength of this study is the longitudinal nature of the sample, which can capture the progression after the first-episode of psychosis of anatomical, cognitive and clinical variables and their intrinsic relationships. The careful parcellation of prefrontal cortex using the longitudinal stream of Freesurfer based on an unbiased within-subject anatomical template (Reuter et al., 2012) allowed us to increase the anatomical sensitivity and hence better detect anatomical changes over time.

The main weakness of the study is the relatively small sample size, which might have reduced the power to detect more subtle differences in cognitive, neuroanatomical and clinical variables. Furthermore, due to the available cognitive battery, we could not assess two important facets of executive functions, inhibition and switching. In addition, to reduce multiple analysis we assessed the prefrontal subregions summed bilaterally and did not explore any lateralised effects or other parts of the brain. We employed a measure of negative symptoms which excluded cognitive symptoms however alternative measurements of core negative symptoms incorporating a scale such as SANS (Andreasen, 1989) may have produced different results (Kirkpatrick et al., 2006).

Conclusion

This longitudinal study tracking the interplay between neuroanatomy, cognition and clinical presentation indicates that working memory and emotional intelligence impairment at the onset of psychotic illness are a trait marker of progressive prefrontal thinning, and that worsening of negative symptoms is associated with prefrontal thickness reduction as the illness progresses. These results suggest that there is already a cognitive signature at the onset of psychosis, which is associated with poorer outcome in terms of other neuroanatomical and clinical measures. Further longitudinal studies with larger sample size,

multimodal assessments and repeated sampling will help to confirm and develop these findings.

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Figure Legends

Figure 1

(A) Sub division of prefrontal cortex based on the Desikan-Killiany atlas. Schematic illustration of two regions of interest (the subregions were added bilaterally): above total prefrontal cortex, below orbitofrontal cortex. SFG = superior frontal gyrus; CMF= caudal middle frontal; RMF= rostral middle frontal; LOF= lateral orbitofrontal; POr= pars orbitalis; PTr= pars traingularis; POp= pars opercularis; CAC= caudal anterior cingulate; RAC= rostral anterior cingulate; FP= frontal pole; MOF= medial orbitofrontal. (B) Graphic representation of differences between groups on cognition at baseline. Legend: FEP= first-episode of psychosis patients; HC= healthy controls; WMS= Wechsler Memory Scale; NAB= Neuropsychological Assessment Battery; MSCEIT= Mayer-Salovey-Caruso Emotional Intelligence Test. Note: years of education included in the model as covariate; *=significant group difference. (C) Partial correlation between working memory: spatial span at baseline in patients and percentage of total prefrontal thickness change. (D) Partial correlation between emotional intelligence at baseline in patients and percentage of orbitofrontal thickness change. Note: years of education, age, gender and ICV included as covariates in all the correlations.

Figure 2

(A) Partial correlation between negative symptoms change and percentage of total prefrontal thickness change. (B) Partial correlation between negative symptoms change and percentage of thickness change in medial orbito frontal region, the strongest correlation among all the prefrontal subregions. Note: age, gender and ICV included as covariates in all correlations.

788 Table 1. Demographic characteristics of the participants.

	Patients (*n*=20)	Controls (*n*=18)	Test statistic / *p*-value
Gender N (m/f)	13/7	10/8	X^2 = 0.35 / 0.552
Age at onset (mean years ± SD)	24.9 ± 9.2		
Age Baseline (mean years ± SD)	28.1 ± 8.1	30.3 ± 7.6	*t*= 0.85 / 0.399
Age Follow-Up (mean years ± SD)	32.8 ± 8.0	33.7 ± 7.8	*t*= 0.36 / 0.724
Education (mean years ± SD)	15.7 ± 2.8	18.1 ± 2.9	*t*= 2.60 / **0.014**
Time between Scans (mean years ± SD)	3.6 ± 1.0	3.2 ± 1.2	**U*= 129.50 / 0.141
NART (Predicted IQ) (mean score ± SD)	112.9 ± 8.0	114.9 ± 7.2	*t*= 0.83 / 0.416

Note: *= variable non-normal distribuited; NART= National Adult Reading Test.

