Do Unremitted Psychotic Symptoms Have an Effect on the Brain? A 2-Year Follow-up Imaging Study in First-Episode Psychosis

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Background: To examine whether the duration of unremitted psychotic symptoms after the onset of a first episode of psychosis (FEP) is associated with cortical thickness and hippocampal volume, as well as structural covariance of these measures.

Method: Longitudinal MRI scans were obtained for 80 FEP patients shortly after entry to FEP clinic (baseline), and then 12 months and 24 months later. The proportion of time patients experienced unremitted positive symptoms for 2 interscan intervals (baseline to 12 mo, 12 mo to 24 mo) was calculated. Changes in cortical thickness and hippocampal volumes were calculated for each interscan interval and associated with duration of unremitted psychotic symptoms. Significant regions were then used in seed-based structural covariance analyses to examine the effect of unremitted psychotic symptoms on brain structural organization. Importantly, analyses controlled for antipsychotic medication. Results: Cortical thinning within the left medial/orbitofrontal prefrontal cortex and superior temporal gyrus were significantly associated with the duration of unremitted psychotic symptoms during the first interscan interval (ie, baseline to 12 mo). Further, changes in cortical thickness within the left medial/orbitofrontal cortex positively covaried with changes in thickness in the left dorsal and ventrolateral prefrontal cortex during this period. No associations were observed during the second interscan interval, nor with hippocampal volumes. Conclusions: These results demonstrate that cortical thickness change can be observed shortly after an FEP, and these changes are proportionally related to the percentage of time spent with unremitted psychotic symptoms. Altered structural covariance in the prefrontal cortex suggests that unremitted psychotic symptoms may underlie reorganization in higher-order cortical regions.

Key words: cortical thickness/hippocampus/prefrontal cortex/relapse/structural covariance

Introduction

Longitudinal brain imaging studies have provided strong evidence for progressive brain changes in schizophrenia. However, the factors underlying such changes remain actively debated. Antipsychotic medications are one likely contributor; one meta-analysis in schizophrenia showed that gray matter tends to be inversely correlated with cumulative exposure to antipsychotic treatment. However, studies in enduring schizophrenia are more prone to the influence of multiple confounds related to illness chronicity, which can be ameliorated by studying early phases of psychosis.

Interestingly, some have suggested that progressive brain changes are more pronounced in the first few years after a first episode of psychosis (FEP). In one of the largest longitudinal imaging studies in FEP, Andreasen et al. observed that maximal gray matter loss occurred within the first 2 years after an FEP, and subsequently found that relapse duration, and not the number of relapses, was significantly related to brain volume decreases. While these represent landmark studies, they were limited by the fact that the majority of follow-up scans were done after 5 or more years, although it is likely that pronounced changes may have been occurring...
earlier. Most of the patients were also initially treated with a first-generation antipsychotic, which is known to have a greater impact on brain anatomy than second-generation antipsychotics. Finally, cannabis use was not systematically controlled for and could represent another important confound.

Recently, Emsley et al. examined changes in gray and white matter volume over the first year of treatment following an FEP in initially antipsychotic-naïve patients, and observed a decrease in overall cortical volume relative to healthy controls, which was driven significantly by antipsychotic dose received during the interscan interval. However, it should be noted that a relatively gross measure of gray matter was used, as well as a total Positive and Negative Syndrome Scale (PANSS) score which does not dissociate positive symptoms from other dimensions of psychopathology.

Here we report on a longitudinal study to examine whether unremitted psychotic symptoms contribute to progressive brain changes over the 2–2.5 years following an FEP while controlling for the potential effect of antipsychotic treatment and cannabis use. Two specific objectives were considered. First, we examined whether the percentage of time spent with clinically significant psychotic symptoms affected the brain longitudinally. We hypothesized that cortical thickness (CT) in frontal and temporal lobe areas and volume of the hippocampus would decrease as a function of the duration of unremitted positive symptoms. Second, we used seed-based structural covariance analyses to examine whether cortical-hippocampal relationships.

