Intersection of Verbal Memory and Expressivity on Cortical Contrast and Thickness in First Episode Psychosis

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Abstract

Background: Longitudinal studies of first episode of psychosis (FEP) patients are critical to understand the dynamicity of clinical factors influencing functional outcomes; negative symptoms and verbal memory (VM) deficits are two such factors that remain a therapeutic challenge. This study uses white-gray matter contrast at the inner edge of the cortex, in addition to cortical thickness, to probe changes in microstructure and their relation with negative symptoms and possible intersections with verbal memory.

Methods: T1-weighted images and clinical data were collected longitudinally for patients (N=88) over a two-year period. Cognitive data were also collected at baseline. Relationships between baseline VM (immediate/delayed recall) and rate of change in two negative symptom dimensions, Amotivation and Expressivity, were assessed at the behavioural level, as well as at the level of brain structure.

Results: VM, particularly immediate recall, was significantly and positively associated with a steeper rate of Expressivity symptom decline (r=0.32, q=0.012). Significant interaction effects between baseline delayed recall and change in expressivity were uncovered in somatomotor regions bilaterally for both white-gray matter contrast and cortical thickness. Furthermore, interaction effects between immediate recall and change in expressivity on cortical thickness rates were uncovered across higher-order regions of the language processing network.

Conclusions: This study shows common neural correlates of language-related brain areas underlying Expressivity and VM in FEP, suggesting deficits in these domains may be more linked to speech production rather than general cognitive capacity. Together, white-gray matter contrast and cortical thickness may optimally inform clinical investigations aiming to capture peri-cortical microstructural changes.

Background

Negative symptoms (e.g. amotivation, flattened affect) and cognitive impairments in individuals with psychotic disorders are strong predictors of poor functional outcome (Albert *et al.* 2011; Lepage *et al.* 2014), and are less responsive to currently available medications compared to positive symptoms (e.g. hallucinations, delusions). Verbal memory (VM) is one of the most strongly impacted of all cognitive domains in individuals with psychotic disorders (Jordan *et al.* 2014; Benoit *et al.* 2015; Guimond *et al.* 2016), and is linked to persistent negative symptoms (Hovington *et al.* 2013). There is some evidence suggesting that VM and negative symptoms, particularly deficits in communication or expressivity, may share common neural substrates. Cohen & Elvevåg (2014) have suggested that expressivity is linked to classic language areas in psychiatric disorders, although such a relationship has not been demonstrated in early stages of psychosis with non-invasive imaging techniques.

Many studies treat VM and negative symptoms as unitary constructs, although these variables are comprised of stable subdomains that are likely to be of clinical relevance; for instance, VM can be broken down into verbal learning vs. retention, and negative symptoms into amotivation and expressivity, all of which have unique environmental and biological correlates (Malla *et al.* 2002; Leeson *et al.* 2009; Millan *et al.* 2014). For instance, different facets of VM have been differentially associated to white matter microstructure (typically assessed using metrics such as fractional anisotropy from diffusion-weighted imaging) in healthy older adults, where white matter tracts subserving left fronto-parietal regions are related to verbal working memory, whereas bilateral fronto-temporal white matter is linked to long-term episodic memory function (Charlton *et al.* 2013). Both grey and white matter abnormalities have been observed in relation to amotivation symptoms (e.g. avolition, apathy) in enduring schizophrenia patients,

particularly decreased cortical thickness and fractional anisotropy underlying left orbital/medial

frontal cortex and cingulate cortex (Ohtani *et al.* 2014; Mørch-Johnsen *et al.* 2015, 2018). A

recent study has also shown that the integrity of white matter underlying the right hemisphere

homologs of these regions is related to affective flattening (Ohtani *et al.* 2015); however, beyond

this study, very few have further investigated the structural brain correlates of expressivity

deficits (Mørch-Johnsen *et al.* 2018), especially in first episode of psychosis (FEP) patients.

Importantly, and of relevance to the current study, longitudinal brain imaging studies of

negative symptoms in FEP are scarce, although altered maturational trajectories of cortical

thickness and limbic structure has been previously observed in patients with persistent negative

symptoms (Makowski *et al.* 2016, 2017). Such longitudinal neuroimaging studies are critical to

characterize the emergence of clinical, cognitive, and neuroanatomical markers that may be

amenable to intervention early in the course of the disorder. Existing literature examining

progressive brain changes after a FEP, irrespective of symptom profiles, have reported

widespread accelerated gray matter loss (Andreasen *et al.* 2011; Gong *et al.* 2016). Various

structural and functional MRI reviews of FEP patients have pinpointed progressive brain changes

occurring across frontal and temporal lobes, particularly within the left hemisphere (Radua *et al.*

2012; Vita *et al.* 2012; Dazzan *et al.* 2015). Further, evidence suggests that the stability of medial

temporal and prefrontal cortices may be essential predictors of symptomatic and functional

outcomes after a first episode of schizophrenia (Dazzan *et al.* 2015).

White matter abnormalities have also been a key focus of studies of schizophrenia and

related disorders, across different disease stages (Kubicki *et al.* 2005; Whitford *et al.* 2007, 2012;

Carletti *et al.* 2012; Lee *et al.* 2013; Birur *et al.* 2017; Klauser *et al.* 2017; Kelly *et al.* 2018).

Evidence from post-mortem studies and diffusion tensor imaging suggests that white matter

abnormalities, particularly within prefrontal regions, are more significantly correlated with negative symptoms compared with positive symptoms (Uranova *et al.* 2011; Asami *et al.* 2014). Other neuroimaging studies have obtained proxy measures of myelin to better understand the nature of white matter alterations in psychosis (Andreasen *et al.* 1991; Lang *et al.* 2014; Ganzetti *et al.* 2015; Iwatani *et al.* 2015). There is certainly a need to shift focus to earlier stages of psychosis, obtaining measures more proximal to a FEP, to better understand the cascade of brain structural alterations that follow.

Although measures of cortical thickness (CT) are often the choice of methodology for investigation of cortical structure in psychiatric disorders from T1-weighted MRI scans, inconsistencies have arisen in a number of studies of longitudinal cortical thickness trajectories in early psychosis, with a handful of studies contesting the evidence of progressive brain change after a FEP (Nesvåg *et al.* 2012; Roiz-Santiáñez *et al.* 2015; Haukvik *et al.* 2016), emphasizing the need for novel approaches to analyze structural data in clinical cohorts. Obtaining a measure of white-gray matter contrast (WGC) from T1-weighted MRI may provide a meaningful marker of myelin content and other biophysical properties that may complement measures of cortical thickness (Salat *et al.* 2009; Westlye *et al.* 2009; Andrews *et al.* 2017; Lewis *et al.* 2018). We have recently shown that WGC captures brain architectural features and putative network-level abnormalities in FEP patients more robustly than measures of cortical thickness (Makowski *et al.* 2019). Thus, using multiple measures to assess the integrity of the cortical mantle, including a proxy measure of peri-cortical myelin, could provide a better understanding of the neurobiological correlates underlying subdomains of negative symptoms and VM, particularly in FEP patients. This is turn could be paramount in developing more effective treatments in early psychosis, and other disorders that are characterized by similar deficits.