Table 2. Clinical features at baseline and follow-up of patient sample (*n*=20)

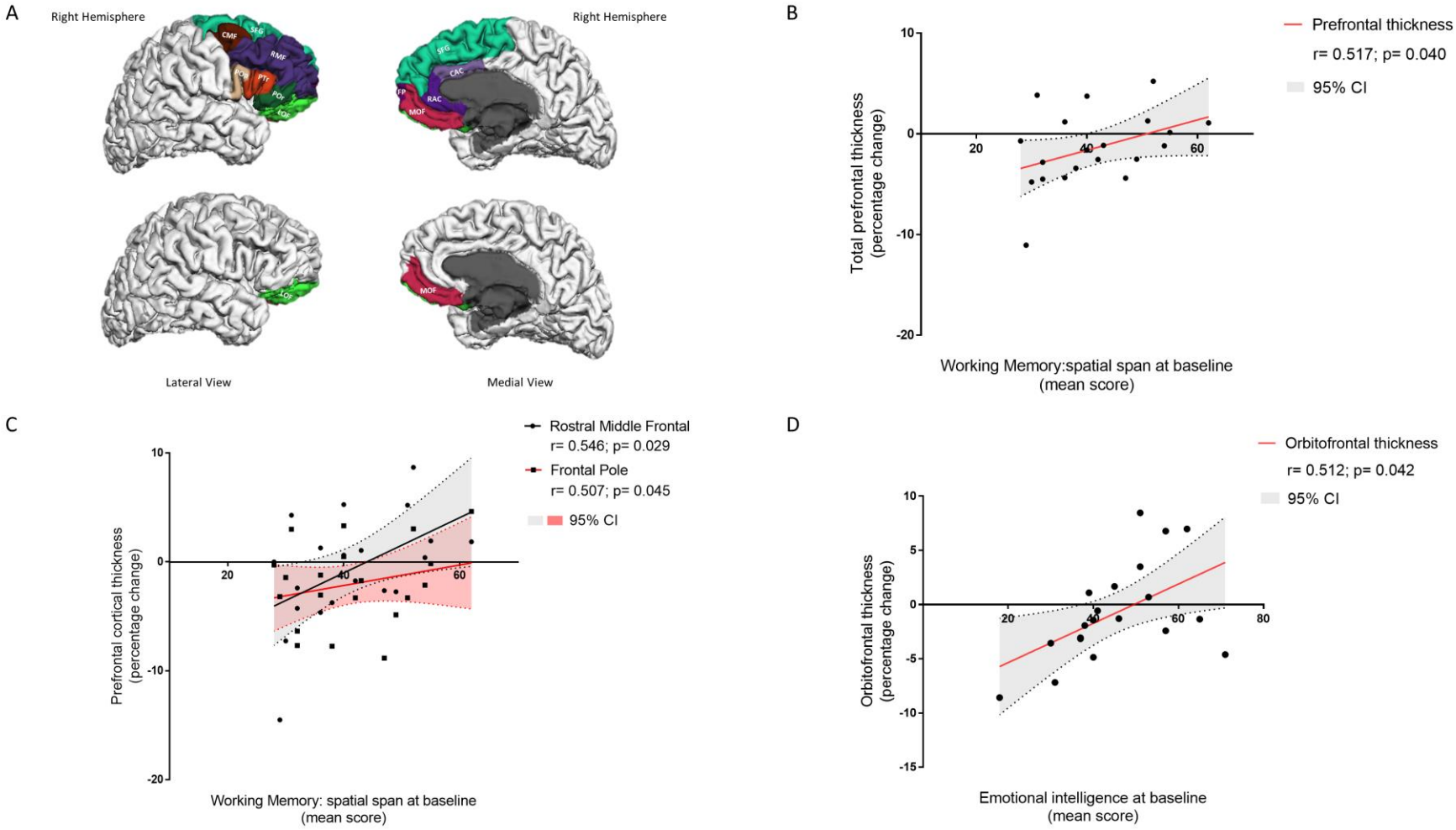
	Baseline	**Follow-up**	**Test statistic / *p*-value**
	Mean ± SD	Mean ± SD	
Duration of untreated psychosis (DUP)(months)	12.9		
Positive and negative Syndrome scale			
PANSS positive score	17.2 ± 4.1	10.4 ± 3.7	*z= -3.41 / **0.001**
PANSS negative score	14.1 ± 4.8	12.0 ± 6.8	*z= -1.57 / 0.115
Negative factor according to Five Factor solution	6.7 ± 4.7	5.75 ± 6.6	*z= -0.78 / 0.438
PANSS general score	31.2 ± 4.3	23.3 ± 6.3	*z= -3.23 / **0.001**
PANSS total score	62.5 ± 8.1	45.6 ± 14.7	*z= -3.46 / **0.001**
Functionality			
Global assessment of functioning	52.0 ± 10.8	72.0 ± 15.5	*z= -3.83/ >**0.001**
Neuropsychological measures			
Category Fluency	48.9 ± 11.7	55.9 ± 9.9	*z=-0.15/0.879
CPT: Identical Pairs	42.0 ± 11.2	50.9 ± 8.3	t= -2.27/ **0.035**
WMS: Spatial Span	41.4 ± 10.0	49.9 ± 9.1	t=-1.12/0.275
Letter Number Span	42.2 ± 8.8	47.5 ± 4.8	t= 1.92/0.071
NAB: Mazes	39.3 ± 7.4	43.1 ± 9.4	t= -2.22/**0.039**
MSCEIT: Managing Emotions	45.5 ± 13.0	55.5 ± 9.7	t= -1.36/0.190
Medication (N)			
Antipsychotics	19	13	
Mood stabilisers	0	2	
Anti-depressants	6	4	
No medication	1	9	
Chlorpromazine equivalent daily dose	204.0 ± 226.3	175.0 ± 276.8	*z= -0.92 / 0.355
Chlorpromazine equivalent total amount of cumulative dose		266642.40 ± 63246.43	