Neuroimaging Component

The neuroimaging study began in 2004 and was completed in 2016 on the same MRI scanner. The study design comprised 3 scheduled visits: baseline (Scan1), 12-month follow-up (Scan2), and 24-month follow-up (Scan3). In total, 80 patients with longitudinal data were included in the study. See supplementary material for complete breakdown of the number of patients who were not retained in the study due to attrition/exclusion criteria. Only individuals ages 18 and over were considered for the neuroimaging study. Exclusion criteria included the presence of a major medical disorder, a history of neurological illnesses and head trauma resulting in loss of consciousness that could affect cognition, presence of neurological disorder determined by medical record examination, lifetime diagnosis of substance dependence, and/or any potential contraindication for the MRI scan.

Clinical Assessment and Demographic Data

Diagnosis for each patient was made on the basis of a structured clinical interview for the DSM-IV, performed by a trained interviewer, and confirmed by at least one senior research psychiatrist (R.J. or A.M.). Positive and negative symptoms were assessed with the Scale for the...
Assessment of Positive/Negative Symptoms (SAPS/ SANS, respectively).\textsuperscript{24,25} Depression was assessed with the Calgary Depression Scale for Schizophrenia (CDSS).\textsuperscript{26} Antipsychotic medication dosages were converted to chlorpromazine equivalents according to the literature,\textsuperscript{27} and multiplied by percent medication adherence over the longitudinal follow-up period. Parental socioeconomic status (SES) was estimated using the Hollingshead SES Rating Scale,\textsuperscript{28} and handedness determined with the Edinburgh Handedness Inventory.\textsuperscript{29}

Proxy Measure of Cannabis Use

Frequency of cannabis use was assessed with the Chemical Use Abuse Dependence (CUAD) Scale.\textsuperscript{30} We calculated the percentage of time a patient used cannabis for each of the 2 interscan intervals (ie, between Scan1-Scan2 and Scan2-Scan3), for direct comparison to the measure of unremitted psychotic symptoms presented below. Specifically, we used the upper bound of cannabis use for each category of cannabis frequency; eg, a score of “0 = No consumption” would be equivalent to 0% of cannabis use per month, a score of “4 = ≤3 times per week” was coded as 3*4 = 12 times per month or 40% of cannabis use per month, a score of “5 = daily” was equivalent to 100%, etc. For the category “1 = <1 time per month,” where a clear upper bound was not available, we coded cannabis use as “0.5 times per month,” which was equivalent to approximately 2% use per month. Percent of cannabis use for each interscan interval thus reflected an average over all clinical timepoints between scans for which data was available.

Measure of Unremitted Psychotic Symptoms

We adapted our definition from Andreasen and colleagues;\textsuperscript{31} however, here we only considered positive symptoms. Unremitted psychotic symptoms were defined as a score of 3 or more on the global items from the SAPS. Data was collected using clinical interviews at multiple timepoints (entry, month 1/2/3/6/9/12/15/18/21/24). For clinical timepoints where data were not available or missing, these data were supplemented by information collected using telephone interviews that were offered to each client on a monthly basis after entering the early intervention program. For each of the 2 interscan intervals, we calculated the duration of unremitted psychotic symptoms, and normalized it by length of the interscan interval, to account for the variation in time of the interscan interval among participants.

MRI Acquisition

All scanning was carried out at the Montreal Neurological Institute (MNI) on a 1.5 T Siemens Sonata whole-body MRI system. Structural T1 volumes were acquired for each participant using a 3-dimensional gradient echo pulse sequence with sagittal volume excitation (repetition time = 22 ms, echo time = 9.2 ms, flip angle = 30, one hundred eighty 1 mm contiguous sagittal slices). The rectangular field of view (FOV) for the images was 256 mm (AP) 204 mm (SI). Information about quality control (QC) is detailed in supplementary material.