The aims of the current study were to i) examine the relationship between two negative symptom dimensions (Expressivity and Amotivation) and deficits in two VM processes (immediate and delayed recall), ii) relate Expressivity and Amotivation negative symptom dimensions to changes in CT and WGC across time, and iii) see how relationships in ii) interact with VM capacity. We expect Expressivity and Amotivation to be uniquely correlated with progressive changes in white-gray contrast, and to be moderated by VM abilities. Specifically, we postulate that immediate recall, a measure of verbal learning, will be more strongly correlated with Expressivity both at the levels of brain and behaviour, given that both constructs have been described as "core" traits in psychosis and less influenced by external factors (Leeson *et al.* 2009; Lutgens *et al.* 2014). On the other hand, we expect delayed recall, a measure of verbal *retention*, to be more related to Amotivation, due to these factors' higher potential to be influenced by environment.

Methods

Sample.

Patients were recruited from the Prevention and Early Intervention Program (PEPP) at the Douglas Institute in Montreal, Canada, and were part of a longitudinal naturalistic outcome study. Details are outlined elsewhere (Iyer et al. 2015). Inclusion criteria at PEPP include a diagnosis of affective (e.g. bipolar disorder, depression with psychotic features) or non-affective psychosis (e.g. schizophrenia, schizoaffective), an IQ above 70, and limited (<1month) to no previous exposure to antipsychotic medication. Patients recruited to PEPP (ages 18-35) were invited to take part in a neuroimaging study, comprising three timepoints (baseline, one/two-year follow-ups) as described in previous work (Makowski et al. 2016, 2017). Patients were recruited

from February 2003 to February 2014. The first baseline scan took place in May 2004. It should

be noted that many of the initial patients recruited for the study did not meet criteria for this

neuroimaging investigation, as more than 6 months passed between entry to the PEPP clinic and

their baseline scan. The last two-year follow-up scan and clinical assessment for the last patient

took place in April 2016.

Non-clinical healthy controls were recruited through advertisements within the same

local catchment area. All participants provided written informed consent, and the research

protocol was approved by the Douglas Institute human ethics review board. From 150 FEP

patients recruited for the study, 88 patients (Male, N=62) were included in analysis. Data from

80 healthy controls were included for calculation of standardized VM scores, as described below.

See Supplementary material for more detailed information on the final included sample and

demographic/clinical data collection. Also see **Supplementary Table 1** for a comparison of

patients included in the study, compared to those who were excluded.

We opted to include both affective and non-affective psychoses in our sample of FEP

patients, as our group has previously shown that clinical diagnoses play a negligible role in

findings related to MRI-derived metrics, including cortical thickness (Makowski *et al.* 2016,

2017). Further, our aims are to investigate individual clinical/cognitive profiles, rather than work

within a diagnostic framework, which is being recognized as a clear setback in the field of

psychiatry (Insel *et al.* 2010; Owen 2018; Wolfers *et al.* 2018). However, we also explored

differences in key variables of interest, namely immediate/delayed recall, and amotivation and

expressivity deficits, between patients on the schizophrenia spectrum and patients with an

affective disorder. No significant differences emerged between groups as can be seen in

Supplementary Table 2.

Negative Symptom Dimensions and Change Over Time.

Negative symptoms were assessed using the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen 1984), which has been shown to have good inter-rater reliability (κ=0.71) at PEPP-Montreal (Jordan *et al.* 2018). Item-level scores from the SANS were used to define two principal dimensions of negative symptoms: Amotivation and (lack of) Expressivity. These dimensions were based on a consistent body of literature reporting a two-factor model of negative symptoms (Malla *et al.* 2002; Blanchard & Cohen 2006; Kirkpatrick *et al.* 2006; Messinger *et al.* 2011; Jang *et al.* 2016; Marder & Galderisi 2017). Items were assigned to either the Amotivation or Expressivity dimension based on a recent confirmatory factor analysis published by our group (Lutgens *et al.* 2019). Although other models have been proposed to categorize negative symptoms, for instance a recent investigation uncovering a 5-factor latent structure of negative symptoms in schizophrenia (Strauss *et al.* 2018), it is important not to dismiss a large breadth of literature that has linked motivation and expressivity dimensions of negative symptoms to functional outcomes in patients. Finally, a two-factor solution minimizes the burden of multiple comparisons and potential false positives for the purposes of our neuroimaging analysis.

Thus, based on Lutgens et al (2019), Amotivation in this study represented summed items from "Avolition-Apathy" and "Anhedonia-Asociality" domains, while the Expressivity dimension represented summed items from "Affective Flattening/Blunting" and "Alogia" domains, excluding Item 6: "Inappropriate Affect" and Item 10: "Poverty of Content of Thought", given that these items do not effectively map onto the clinical construct of Expressivity (Lutgens *et al.* 2019). To assess the mean rate of change in symptoms over time, a linear model was fit to each

subject's longitudinal amotivation and expressivity symptom data against the participants' age

over all available timepoints for that participant. A slope was calculated and extracted for each

subject to represent a single metric of change over time in symptoms.

Verbal Memory Performance.

VM data were collected from a larger neuropsychological battery database for patients

followed at PEPP. Due to a change in neuropsychological testing protocol, VM data were

compiled from two different protocols: 1) a pen and paper format administered to patients who

took part in the study from 2003 to 2010, using Logical Memory subtests of the Wechsler

Memory Scale–Third Edition (WMS-III) (Wechsler 1997); and 2) the CogState Research

Battery (Pietrzak *et al.* 2009), administered from September 2010 onwards, using the

International Shopping List task. Further details of both testing protocols and tasks have been

described before (Benoit *et al.* 2015). Z-scores were calculated for each neuropsychological

test battery separately, using the mean and standard deviation of controls for

immediate/delayed recall measures. Previous work from our group (Benoit *et al.* 2015) has

shown that participants tested with the CogState Research Battery tended to perform better.

Thus, in addition to using standardized scores, test version was used as a covariate in analyses

using VM data. Supplementary Table 3 demonstrates there are no significant version or

group*version effects on verbal memory performance.

MRI acquisition.

Scans were collected at the Montreal Neurological Institute, all on the same 1.5-Tesla Siemens

Sonata MRI scanner. Structural T1-weighted volumes were acquired for each participant using a

3D gradient echo pulse sequence with sagittal volume excitation (resolution=1mm^3, repetition time=22ms, echo time=9.2ms, flip angle=30°, 180 1mm contiguous sagittal slices). The rectangular field of view (FOV) for the images was 256mm (AP) 204mm (SI).

MRI Post-Processing.

