

1 Title

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

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6 Authors

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29 *Abstract*

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

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59 *Keywords*

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

## 62 1. Introduction

63 Patients experiencing their first-episode of psychosis display cognitive impairments  
64 compared with healthy controls across different domains, such as verbal learning, executive  
65 functions, general intelligence, social cognition, attention and working memory (Aas et al.,  
66 2014; Kenney et al., 2015). Recent findings have identified executive impairments as one of  
67 the most central deficits in patients with schizophrenia (Chan et al., 2006a, 2006b; Orellana  
68 and Slachevsky, 2013). In neuropsychology, the term executive function is used to indicate  
69 higher-order cognitive processes, which enable people to control and plan their behaviours.  
70 This set of cognitive abilities includes planning, working memory, attention, problem solving,  
71 verbal reasoning, inhibition, mental flexibility and monitoring of actions (Chan et al., 2008).  
72 Neuroimaging, neuropsychological and lesion studies have shown that optimal executive  
73 functioning depends on healthy prefrontal cortex (Gazzaniga, 2004).

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

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

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

96         Although executive dysfunction reflects a cognitive impairment and negative  
97 symptoms are a characteristic of schizophrenic illness, these two indices of dysfunction tend  
98 to overlap and are associated with similar behaviours, such as incongruous emotional  
99 responses, reductions in speech, impaired attention and loss of spontaneity (Orellana and  
100 Slachevsky, 2013). Cross-sectional studies tend to report a significant correlation between  
101 executive impairment and negative symptoms in schizophrenia (Bagney et al., 2013;  
102 Nieuwenstein et al., 2001) and first-episode of psychosis (Faerden et al., 2009). The large  
103 ENIGMA cross-sectional meta-analysis reported a significant association between prefrontal  
104 thinning and negative symptom severity in schizophrenia, specifically in the left medial  
105 orbitofrontal cortex, left lateral orbitofrontal gyrus and left pars opercularis (Walton et al.,  
106 2018). This relationship has also been explored using a longitudinal design, with reports that  
107 less improvement in negative symptoms was significantly correlated with volume loss in  
108 middle and inferior frontal gyrus over time (Asami et al., 2012). These studies emphasise how  
109 both negative symptoms and executive dysfunction can occur with abnormalities in  
110 prefrontal regions.

111         Emotional intelligence, a domain of social cognition, has also been reported to be  
112 impaired in patients experiencing their first-episode of psychosis compared with healthy  
113 volunteers (Healey et al., 2016; Kenney et al., 2015). Emotional intelligence is a subset of  
114 social intelligence described by Salovey and Mayer (1990) as the ability to monitor one's own  
115 and others' feelings and emotions, to discriminate among them and to use this information  
116 to guide one's thinking and actions' (Salovey and Mayer, 1990). The prefrontal cortex plays  
117 an important role in the regulation of emotional processing (Forbes and Grafman, 2010); in  
118 particular the orbitofrontal cortex is implicated in emotional and social cognition (Beer et al.,  
119 2006; Nestor et al., 2013), while emotional intelligence is reduced in those with lesions in the  
120 right orbitofrontal cortex (Barbey et al., 2014).

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

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

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## 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).

181        2.3 Clinical assessment

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

196        2.4 MRI data acquisition

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

203        2.5 MRI processing

204 Volumetric T1-weighted images were intensity inhomogeneity corrected using non-  
205 parametric, non-uniform intensity normalisation (N3) (Sled et al., 1998) as previously  
206 described (Ahmed et al., 2015; Scanlon et al., 2014). The longitudinal stream (Reuter et al.,  
207 2012) of Freesurfer v.5.3.0 (“FreeSurfer,” 2013) was employed to parcellate prefrontal  
208 cortical regions at two time points. This technique has sufficient sensitivity and reliability for  
209 small sample sizes and uses a robust and inverse consistent registration method to create an  
210 unbiased within-subject anatomical template, overcoming the risk of underestimating change  
211 and avoiding over-regularization or temporal smoothness constraints (Reuter et al., 2012,