Post-Processing

All raw scans that passed QC were submitted to the CIVET pipeline (Version 2.1.0: http://www.bic.mni.mcgill.ca/ServicesSoftware/CIVET;\textsuperscript{32,33}) CT was estimated using the Laplacian distance between the gray-white matter boundary surface and pial surface\textsuperscript{34} across 81,924 vertices. Detailed steps have been described by our group elsewhere,\textsuperscript{35} and are also detailed in supplementary material.

Hippocampal Volume

Hippocampal structures were extracted bilaterally using the Multiple Automatically Generated Templates (MAGeT)-Brain algorithm\textsuperscript{36} (https://github.com/CobraLab/MAGeTbrain). This technique utilizes a limited number of high-resolution atlases that have been manually segmented (https://github.com/CobraLab/atlases). Extensive validation of MAGeT has been done previously, as shown in several references from our group,\textsuperscript{36,37} which have also included subsets of the described patient sample here, with data acquired on a 1.5T scanner. The pipeline yields 10 hippocampal labels per subject, corresponding to 5 hippocampal subfields per hemisphere. For the purpose of this analysis, the subfield volumes per hemisphere were summed, such that only total left and right hippocampal volumes were considered. Additional details on processing with MAGeT are included in supplementary material.

Statistical Analyses

Demographic and clinical variables were analyzed with 1-way ANOVAs for continuous variables or Kruskall-Wallis H-tests for nominal variables. For IQ, an ANCOVA was used to covary for test version. Analyses of clinical variables were conducted using PASW Statistics 21 (SPSS Inc., 2009), and were 2-tailed with a critical $P$-value of .05.

Relationship Between Unremitted Psychotic Symptoms and Cannabis Use Frequency

Partial correlations were applied between the percent of time with unremitted psychotic symptoms and percent of time using cannabis for the 2 interscan intervals, covarying for age and cumulative antipsychotic medication exposure.

Main Effect of Unremitted Psychotic Symptoms on Brain Structure

Relationship With Change in CT. Statistics were performed across 81,924 vertices of the cortical surface.
using the SurfStat toolbox (http://www.math.mcgill.ca/keith/surfstat/). First, we assessed the main effect of duration of unremitted symptoms on changes in CT. Changes in CT were calculated as the difference in cortical thickness between 2 scans for each subject per vertex; only changes between Scan1-Scan2, and between Scan2-Scan3 were considered. The linear model defined below was applied to the change in CT data:

\[
Y = \text{intercept} + \beta_1(\text{Unremitted Symptoms}) + \beta_2(\text{Centered Age}) + \beta_3(\text{Sex}) + \beta_4(\text{AP Medication}) + \beta_5(\text{Mean CT}) + \varepsilon
\]

where Y represents changes in CT for each vertex, \( \beta_1 \) represents the regression coefficient of interest, \( \beta_2-5 \) represents regression coefficients that were covaried for in the model, and \( \varepsilon \) is residual error. \( \beta_1 \) and \( \beta_4 \) were taken from the first scan (ie, Scan1 for the first interscan interval, Scan2 for the second interscan interval). \( \beta_1 \) is cumulative antipsychotic medication exposure expressed as chlorpromazine equivalents, taking percent adherence into account, as reported at the second scan for each of the interscan pairs (ie, Scan2 for the first interscan interval, Scan 3 for the second interscan interval). Mean CT was included in the model as it improved the model fit, as determined by a lower value when applying the Akaike Information Criterion.

**Relationship With Change in Hippocampal Volume.** Similar to the CT analysis, hippocampal volume changes were assessed by calculating the difference in volume between the 2 interscan intervals of interest. The same linear model as above was used, except the dependent variable Y was the change in hippocampal volume, and instead of covarying as above was used, except the dependent variable Y was the change in hippocampal volume, and instead of covarying for mean CT, total brain volume was included as a covariate.