Cortical Thickness. Raw T1-weighted images were submitted to the CIVET pipeline (Version 2.1.0: http://www.bic.mni.mcgill.ca/ServicesSoftware/CIVET) (June *et al.* 2005) for extraction of gray and white matter surfaces. Main processing steps include: 1) Registration of T1-weighted images to standardized space (Collins *et al.* 1994) and correction for non-uniformity artefacts (Sled *et al.* 1998); 2) segmentation of gray, subcortical gray and white matter, and cerebral spinal fluid (Zijdenbos *et al.* 2002; Tohka *et al.* 2004); 3) extraction of the white matter surface using a marching-cubes algorithm and extraction of the gray matter surface using the CLASP algorithm (Kim *et al.* 2005); 4) surface registration to a template for inter-subject correspondence (Lyttelton *et al.* 2007); 5) reverse transformation (initially done in step 1) to estimate CT in native space for each subject at 81,924 vertices using the t-laplace metric (Lerch & Evans 2005); and 6) smoothing the data in native space with a 20mm FWHM Gaussian kernel to diminish the impact of noise (Boucher *et al.* 2009). CT was estimated using the Laplacian distance between the two surfaces (Jones *et al.* 2000) across 81,924 vertices.

White-Gray Matter Contrast. Measures of WGC were generated as follows, similarly to what is described in Makowski et al (2019): 1) additional surfaces were created 1mm on either side of the surface at the gray-white matter boundary (i.e. +1mm corresponds to supra-white surface, and -1mm corresponds to sub-white surface); 2) surface maps of the intensity of the T1-weighted

MRI were generated and smoothed; and 3) a ratio was calculated, by dividing the intensity of the

-1mm point by the corresponding +1mm point, as defined by Lewis et al (2018). WGC values

ranged from approximately 1.15 to 1.35 where lower values, closer to 1, reflect lower contrast

(i.e. reduced gray-white matter distinction) whereas higher values reflect higher contrast (i.e.

clearer distinction between gray and white matter). The WGC method is depicted in **Figure 1.**

More details of imaging methods and quality control procedures are outlined in Supplementary

Material.

Statistical Analyses of Behavioural/Clinical Data.

Demographic and clinical variables were analysed with one-way ANOVAs for continuous

variables or Kruskall-Wallis H tests for nominal variables. An ANCOVA was used to analyse

differences in VM performance at baseline between patients and controls, covarying for test

version and years of education. Additional tests to compare the effect of version on results with

VM data, as well as exploratory analyses between change in negative symptoms and change in

verbal memory scores for a subset of patients with longitudinal data available (N=49), are in

Supplementary material. Associations between rates of change in Amotivation/Expressivity

negative symptom domains and immediate/delayed recall in FEP patients were evaluated with

Pearson r-correlations, adjusting verbal memory values for age, sex, and test version, and taking

into account multiple comparisons with a false discovery rate (FDR) correction (Benjamini &

Hochberg 1995). Analyses of behavioural and clinical variables were conducted using PASW

Statistics 21 (SPSS inc., 2009, Chicago, IL, USA) and were two-tailed with a critical *p*-value of

0.05. Normality of continuous data was assessed with the Shapiro-Wilk test of normality. Non-

parametric tests were used to compare demographic variables between patients and controls that

were found not to be normally distributed. Demographic and clinical information was also compared between patients included in this manuscript (N=88) and patients excluded from the study (N=47) despite meeting criteria for a FEP, due to the cross-sectional nature of their data and/or failed imaging data after QC.

Surface-Based Brain Analyses.

Vertex-wise analysis of WGC and CT were conducted using SurfStat in Matlab (http://www.math.mcgill.ca/keith/surfstat/). As with the negative symptom data and as described in Raznahan et al (2011), a linear model was fit to each vertex for the WGC and CT data, yielding a single metric for each subject describing the rate of change in years in WGC and CT. To determine which covariates should be used for analyses, the Akaike Information Criterion (Akaike 1998) was used to determine the best model. AIC values were compared to a 'baseline' model that included centered age and sex as covariates, given the well-documented impact of age and sex on neuroanatomy, as well as their influence on the onset and progression of psychosis (Tamnes *et al.* 2010; Ochoa *et al.* 2012; Makowski *et al.* 2016, 2017) . Details are included in the Supplementary material, including an analysis testing the effect of antipsychotic medication on WGC and CT (Supplementary Figure 1) and justification on the exclusion of medication as a covariate.

The following model was used to assess the main effect of change in negative symptoms (η, representing either amotivation or expressivity deficits) on change in Y (representing either WGC or CT), covarying for centered age, sex, and mean σ (reflecting mean WGC or mean CT across the entire cortical surface for each participant):

$$\Delta Y = intercept + \beta_1(\Delta\eta) + \beta_2(CenteredAge) + \beta_3(Sex) + \beta_4(Mean(\sigma)) + \varepsilon$$

Here, β_1 is the slope for the main effect of interest, namely, rate of change (Δ) in negative symptoms per year. Note, β_2 and β_4 reflect measures at baseline. Positive values of the rate of Y change reflect an increase in either WGC and CT per year, whereas positive values in negative symptom reflect an increase (i.e. worsening) in symptoms per year.

The interaction between baseline VM abilities (ν, reflecting Immediate Recall or Delayed Recall) and change in negative symptoms over time (η) on rate of change in WGC and CT (ΔY) was tested with the following model:

$\Delta Y = \text{intercept} + \beta_1(\Delta\eta) + \beta_2(\nu) + \beta_3(\text{TestVersion}) + \beta_4(\text{Centered Age}) + \beta_5(\text{Sex}) + \beta_6(\text{Mean}(\sigma)) + \beta_7(\Delta\eta^*\nu) + \varepsilon$

where $\beta_7(\Delta\eta^*\nu)$ represented the slope for the main predictor of interest; that is, the interaction between change in negative symptoms and baseline verbal memory. Here, β_2, β_3, β_4 and β_6 were measures taken at baseline. For visualization purposes only, patients were divided using a median split into two groups, on the basis of their verbal memory performance: "mild to moderate VM deficits" and "high VM deficits". Specific details of these groups are outlined in the Results section.

Random field theory (RFT) (Worsley *et al.* 2004) was used for multiple comparison correction using a stringent p-cluster threshold of p=0.001. Significant results are also presented with a more liberal cluster threshold of p=0.01 (p-corrected<0.05), to show the extent of sub-threshold results. For all significant clusters found with the more stringent cluster threshold (p=0.001), the WGC and CT, or rate of change in WGC and CT, at the peak t-statistic was extracted and adjusted for centered age, sex, and Mean(σ), and used to generate scatterplots to visualize results.