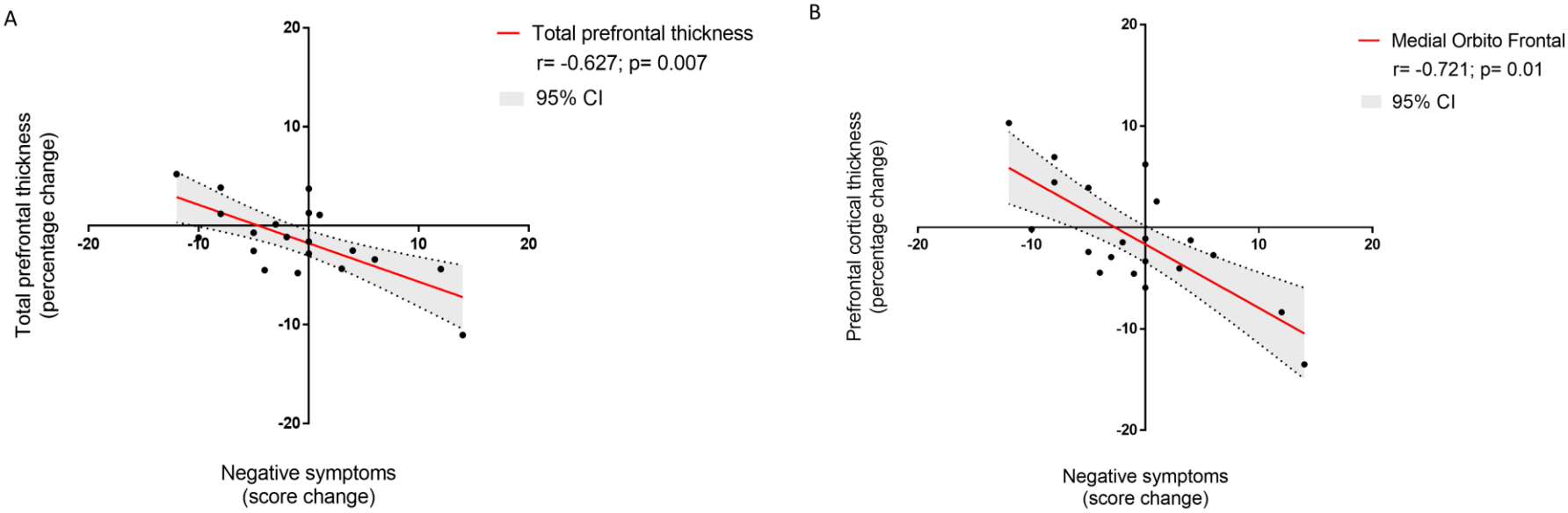
Note: *= variable non-normal distribuited; Medication at baseline= 6 patients were taking antidepressant + antipsychotic medications; 9 patients were taking more than one antipsychotic medication. Medication at follow-up= 4 patients were taking more than one antipsychotic medication; 2 patients were taking antidepressant + antipsychotic medications. Chlorpromazine equivalent= antipsychotic medication was converted to chlorpromazine (CPZ) equivalents (Lehamn and Steinwaschs,1998; Woods, 2003).