**Structural Covariance Analyses**

Significant cortical/hippocampal regions extracted from analyses above were used as seeds to map structural covariance networks involved with unremitted psychotic symptoms. Thus, the interaction between changes in cortical thickness or hippocampal volume seeds of interest and duration of unremitted symptoms was evaluated against CT changes across 81,924 vertices of the brain surface, for the 2 interscan intervals. The following model was used:

\[
Y = \text{intercept} + \beta_1(\text{Unremitted Symptoms}) + \beta_2(\%\text{Unremitted Symptoms}) + \beta_3(\text{Change in CT Seed}) + \beta_4(\text{Centered Age}) + \beta_5(\text{Sex}) + \beta_6(\text{AP Medication}) + \beta_7(\text{Mean CT}) + \varepsilon
\]

Where variables are defined similarly as above; \( \beta_1 \) reflects the main interaction of interest, and **“Change in CT Seed”** is the value of CT change for the seed vertex informed by prior regression analysis. A similar model would be applied for potential significant findings with the hippocampus, using total brain volume as a covariate instead of Mean CT. All results were corrected for multiple comparisons using Random Field Theory (RFT), using a P-cluster threshold of \( P = .005 \).

**Table 1. Demographic and Clinical Information for Longitudinal Sample**

| Variable                              | Scan1-Scan2 (N = 80) | Scan2-Scan3 (N = 60) |
|---------------------------------------|----------------------|----------------------|
| Age \( ^a \)                          | 24.18 (3.99)         | 24.97 (4.08)         |
| Sex, M (%)                            | 56 (70%)             | 44 (73.3%)           |
| Right-handedness                      | 67 (83.8)            | 53 (88.3%)           |
| SES \( ^a \)                          | 3.12 (1.04)          | 3.09 (0.97)          |
| IQ                                     | 99.96 (15.73)        | 100.88 (16.12)       |
| Years education                       | 11.93 (2.60)         | 11.77 (2.60)         |
| Interscan interval (mo)               | 13.23 (1.29)         | 12.64 (1.82)         |
| % Non-remission                       | 59.91 (37.3)         | 24.84 (32.47)        |
| % Cannabis exposure \(^b\)            | 14.34 (26.52) \[^52\] | 24.21 (38.90) \[^35\] |
| CPZ equivalents \(^c\)                | 3258.00 (2745.73)    | 5090.50 (4776.30)    |
| Adherence                             | 80.1 (24.3)          | 75.27 (29.95)        |
| DUP (wk)                              | 75.40 (145.94)       | 77.84 (157.87)       |
| Diagnosis \( ^N, \% \) \(^d\)         |                      |                      |
| Schizophrenia spectrum                | 59 (73.8)            | 42 (70.0)            |
| Affective                             | 14 (17.5)            | 12 (20.0)            |
| Delusional disorder                   | 2 (2.5)              | 2 (3.3)              |
| Psychosis NOS                         | 5 (6.3)              | 4 (6.7)              |
| Other medication \( ^N, \% \) \(^e\)  |                      |                      |
| Antidepressants                       | 11 (14.3)            | 9 (16.7)             |
| Benzodiazepines                       | 3 (3.9)              | 3 (5.6)              |
| Anticholinergics                      | 2 (2.6)              | 1 (1.9)              |
| Mood stabilizers                      | 8 (10.4)             | 7 (13.0)             |

Note: CPZ, chlorpromazine; DUP, duration of untreated psychosis; FUP1, follow-up year 1; FUP2, follow-up year 2; NOS, not otherwise specified; SES, socioeconomic status.

General Demographics for whole sample are presented as a function of the 2 interscan intervals. Please see supplementary table 1 for clinical data presented separately for each timepoint.

\( ^a \) Refers to value at first scan in the contrast, ie, for Baseline-FUP1, age/SAPS at baseline is reported. For FUP1-FUP2, age/SAPS at FUP1 is reported.

\( ^b \) Data missing for several patients. Number in square brackets represents adjusted N.