Results

The final sample comprised 88 FEP patients, of which 59 patients completed all three scans, and the remainder had two scans. See **Table 1** for descriptive statistics and clinical information. Importantly, FEP patients had a median duration of untreated psychosis of approximately 20 weeks, highlighting the efforts that have been put forth by the PEPP-clinic to minimize patients' pathways to care within our early intervention service (Iyer *et al.* 2015; MacDonald *et al.* 2018). This also emphasizes that our FEP patients are indeed highly representative of the first-episode time period. Included patients were also compared to 47 patients that were excluded from the current study on variables collected at baseline, and these results can be found in Supplementary Table 1. In summary, included patients did not differ largely from the excluded patients, except included patients had longer duration of untreated psychosis and untreated illness compared to excluded patients.

Summary statistics for rate of change in negative symptoms domains for 88 FEP patients with longitudinal data were as follows: Mean ΔAmotivation=-1.80 (SD=4.22 Range=-11.72 – 13.61), Mean ΔExpressivity=-1.22 (SD=5.19 Range=-19.63 – 14.66). For amotivation symptoms, 5 patients had the same level (or absence) of symptoms over time (Mean Δ=−0.0038, SD=0.0086), 25 patients had worsening symptoms (Mean Δ= 3.12, SD=2.91), and 58 patients improved (Mean Δ= −4.08, SD=2.72). For expressivity symptoms, 16 patients had the same level (or absence) of symptoms over time (Mean Δ=0, SD=0), 22 patients had worsening symptoms (Mean Δ= 4.64, SD=4.02), and 50 patients improved (Mean Δ= −4.18, SD=4.01). See Supplementary Figure 2 for spread of longitudinal Amotivation and Expressivity negative symptom data.

Relationship between Verbal Memory and ΔNegative Symptoms.

Cross-sectional relationships between VM and negative symptoms at baseline are reported in Supplementary material, where significant negative associations between baseline expressivity and immediate recall (r=-0.35, q<0.001) and delayed recall (r=-0.28, q=0.036) were found; no relationships were found with amotivation. The relationship between VM (i.e. z-scores of immediate and delayed recall) at baseline and ΔNegative Symptoms was assessed in 87 patients (degrees of freedom=82), for which baseline VM and longitudinal negative symptom data were available, using Pearson r correlations, adjusting verbal memory data for age, sex, and test battery. The only significant finding that survived FDR correction for multiple comparisons was a positive relationship between immediate recall at baseline and ΔExpressivity (r=0.32, q=0.012). In other words, better VM (i.e. less severe deficits) at baseline was associated with *worsening* Expressivity deficits over time. A trend-like association in the same direction was also found between delayed recall and ΔExpressivity (r=0.19, p-uncorrected=0.083). No significant associations were found with either immediate or delayed recall and ΔAmotivation (Immediate: r=0.079, q=0.476; Delayed: r=0.077, q=0.486). Finally, we assessed the relationship between change in VM and change in negative symptoms over the first year after a FEP for a subset of patients (N=49) for which data were available. No significant relationships were found, as reported in Supplementary Material.

Associations between ΔNegative Symptoms and ΔWGC and ΔCT.

Worsening of Amotivation symptoms was associated with greater increases in WGC over time within the left superior parietal lobule and right dorsal primary motor cortex and paracentral lobule. Overlapping findings were found with respect to ΔExpressivity, with additional peaks in

the left dorsal precentral gyrus and right cuneus. With respect to CT, ΔExpressivity was

negatively associated with ΔCT (i.e. cortical thinning with worsening symptoms) within left

frontal regions. ΔAmotivation was not found to be significantly associated with changes in CT.

Results are shown in **Figure 2**, along with the brain regions that survived correction for multiple

comparisons with a relaxed p-cluster threshold of p=0.01**.** Plots were generated for regions that

survived correction for multiple comparison with a stringent threshold of p<0.001.

Interaction between Verbal Memory and ΔExpressivity on ΔWGC and ΔCT.

Given that no significant associations were found between verbal memory and ΔAmotivation at

the behavioural level, we did not explore this contrast. No significant regions survived the

stringent threshold for WGC, however results with a relaxed threshold are in **Figure 3.** For CT,

both immediate and delayed recall interacted significantly and uniquely with changes in

Expressivity. The interaction between immediate recall and ΔExpressivity was significantly

associated with changes in thickness along the left hemisphere ventrally, including the left orbital

and medial frontal, insular, temporal pole, and middle temporal regions. The interaction term

between delayed recall and ΔExpressivity showed significant effects on the right cuneus/primary

visual cortex. Results are shown in **Figure 3**, along with brain regions that survived correction

for multiple comparisons with a relaxed p-cluster threshold of p=0.01**.** Plots were generated for

regions that survived correction for multiple comparison with a stringent threshold of p<0.001.

Even though no results survived correction for multiple comparisons with WGC with our

stringent threshold, we also generated two additional plots with WGC data for right retrosplenial

cortex and left central sulcus, to compare the nature of the associations against CT data.

To better visualize the direction of results, patients were divided into two groups based

on their verbal memory performance using a median split, as described in the methods.

Specifically, the groups were broken down as follows: "mild to moderate VM deficits" (N=43;

for immediate recall patients had a z-score higher than -1.15; for delayed recall, patients had a z-

score higher than -0.91) and "high VM deficit" (N=44; for immediate recall, patients had a z-

score lower than or equal to -1.15; for delayed recall, patients had a z-score lower than or equal

to -0.91). Note, one patient had missing verbal memory data at baseline, thus 87 patients were

included in this analysis. Visualization of these groups generally revealed that patients with mild

to moderate VM deficits (i.e. more preserved VM ability) at baseline drove the *positive*

association between changes in expressivity symptoms and changes in WGC. For CT, patients

with mild to moderate VM deficits at baseline predominantly drove the *negative* association

between changes in expressivity and changes in thickness (**Figure 3**).

Results were also generated *excluding* mean(σ) as a covariate; results were largely

similar (Supplementary Figure 3). To ensure results in the final analysis were specific to verbal

memory, a general cognitive index was calculated across five domains (i.e. attention, executive

function, speed of processing, working memory, visual memory) and controlled for in analyses,

yielding similar results (Supplementary Figure 4). Additional methods pertaining to cognitive

data can be found in captions of Supplementary Figure 4/Supplementary Table 3.

DISCUSSION/CONCLUSIONS

These results provide insight into the relationship between surface-based brain metrics

and two behavioural domains that contribute strongly to outcome in FEP patients, namely

negative symptoms and VM. Two novel findings emerged: 1) rate of change in expressivity and

amotivation negative symptoms over the two-year period following a FEP are associated with

both overlapping and distinct changes in WGC, and are also associated with changes in left

prefrontal regions in relation to CT; and 2) links between baseline VM and change in

expressivity deficits are found both at the behavioural and neuroanatomical level, where

significant interactions on rate of change over time in neuroanatomy were uncovered, most

pronounced with CT.