212 2010). The processing pipeline included skull-stripping (Ségonne et al., 2004), Talairach  
213 transformation, subcortical gray/white matter segmentation according to the Desikan-  
214 Killiany atlas (Desikan et al., 2006; Fischl et al., 2002), intensity normalization (Sled et al.,  
215 1998), tessellation of the gray/white matter boundaries, automated topological correction  
216 (Fischl et al., 2001; Ségonne et al., 2007) and surface deformation following intensity  
217 gradients in the subject template (Dale et al., 1999). At each step, the output was visually  
218 inspected, and if necessary corrected according the protocol (“FreeSurfer Quality Control  
219 Guide,” 2013). The selection of subregions of the prefrontal cortex (Carlen, 2017) included  
220 the following bilaterally: superior frontal gyrus; middle frontal gyrus subdivided into rostral  
221 and caudal division; inferior frontal gyrus subdivided into pars opercularis, triangularis and  
222 orbitalis; orbito frontal subdivided into lateral and medial division and frontal pole. These  
223 regions were all added to create a total prefrontal cortical region of interest (ROI) (Figure 1A).  
224 The orbitofrontal ROI was created by adding the lateral and medial orbitofrontal subregions  
225 (Figure 1A). Lastly, the thickness, defined as the average distance between the gray-white  
226 boundary and the pial surface within each ROI, was extracted at baseline and follow-up for all  
227 the regions of interest for all the patients.

## 228 2.6 Statistical analysis

### 229 2.6.1 Clinical and demographics

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

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242 2.6.2 Cognitive impairment at baseline & prefrontal cortical thickness change over time

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

252 2.6.3 Negative symptoms severity at baseline & prefrontal cortical thickness change over time

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

257 2.6.4 Cognitive and clinical change & prefrontal cortical thickness change

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

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### 269 3. Results

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

#### 278 3.1 Groups Differences at Baseline in Cognition

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

#### 285 3.2 Executive Impairment & Prefrontal Cortical Thickness

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

299 was significantly different ( $z=2.28$ ;  $p=0.02$ ) in patients compared to controls. Exploratory  
300 analyses investigating the relationship between change in cognitive performance and change  
301 in total prefrontal thickness did not reveal any significant associations ( $r=-0.273-0.327$ ;  $p=$   
302  $0.216-0.959$ ).

### 303 3.3 Emotional Intelligence Impairment & Orbitofrontal Thickness

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

### 310 3.4 Negative Symptoms & Prefrontal Cortical Thickness

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

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#### 329 4. Discussion

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

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

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

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

380 The neurobiological mechanism that underlies the progressive loss of prefrontal thickness  
381 is still unknown, although some evidence suggests that neuropil pruning could be the cause  
382 of this progressive reduction of grey matter in schizophrenia (Selemon and Goldman-rakic,  
383 1999). Reduced N-acetyl aspartate (NAA), which is an amino acid involved in the synthesis  
384 pathway of glutamate and used as a marker of neural viability, is reduced in prefrontal regions  
385 in schizophrenia (Abbott and Bustillo, 2006) and in the left frontal lobe of patients at risk of  
386 developing schizophrenia (Jessen et al., 2006). NAA reduction might be due to reduced  
387 neuropil, as indicated by post-mortem studies (Selemon and Goldman-rakic, 1999). Although  
388 the pathogenetic mechanisms underlying neuropil reduction requires further clarification, we  
389 speculate that cognitive deficits, such as spatial working memory and emotional intelligence  
390 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.,

422 2018). Other longitudinal studies failed to find any association over time (Cobia et al., 2012;  
423 Gutiérrez-Galve et al., 2015). The observation from the current study that prefrontal  
424 neuroanatomical progression more closely aligned with progression of negative symptoms  
425 than of cognitive impairment suggests a progressive pathophysiological process plays an  
426 important role in the worsening of clinical symptoms.