\( ^c \) Cumulative CPZ equivalents at the second timepoint in the contrast are reported.

\( ^d \) and \( ^e \) patients were missing other medication data for the first and second interscan interval, respectively. Other medication data is reported based on the second timepoint in contrast, and proportions were calculated based on adjusted sample size.
Results

Sociodemographic and Clinical Results

In total, 80 FEP patients had usable positive symptom remission data and neuroimaging data at Scan1 and Scan2, and 60 FEP patients had sufficient clinical and neuroimaging data at Scan2 and Scan3. In the FEP group, Scan1 was performed on average 4.0 (SD = 1.9) months from entry into PEPP. For the entire group, including controls, interscan intervals were approximately 13.1 (SD = 1.3) months between Scan1 and Scan2, and 12.6 (SD = 1.7) months between Scan2 and Scan3. All FEP patients were on second-generation antipsychotics. Supplementary table 1 presents the socio-demographic and clinical variables for the whole group of FEP participants. Table 1 presents clinical/demographic variables comparing the 2 interscan intervals.

Relationship Between Unremitted Psychotic Symptoms and Cannabis Use Frequency

Fifty-two of 80 patients and 35/60 patients had sufficient data entered in the CUAD scale for assessment of cannabis use frequency for the first and second interscan interval, respectively. Partial correlations, controlling for age and chlorpromazine equivalents, revealed no significant associations between percent of time with unremitted psychotic symptoms and percent of time using cannabis for either of the 2 interscan intervals (first interscan interval: $r = -0.092$, $P = .527$, df = 48; second interscan interval: $r = -0.064$, $P = .723$, df = 31).

Cortical Thickness Analyses

The main effect of unremitted psychotic symptoms on changes in CT for the first interscan interval revealed a significant negative association with 2 clusters (ie, more time spent with unremitted psychotic symptoms associated with cortical thinning) (Figure 1). One cluster encompassed medial and orbitofrontal areas of the left medial prefrontal cortex and the second encompassed the left superior temporal gyrus spanning anteriorly to the ventrolateral prefrontal cortex and frontal insula ($P < .05$, RFT-corrected; df = 74). No significant

Fig. 1. Main effect of unremitted psychotic symptoms on change in cortical thickness. Significant negative effect of unremitted psychotic symptoms on change in cortical thickness over the first interscan interval using a general linear model, covarying for centered age, sex, chlorpromazine equivalents, and medication adherence. Brain map shows RFT-corrected results ($P < .05$).
associations were observed for the second interscan interval (see figure 2).

**Hippocampal Volumes**

No significant associations between unremitted psychotic symptoms with change in left or right hippocampal volume were observed for either interscan interval.

**Structural Covariance Analyses: Interaction With Unremitted Psychotic Symptoms**

The next set of analyses were limited to changes in CT over the first interscan interval. We first extracted the vertices at the peak $t$-statistic for each of the 2 significant clusters discovered above: left medial prefrontal cortex ($x = −9; y = 47; z = 11$; peak $t$-statistic = 3.47) and the left superior temporal gyrus ($x = −50; y = 17; z = −22$; peak $t$-statistic = 3.64), and correlated changes in CT between each of these vertices and their interaction with unremitted psychotic symptoms on CT changes of the remaining 81,923 vertices of the brain. A significant interaction between unremitted psychotic symptoms and change in CT within the left medial prefrontal seed emerged, on changes in a large cluster of the left lateral frontal cortex, including both dorsolateral and ventrolateral prefrontal cortex ($P < .05$, RFT-corrected; $df = 72$).

To better visualize the direction of the effect of the interaction between 2 continuous variables, patients were split into 2 categories: “Remitted” (0%–25% of time spent with unremitted psychotic symptoms) and “Unremitted” (>25% of time spent with unremitted psychotic symptoms), as can be seen in figure 3. This plot suggests that the “Unremitted” group drove this significant association, where more positive covariation was found between changes in CT of the left medial prefrontal seed and left lateral cortex. The same structural covariance analysis using the superior temporal gyrus seed did not reveal any significant association with change in other cortical regions over the first interscan interval.