We also extend a key finding of cortical thinning of the prefrontal cortex in relation to

negative symptoms in psychosis (Galderisi *et al.* 2015; Walton *et al.* 2017), a finding that

supports long-standing evidence that the frontal lobes are key contributors underlying negative

symptom severity (Turetsky *et al.* 1995; Wible *et al.* 2001). Importantly, our findings suggest

thinning is more specific to changes in Expressivity over a one to two year period. However, no

associations were uncovered in the prefrontal cortex when examining WGC and negative

symptom progression, suggesting these cortical thinning patterns may be due to neuroanatomical

changes within more superficial layers. This idea is supported by several studies that cortical

thinning of superficial layers as a key biological mechanism underlying altered neuroanatomy of

the prefrontal cortex in schizophrenia (Wagstyl *et al.* 2016; Lake *et al.* 2017). Significant

associations still emerged between expressivity deficits and WGC, but within primary sensory

and motor regions. Similar patterns were uncovered with amotivation. We have previously

shown that WGC of primary sensory and motor regions is related to general psychopathology in

FEP patients (Makowski et al. 2019), and may be related to alterations within the high levels of

intracortical myelin that typically characterize these regions (Glasser & Van Essen 2011). It is

possible that the association between contrast changes in primary sensory and motor regions and

negative symptom severity is not specific to negative symptoms, but could also be related to

general positive symptoms and cognitive deficits more generally. Although there are few studies

that have looked at the neural correlates of expressivity and amotivation separately, one of the

key regions that has emerged in several investigations is that of the association between avolition

and activation of the striatum (Galderisi et al. 2015). Given our conjecture of WGC as a proxy

measure of peri-cortical myelin, putatively tapping into integrity of cortico-cortical and cortico-

subcortical connections, it is interesting to consider this finding in light of potential aberrancies

between cortico-striatal circuitry (Haber 2016).

A key discovery in our behavioural findings was the stronger association between VM

specifically with Expressivity, as opposed to both negative symptom dimensions. Consistent

with previous literature, we uncovered a negative association between VM performance and

negative symptoms in psychosis cross-sectionally (Hartmann-Riemer et al., 2015). However,

when assessing baseline VM performance against rate of change in symptoms, we identified a

relationship that, at first glance, runs counter to intuition. Namely, it was found that patients with

better VM at baseline (i.e. a mild level of VM deficits, particularly with immediate recall) had

worsening of Expressivity symptoms, a relationship that has largely been unexplored

longitudinally in psychosis. Our results suggest that having less striking VM deficits at intake

does not necessarily protect against progressive changes in Expressivity. Other key cognitive

factors, such as insight, may also contribute to this relationship. Based on previously identified

positive relationships between cognitive insight and VM (Lysaker *et al.* 2005; Lepage *et al.*

2008), we can consider that patients with a better ability to recall stored information are also

likely to have lower self-certainty and more self-reflectiveness (a profile that characterizes high

levels of cognitive insight), which could set the stage for a trajectory of worsening Expressivity

as the patient internalizes their mental illness. It is also important to note that many of the

patients included in this study had an improving course of negative symptoms after the first two

years after a FEP, consistent with a previous study (Lutgens *et al.* 2019). In this context, several studies have suggested that negative symptoms can improve in the absence of any change in verbal memory performance (Nopoulos *et al.* 1994; Cantor-Graae *et al.* 1995; Hoff *et al.* 1999). In a related vein, we also conducted a supplementary analysis exploring the potential relationship between change in verbal memory and change in negative symptoms over the first year after a FEP, for a subset of patients (N=49) for which data were available. No significant association was found, consistent with the studies cited above, but it is still possible that more timepoints would be needed to elucidate such longitudinal relationships. Many studies have suggested that cognition, including verbal memory, is a set of static traits, as suggested by evidence showing stability of cognitive performance from the clinical high risk state to transition to psychosis (Green & Harvey 2014; Carrión *et al.* 2015). However, future studies are encouraged to further investigate longitudinal cognition-symptom relationships after psychosis onset; a future direction that our group is currently investigating as well.

It is also worth discussing the granularity of results with respect to immediate vs. delayed recall in relation to Expressivity. It has been shown that immediate recall is highly related to performance on other measures of cognition in schizophrenia (Leeson *et al.* 2009). Immediate recall may also have a stronger biological and/or genetic predisposition; deficits in immediate recall predict conversion to psychosis (Lindgren *et al.* 2017) and are present in non-affected siblings of schizophrenia twins (Goldberg *et al.* 1993). Together, this suggests that immediate recall may be a more "hard-coded" feature of psychosis compared to retention of information (i.e. delayed recall), with stronger biological and genetic influences. Further, Expressivity has also been recently posited to be a more primary negative symptom domain, and less influenced by environmental factors, such as community resources, compared to Amotivation (Lutgens *et*

al. 2019). Our data present a feasible model whereby Expressivity and immediate recall or *verbal learning* may share common etiology and a potential endophenotype of interest for future studies.

More preserved immediate recall abilities contributed to the relationship between worsening of Expressivity deficits and cortical thinning across higher order language processing areas in ventral frontal areas and middle/inferior temporal gyri of the left hemisphere, which contributes to the semantic encoding of language (Saur *et al.* 2008) and for keeping verbal information active in working memory (Smith & Jonides 1999). These areas are subserved by white matter tracts such as the uncinate and superior longitudinal fasciculi (Friederici 2011), which have been shown to be disrupted in schizophrenia patients with predominant negative symptoms (Sigmundsson *et al.* 2001). With WGC, an interesting relationship also emerged between expressivity deficits and increases in contrast between patients with different levels of immediate recall performance within the retrosplenial cortex bilaterally. Although these results were only significant with a relaxed threshold when correcting for multiple comparisons, the retrosplenial cortex is interesting to consider in this context as it is a region that has been strongly linked to memory function (Vann *et al.* 2009), as well as more recently, to the reinforcement of salient behavioural cues (Smith *et al.* 2012, 2018), which is likely to contribute during immediate learning phases of memory. A previous study has also shown that white matter volume abnormalities exist within the retrosplenial cortex in schizophrenia patients (Mitelman *et al.* 2005).

Meanwhile, the interaction between delayed recall and expressivity uncovered regions of the dorsal language processing stream, namely superior parietal lobule, dorsal primary somato-motor and premotor areas, which relates more to language production (Saur *et al.* 2008).

Disruptions in these cortical regions could plausibly support a mechanistic explanation of the lowered rate of speech production and/or increased psychomotor retardation observed in patients with expressivity deficits (Cohen *et al.* 2014; Marder & Galderisi 2017), as well as the necessity for preserved structure/function of the left posterior dorsolateral prefrontal cortex in delayed retrieval (Alexander *et al.* 2003). Our results also did not change when accounting for a general cognitive index that comprised five cognitive domains. Together, these results suggest that the relationship between Expressivity deficits and VM may be more closely linked to speech articulation or language production mechanisms, as opposed to general cognitive abilities.