#### 427 *Strengths and limitations*

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

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

#### 443 *Conclusion*

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

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

453

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760 **Figure Legends**

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762 **Figure 1**

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

777 **Figure 2**

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

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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	$\chi^2 = 0.35 / 0.552$
Age at onset (mean years $\pm$ SD)	24.9 $\pm$ 9.2		791
Age Baseline (mean years $\pm$ SD)	28.1 $\pm$ 8.1	30.3 $\pm$ 7.6	$t = 0.85 / 0.399$
Age Follow-Up (mean years $\pm$ SD)	32.8 $\pm$ 8.0	33.7 $\pm$ 7.8	$t = 0.36 / 0.724$
Education (mean years $\pm$ SD)	15.7 $\pm$ 2.8	18.1 $\pm$ 2.9	$t = 2.60 / \mathbf{0.014}$
Time between Scans (mean years $\pm$ SD)	3.6 $\pm$ 1.0	3.2 $\pm$ 1.2	* $U = 129.50 / 0.141$
NART (Predicted IQ) (mean score $\pm$ SD)	112.9 $\pm$ 8.0	114.9 $\pm$ 7.2	$t = 0.83 / 0.416$

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

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

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	<b>Baseline</b>	<b>Follow-up</b>	<b>Test statistic / p-value</b>
	Mean ± SD	Mean ± SD	
Duration of untreated psychosis (DUP)(months)	12.9		
<b>Positive and negative Syndrome scale</b>			
PANSS positive score	17.2 ± 4.1	10.4 ± 3.7	*z= -3.41 / <b>0.001</b>
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 / <b>0.001</b>
PANSS total score	62.5 ± 8.1	45.6 ± 14.7	*z= -3.46 / <b>0.001</b>
<b>Functionality</b>			
Global assessment of functioning	52.0 ± 10.8	72.0 ± 15.5	*z= -3.83/ > <b>0.001</b>
<b>Neuropsychological measures</b>			
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/ <b>0.035</b>
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/ <b>0.039</b>
MSCEIT: Managing Emotions	45.5 ± 13.0	55.5 ± 9.7	t= -1.36/0.190
<b>Medication (N)</b>			
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 distributed; 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				<i>F</i> (6,30)	<i>p</i>			<i>F</i> (6,30)	<i>p</i>	<i>F</i> (5,18)	<i>p</i>
				4.82	<b>0.001</b>			4.47	<b>0.002</b>	1.60	0.160
		FEP	HC			FEP	HC				
TEST SCORES USED		Mean ± SD	Mean ± SD	<i>F</i> (1,34)	<i>p</i>	Mean ± SD	Mean ± SD	<i>F</i> (1,35)	<i>p</i>		
<b>Category fluency</b>	Total number of animals named	48.9 ± 11.7	48.9 ± 9.2	4.50	<b>0.041</b>	55.9 ± 9.9	59.9 ± 12.5	12.87	<b>0.001</b>		
<b>CPT: identical pairs</b>	Mean <i>d'</i> value across 4 conditions	42.0 ± 11.2	46.5 ± 12.1	6.03	<b>0.019</b>	50.9 ± 8.3	51.7 ± 4.7	3.40	0.089		
<b>WMS: spatial span</b>	Sum of raw scores	41.4 ± 10.0	44.4 ± 13.2	10.16	<b>0.003</b>	49.9 ± 9.1	54.7 ± 9.2	9.98	0.222		
<b>Letter number span</b>	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		
<b>NAB: mazes</b>	Total raw score	39.3 ± 7.4	43.1 ± 9.4	20.21	<b>&lt;0.001</b>	51.5 ± 8.7	53.3 ± 10.0	8.83	0.201		
<b>MSCEIT: managing emotions</b>	Branch score using general consensus scoring	45.5 ± 13.0	48.1 ± 10.3	7.32	<b>0.010</b>	55.5 ± 9.7	52.8 ± 9.7	1.61	<b>0.044</b>		

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.