**Discussion**

In this study, we examined the influence of unremitted psychotic symptoms on progressive brain changes while controlling for exposure to antipsychotics in a longitudinal cohort of FEP patients. We observed a significant association between the duration of unremitted psychotic
symptoms and cortical thinning within left medial and orbitofrontal cortex and in left superior anterior temporal gyrus over the first year after an FEP. This was not observed over the second interscan interval, indicating that progressive brain changes in relation to unremitted psychotic symptoms occur shortly after an FEP, and plateau thereafter. Intriguingly, hippocampal volume was not modulated by the duration of unremitted positive symptoms. Using the 2 identified cortical regions as seeds for a structural covariance analysis and limiting our exploration to the first interscan interval, we observed a significant association between cortical thinning in the left medial prefrontal seed and changes in CT within areas of left dorsolateral and ventrolateral prefrontal cortex as a function of unremitted psychotic symptoms. This finding shows that localized CT changes in FEP co-occur with changes in other cortical regions, suggesting spatially distributed cortical reorganization with more exposure to unremitted psychotic symptoms. Importantly, we also found no significant association between our measure of unremitted psychotic symptoms and frequency of cannabis use, a potentially strong confounder, increasing the confidence of the observed associations.

Evidence of Progressive Changes Related to Unremitted Psychotic Symptoms

Several studies have shown an association in early psychosis between the persistence of symptoms (psychotic and/or negative) and brain structure. For instance, Bodnar et al., observed cross-sectionally that patients who did not show early symptoms remission had significantly smaller posterior hippocampal and parahippocampal volumes. Several longitudinal studies have similarly observed that FEP patients with a non-remitting symptom course exhibited a greater reduction in gray matter in the frontal lobes and left superior temporal gyrus, consistent with our findings. The idea that unremitted psychotic symptoms may impact the brain is not specific to psychosis. Of relevance, several studies in depression have demonstrated greater volume reduction in unremitted patients relative to patients in remission.

Structural Covariance Changes and Cortical Reorganization

MRI-based structural covariance analysis is thought to map structural networks that are affected by common
Factors including neurodevelopmental (ie, coordinated maturation) and/or environmental factors.\textsuperscript{18} In the context of psychosis, few studies have examined structural covariance and how it can relate to psychotic symptoms. One study\textsuperscript{44} found that the severity of auditory hallucinations modulated cortico-cortical interactions of language-related areas (ie, left superior temporal and inferior frontal gyri) in patients with schizophrenia. Similarly, we have found altered structural covariance in such language-related regions in the first 1–1.5 years after an FEP, in relation to unremitted psychotic symptoms.

An emerging theory of cortical reorganization in response to a pathological process\textsuperscript{7} could help explain these alterations in structural organization. It has been suggested that several factors affecting neural activity (including sensory loss, new learning, etc.) can trigger this cortical reorganization.\textsuperscript{7} In line with this view, it could be suggested that the duration of unremitted psychotic symptoms is one of these factors that can influence structural (co)variance of cortical regions. Indeed, it is possible that psychosis or schizophrenia is not necessarily a disorder with a neurodegenerative disease course, wherein disease propagates in a predictable structural neuronal sequence. Rather, our data and that of others shed light on a hypothesis of the organizational.\textsuperscript{7} In line with this view, it could be suggested that several factors affecting neural activity (including sensory loss, new learning, etc.) can trigger this cortical reorganization.\textsuperscript{7} In line with this view, it could be suggested that the duration of unremitted psychotic symptoms is one of these factors that can influence structural (co)variance of cortical regions. Indeed, it is possible that psychosis or schizophrenia is not necessarily a disorder with a neurodegenerative disease course, wherein disease propagates in a predictable structural neuronal sequence. 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