It is worth noting that WGC and CT are related metrics, but they also tap into different neurobiological properties (Westlye *et al.* 2009). WGC may take myelination patterns into account more strongly than CT, and may shed light on a compartment of the cortex that may be more amenable to short-term changes (Wenger *et al.* 2017), which in turn may be a more viable biomarker target in FEP patient samples as measured on MRI.

Several limitations should be considered. Our model did not capture patients who had a consistently high or low level of negative symptoms, as well as the distinction between primary and secondary negative symptoms. These individual patterns of negative symptoms have been touched upon by some of our previous work (Makowski *et al.* 2016, 2017), but future investigations are encouraged to parse apart such trajectories in myelin and/or other microstructural compartments. The rates of change in both cortical metrics and negative symptoms should also be interpreted as a proxy measure of negative symptom/cortical change, as subtle non-linear fluctuations over time are not captured by the measures presented in this manuscript. Limitations in accurately and objectively assessing negative symptoms should also be considered, where rater bias may preclude the treatment of Amotivation and Expressivity as

completely independent domains. Automated unbiased assessments of negative symptoms, such as software that has been developed to assess communication deficits and natural language in patients with schizophrenia (Cohen & Elvevåg 2014), may provide data with higher construct validity in this respect. It should also be noted that many patients ultimately showed an improvement in negative symptoms; although this improvement has been reported before in the first two years after a FEP (Lutgens *et al.* 2019), we cannot rule out that patients with improvement in negative symptoms ultimately comprise a subset of patients that are more motivated to participate in longitudinal studies such as the one described here. With respect to cognitive data, we collected VM from two batteries, although examination of the tests and standardization of our data suggests test version likely did not significantly impact our findings. Our VM data was also limited by the fact that it was largely cross-sectional; as mentioned, future studies would benefit from studying potential temporal changes in such cognitive performance after a FEP. Finally, although our patient sample was largely antipsychotic-naïve at the beginning of the study, many of these patients were prescribed antipsychotic medications. Our exploration of antipsychotic medication on rate of change in WGC and CT showed no notable effect, however individual medication classes could have differential effects on gray/white matter (Bartzokis *et al.* 2009; Szeszko *et al.* 2014; Abramovic *et al.* 2016).

Although further work is needed to clarify the longitudinal relationships between cognition and negative symptoms, this avenue is promising in understanding domains of psychosis which have largely gone untreated. These findings may also hold implications for other neurological and psychiatric disorders characterized by negative symptom presentation and verbal memory deficits. Given that structural MRI is one of the most commonly used imaging

techniques in psychiatric neuroimaging studies, extracting WGC and CT together may be fruitful

in the broader search for a valid and easy-to-measure biomarker in psychiatry.

Role of the Funder/Sponsor: The funding organizations had no role in the design and conduct

of the study; collection, management, analysis, and interpretation of the data; preparation,

review, or approval of the manuscript; and decision to submit the manuscript for publication.

FIGURE AND TABLE CAPTIONS

Table 1. Demographic and clinical information. General Demographics for whole sample are presented, followed by information corresponding to each scan. All data represented as Mean (SD), unless otherwise specified. Square brackets [] include adjusted sample size included in statistical analysis due to missing datapoints. All antipsychotic totals are presented as *cumulative* chlorpromazine equivalents in mg (i.e. a composite measure of the total amount of antipsychotic medication prescribed during the entire study), as prescribed by a psychiatrist, and are reported along with a percentage of medication adherence. SAPS totals are presented as mean scores of the sum of item-level scores. Duration of untreated psychosis and illness reflect length of time between onset of psychotic symptoms and onset of other psychiatric symptoms until initiation of antipsychotic medication treatment, respectively. Further details on collection of clinical data can be found in Supplementary Methods (section ii). Years of education, socioeconomic status, performance and verbal IQ were found to be non-normally distributed; thus, non-parametric tests to compare group means were used.

*FEP patients had significantly lower levels of verbal memory performance (immediate/delayed recall), lower performance and verbal IQ, and less years of education compared to HC (p<0.05).

aDegrees of freedom adjusted, as age did not meet the assumption of equal variance between groups as assessed with Levene's test.

bCovaried by test version. Specifically, IQ was collected with WAIS-III and WASI (more details in Supplementary Material), and verbal memory was collected with a Pen and Paper neuropsychological test battery, and CogState Research Battery.

[c]Note, Mean and Standard Deviation of Verbal Memory in Controls does not equate to exactly 0 and 1, respectively, as the norms for verbal memory were calculated before exclusion of a subset of controls for this study due to imaging quality control.

Abbreviations: CDSS, Calgary Depression Scale for Schizophrenia. CPZ, chlorpromazine. FEP, First Episode of Psychosis. FUP, follow-up. SAPS, Scale for Assessment of Positive Symptoms.

Figure 1. White-gray matter contrast method. Illustration of 3 key steps in calculation of WGC, as described in the main manuscripts. Method was initially presented in Lewis et al (2018) (Lewis *et al.* 2018) and also applied by our group recently to a cross-sectional FEP cohort (Makowski *et al.* 2019). Left-hand panel is an example of a T1-weighted image from a participant included in the study, with the gray-white matter boundary and +/-1mm surfaces overlaid, as defined in Step i. Surfaces maps of the intensity of the T1-weighted MRI were then generated and smoothed with a 20mm blurring kernel (Step ii). Smoothing is done for both the -1 and +1mm surfaces before calculation of WGC (Step iii). One example vertex is identified to illustrate calculation of WGC (Step iii). Note, in some areas the surfaces do not appear to be consistently 1mm from the gray-white matter boundary; this is because a 2D visualization of the surfaces is depicted here, without taking into consideration the third dimension of the T1-weighted image.

Figure 2. **Change in Amotivation and Expressivity deficits associated with change in WGC/CT across time**. Results are RFT-corrected, where blue colours represent significant results cluster-thresholded at a "stringent" threshold of p=0.001, whereas red/pink colour represent significant results at a "relaxed" threshold of p=0.01. Selected regions for scatterplots are those that survived multiple comparisons with the more stringent cluster threshold of p=0.001. Plots with Amotivation are plotted with a dotted line and crosses, whereas Expressivity data are plotted with a solid line and circular markers. For overlapping cluster within right paracentral gyrus of the effect of negative symptoms on WGC (top two rows), a common peak was selected where amotivation and expressivity are included on the same plot.

Abbreviations: SPL, Superior Parietal Lobule.

Orientation: Surfaces from left to right in each row: left lateral, right lateral, left medial, right

medial, dorsal.

Figure 3. **Interaction between baseline verbal memory and change in Expressivity on WGC**

and CT. Results are RFT-corrected, where blue colours represent significant results cluster-

thresholded at "original" stringent threshold of p=0.001, whereas red/pink colour represent

significant results at a "relaxed" threshold of p=0.01. "Immediate" and "Delayed" labels of left-

hand side panel refer to immediate and delayed recall of verbal memory domain, respectively.