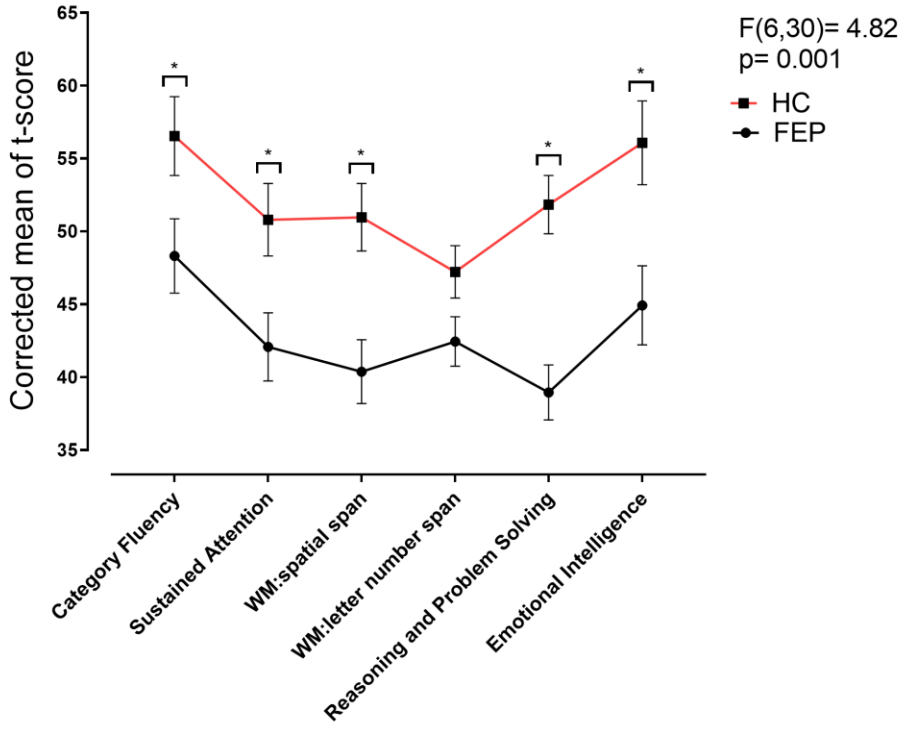
Table 3. Difference between first-episode of psychosis group and healthy control group on cognition