Inflated brain is presented to better visualize results within cortical folds. Selected regions for

scatterplots are those that survived multiple comparisons with the more stringent cluster

threshold of p=0.001 for cortical thickness data. Although nothing survived correction after

stringent correction for WGC analyses, peaks within left central sulcus and right retrosplenial

cortex were plotted to explore the direction of results with WGC. To better visualize the

interaction effect of two continuous variables (rate of change in expressivity and baseline VM),

patients were divided based on low/moderate VM deficit (purple) and high VM deficit (yellow).

Plots separating patients on the basis of immediate recall are depicted with crosses, and delayed

recall with diamonds. Orientation: Surfaces from left to right in each row: left lateral, right

lateral, left medial, right medial, dorsal (with the exception of the third row, where the last

surface is a ventral view).

| Table 1.		FEP N=88	Controls N=80				
		N (%)		**Statistic**	**df**	**p-value**	
	Male	62 (70)	52 (65)	χ^2=0.57	1	0.51	
	Right Handed	73 (83)	73 (91)	χ^2=2.53	1	0.17	
	Diagnosis						
	Schizophrenia/ Schizophreniform	63 (72)					
	Affective Disorder	16 (18)					
	Delusional Disorder	3 (3)					
	Psychosis Not Otherwise Specified	6 (7)					
		Mean (SD)		**Statistic**	**df**	**p-value**	**Mean Difference Control-FEP**
General Demographics	Age at Baseline[a]	24.3 (4.1)	24.27 (3.3)	t=-0.009	164.1	0.99	-0.005
	Verbal Memory - Immediate*[b,c]	-1.3 (1.4) [87]	0.03 (1)	F=23.38	1, 163	<0.001	1.38
	Verbal Memory - Delayed*[b,c]	-0.9 (1.1) [87]	0.02 (0.8)	F=16.77	1, 163	<0.001	0.92
	Education in Years*	12.0 (2.5)	14.3 (2.4)	U=1887.00		<0.001	2.3
	Socioeconomic Status	3.2 (1.1) [81]	3.0 (1.0) [76]	U=2817.00		0.34	-0.16
	Performance IQ*[b]	98.7 (17.1)	106.9 (12.7)	U=2447.50		0.001	8.15
	Verbal IQ*[b]	99.8 (16.1)	110.0 (14.9)	U=2345.50		<0.001	10.16
	Cumulative CPZ equivalent (in mg)	4753.1 (4770.7)					
	Adherence (%)	80 (24)					
	Duration Untreated Psychosis (weeks)	76.4 (142.0) Median: 20.1					
	Duration Untreated Illness (years)	7.3 (6.5) Median: 6.1					
		Mean (SD)					
Baseline Symptoms (N=88)	Amotivation	11.3 (6.1)					
	Expressivity	7.1 (7.2)					
	SAPS	9.5 (12.3)					
	CDSS	2.4 (2.9)					
	Window |Scan - Symptom Eval| (months)	0.7 (0.6)					
1-year FUP Symptoms (N=80)	Amotivation	8.7 (7.0)					
	Expressivity	5.8 (6.5)					
	SAPS	7.9 (10.2)					
	CDSS	1.5 (2.7) [79]					
	Window |Scan - Symptom Eval| (months)	2.1 (2.0)					
2-year FUP Symptoms (N=65)	Amotivation	7.4 (6.8)					
	Expressivity	5.1 (6.6)					
	SAPS	7.9 (13.9)					
	CDSS	1.9 (2.6) [60]					
	Window |Scan - Symptom Eval| (months)	0.6 (1.2)					

Figure 1.
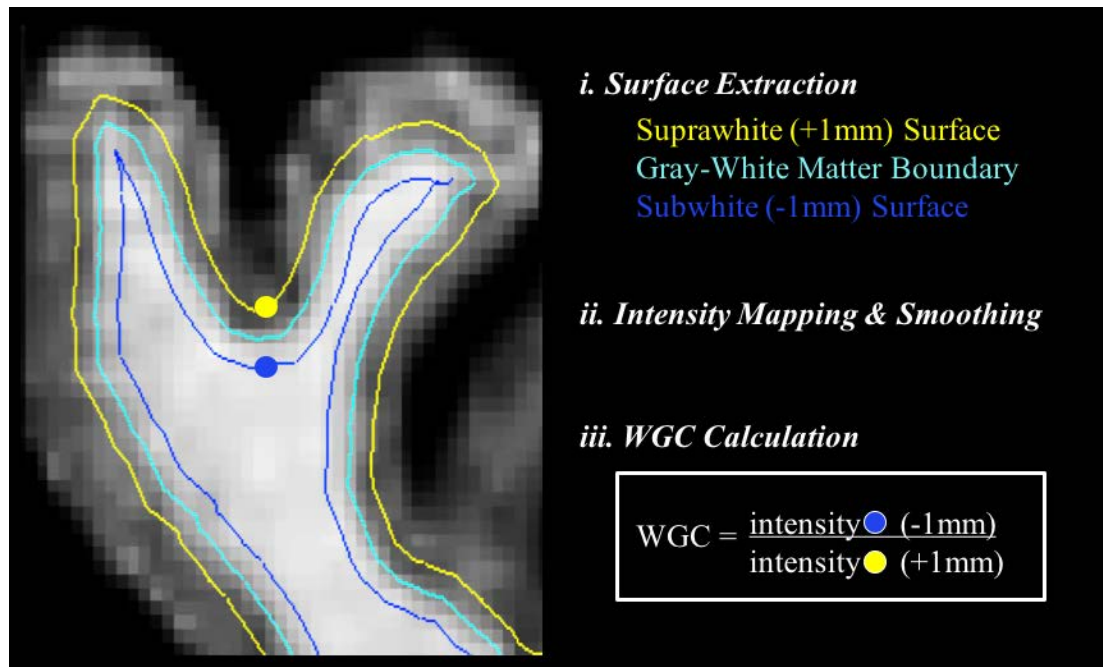
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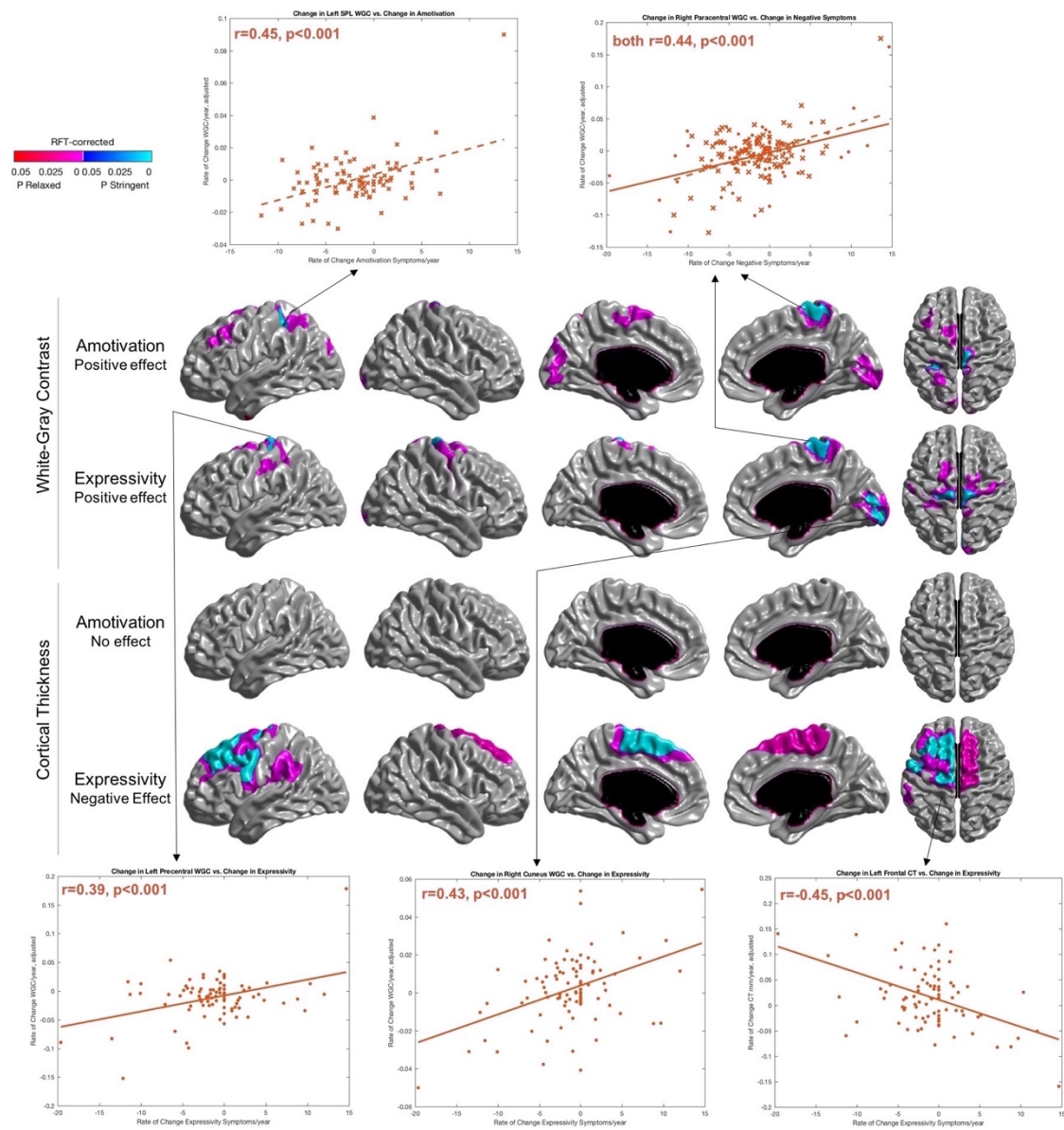
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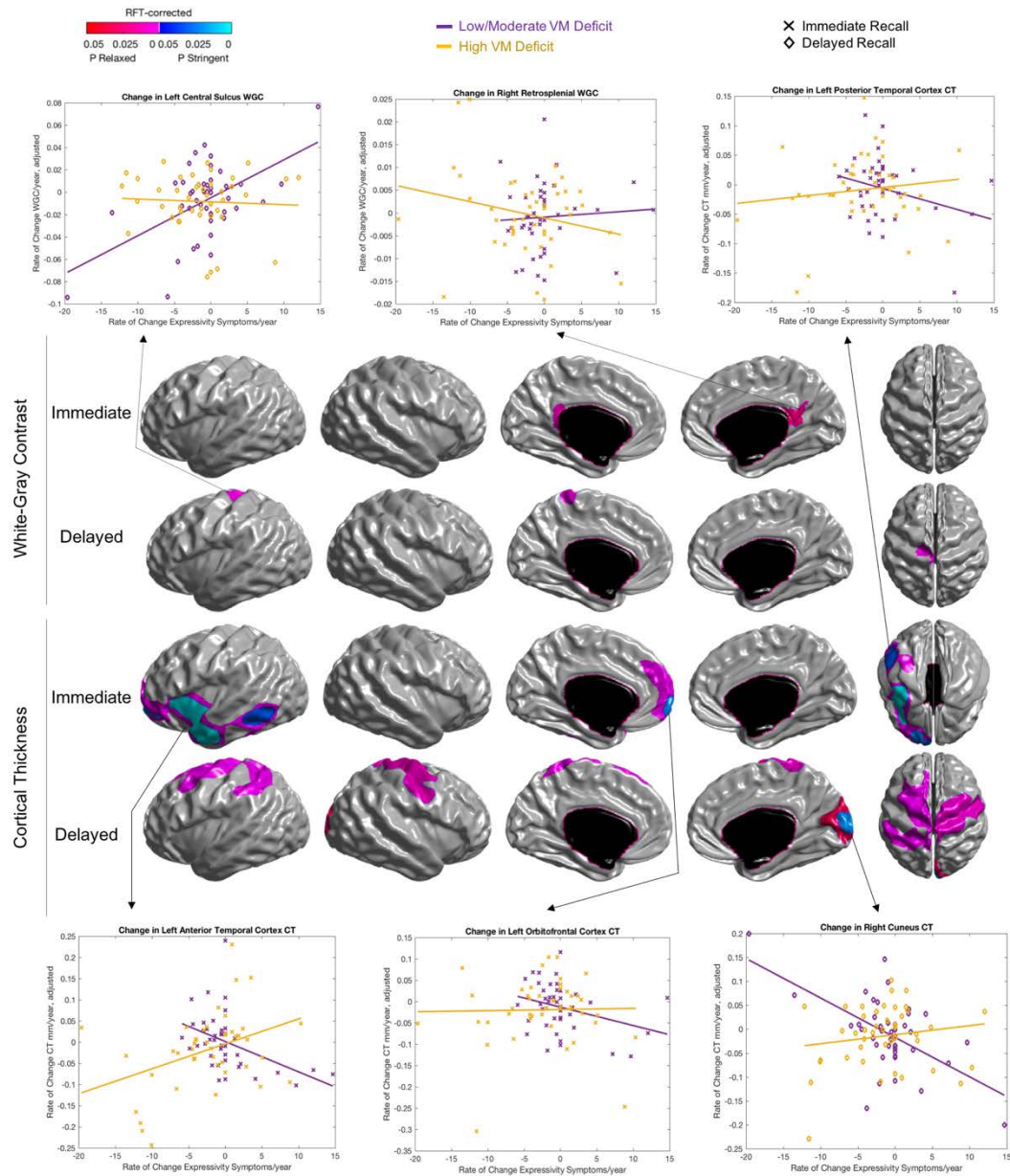
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