		BASELINE				FOLLOW-UP				GROUP * TIME	
GLM				*F* (6,30)	*p*			*F* (6,30)	*p*	*F* (5,18)	*p*
				4.82	**0.001**			4.47	**0.002**	1.60	0.160
		FEP	**HC**			**FEP**	**HC**				
	TEST SCORES USED	Mean ± SD	Mean ± SD	*F* (1,34)	*p*	Mean ± SD	Mean ± SD	*F* (1,35)	*p*		
Category fluency	Total number of animals named	48.9 ± 11.7	48.9 ± 9.2	4.50	**0.041**	55.9 ± 9.9	59.9 ± 12.5	12.87	**0.001**		
CPT: identical pairs	Mean d' value across 4 conditions	42.0 ± 11.2	46.5 ± 12.1	6.03	**0.019**	50.9 ± 8.3	51.7 ± 4.7	3.40	0.089		
WMS: spatial span	Sum of raw scores	41.4 ± 10.0	44.4 ± 13.2	10.16	**0.003**	49.9 ± 9.1	54.7 ± 9.2	9.98	0.222		
Letter number span	Number of correct trials	42.2 ± 8.8	46.7 ± 12.2	3.45	0.072	47.5 ± 4.8	52.7 ± 6.9	4.53	0.115		
NAB: mazes	Total raw score	39.3 ± 7.4	43.1 ± 9.4	20.21	**<0.001**	51.5 ± 8.7	53.3 ± 10.0	8.83	0.201		
MSCEIT: managing emotions	Branch score using general consensus scoring	45.5 ± 13.0	48.1 ± 10.3	7.32	**0.010**	55.5 ± 9.7	52.8 ± 9.7	1.61	**0.044**		

Note: the table shows the difference between FEP group and HC group on tests assessing executive functioning and emotional intelligence at baseline (F(6,30)=4.82,p=0.001), at follow-up (F(6,30)=4.47;p=0.002) and over time (F(5,18)=1.60;p=0.160). Legend: FEP= first-episode of psychosis patients; HC= healthy controls; GLM= generalized linear model. CPT= Continuous performance Test; WMS= Wechsler Memory Scale; NAB= Neuropsychological Assessment Battery; MSCEIT= Mayer-Salovey-Caruso Emotional Intelligence Test; Test scores used = description of test scores used reported in Nuechterlein et al. (2008); d' value: ability of the participant to discriminate between signal and noise.


A
Right Hemisphere
Right Hemisphere
CMF
SFG
RMF
POr
LOr
PTr
FP
CAC
RAC
MOF
Lateral View
Medial View
B
Prefrontal thickness
r= 0.517; p= 0.040
95% CI
Total prefrontal thickness (percentage change)
Working Memory:spatial span at baseline (mean score)
C
Rostral Middle Frontal
r= 0.546; p= 0.029
Frontal Pole
r= 0.507; p= 0.045
95% CI
Prefrontal cortical thickness (percentage change)
Working Memory: spatial span at baseline (mean score)
D
Orbitofrontal thickness
r= 0.512; p= 0.042
95% CI
Orbitofrontal thickness (percentage change)
Emotional intelligence at baseline (mean score)


A
Total prefrontal thickness
r= -0.627; p= 0.007
95% CI
Total prefrontal thickness
(percentage change)
Negative symptoms
(score change)
20
10
-10
-20
-20
-10
10
20
B
Medial Orbito Frontal
r= -0.721; p= 0.01
95% CI
Prefrontal cortical thickness
(percentage change)
Negative symptoms
(score change)


Corrected mean of t-score
65
60
55
50
45
40
35
F(6,30)= 4.82
p= 0.001
HC
FEP
*
*
*
*
*
Category Fluency
Sustained Attention
WM:spatial span
WM:letter number span
Reasoning and Problem Solving
Emotional Intelligence