Developmental trajectories of subcortical structures in relation to dimensional schizotypy expression along adolescence

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Abstract

Morphological abnormalities of subcortical structures have been consistently reported along the schizophrenia clinical spectrum, and they may play an important role in the pathophysiology of psychosis. However, the question arises whether these subcortical features are consequences of medication and illness chronicity, or if they contribute to the vulnerability to develop schizophrenia spectrum disorders. If some of the subcortical abnormalities could be evidenced in community adolescents expressing higher schizotypal traits (*psychometric schizotypy*), they could potentially shed light on vulnerability markers. To date, very few studies have examined the link between psychometric schizotypy and volumes of subcortical regions, and none of them have used a longitudinal design. This study sets out to investigate developmental trajectories of subcortical volumes in 110 community adolescents (12 to 20 years old), for whom MRI-scans were acquired over a period of 5 years, reaching a total of 297 scans. Analyses were conducted using Freesurfer, and schizotypal traits were measured with the Schizotypal Personality Questionnaire (SPQ). Using mixed model regression analyses following a region-of-interest approach, we observed differential linear developmental trajectories in four subcortical structures when comparing higher versus lower scorers on the disorganized schizotypy dimension (bilateral hippocampus, left-lateral ventricle and left-pallidum) and the negative schizotypy dimension (bilateral pallidum, and right-thalamus). All results survived a threshold of $p<.05$ (FDR-corrected) while covarying for the effect of other psychological problems (externalized and internalized psychopathology). These results indicate that expression of higher levels of negative and disorganized schizotypy during adolescence was associated with neural markers linking schizotypy personality features to schizophrenia spectrum disorders.

Key words: Adolescence, Schizotypy, Structural MRI, Developmental trajectories, Schizophrenia.

1. Introduction

A large number of reviews and meta-analyses of magnetic resonance imaging (MRI) studies have provided empirical quantification on subcortical volume alterations in patients with schizophrenia (Olabi et al., 2011) ; (Haijma et al., 2013). The most frequently replicated findings are smaller bilateral hippocampi, amygdala, thalamus, nucleus accumbens (NA) and intracranial volumes (ICV), and larger lateral ventricle and pallidum volumes in patients with schizophrenia. Importantly, studies in first episode psychosis patients (FEP) have also identified hippocampus (Adriano et al., 2011), right caudate (Ellison-Wright et al., 2008) and thalamic (Gilbert et al., 2001) volumetric reductions compared to healthy controls. Furthermore, in clinical high-risk (CHR) for psychosis individuals, reductions in hippocampal (Fusar-Poli et al., 2012) and thalamic (Harrisberger et al., 2016a) volumes have also been described, thus suggesting that such abnormalities may be apparent before the onset of frank psychosis. In addition, further evidence that subcortical volume abnormalities are related to schizophrenia and risk thereof come from studies in patients with schizotypal personality disorders (SPD), with converging volumetric abnormalities in the hippocampus, lateral ventricle and thalamus being reported (Buchsbaum et al., 1997; Cannon, 1994; Raine et al., 1992; Fervaha & Remington, 2013). However, other studies found no differences in the thalamus volume of SPD patients when compared to schizophrenic patients or controls (Byne et al., 2001). For a review of SPD and structural neuroimaging studies, see (Dickey et al., 2002).

Taken together, these results imply that subcortical volume alterations are already observable at the earliest stages of the clinical manifestations of schizophrenia spectrum and other psychotic disorders. Nevertheless, factors such as severity of symptoms, psychological impact of hospitalizations, and antipsychotic treatment potentially contributes to the morphological modifications of the brain observed along the development of spectrum disorders (Jørgensen et al., 2016; Moncrieff & Leo, 2010; Navari & Dazzan, 2009). Thus, studying schizotypy, a personality trait conferring a liability to develop psychosis, provides a unique framework to observe neurobiological mechanisms involved in psychosis phenotypes while avoiding confounding effects of collateral factors such as medication and disease progression. When investigating adolescents from the general population experiencing subclinical psychotic (delusional and hallucinatory) experiences (SPEs), Okada and colleagues (Naohiro Okada et al., 2018) found significant volumetric enlargements in the left hippocampus, right caudate and right lateral ventricle, as well as a marginally significant enlargement in the left pallidum. The authors hypothesized that subtle volumetric alterations in the left pallidum of adolescents

with SPEs who have not reached a diagnostic level might represent a predisposing factor for developing psychosis. They also suggested that the enlargement of hippocampus volume might reflect changes as compensation to prevent conversion to higher-risk states. In another study investigating subcortical structures in relation to psychometric schizotypy, Kühn (Kühn et al., 2012a) and colleagues showed a correlation between high schizotypy total score and reductions in thalamic volume. These studies suggest that detailed examination of the associations between the expression of schizotypal personality features during adolescence and morphological brain development may reveal relevant information to understand schizophrenia spectrum and other psychotic disorders.

In terms of typical neurodevelopment, subcortical structures dynamically develop throughout childhood and adolescence and sustain functional roles including attention, memory, executive functioning and emotional processing (Hill et al., 2017). A recent study examining the normative development of subcortical structures (Wierenga et al., 2014a) (n=147, from 7 to 23 years old) suggests that the volumes of the caudate, putamen and nucleus accumbens (N.Acc) decrease with age, that the hippocampus, amygdala and pallidum showed an inverted U-shaped trajectory, and that the thalamus exhibited an initial slight increase followed by a reduction in volume. These results provide a framework for the typical developmental trajectory of the aforementioned structures and allow for a comparison with adolescents who express higher level of schizotypy.

To date, studies investigating psychometric schizotypy have employed cross-sectional designs with success in identifying cerebral alterations linked to the expression of schizotypy (Kühn et al., 2012a; Naohiro Okada et al., 2018), but their ability to provide information about developmental trajectories is limited. The present study investigates dynamic changes in subcortical structure development in relation to the three dimensions of schizotypy (positive, negative and disorganized). Specifically, we explored volumetric changes of caudate nucleus, putamen, pallidum, nucleus accumbens, thalamus, amygdala, hippocampus and lateral ventricle using longitudinal mixed regression, in 110 adolescents with one up to 5 visits. These structures are of particular interest, as they have been implicated in schizophrenia (Ballmaier et al., 2008; Mamah et al., 2008). The present prospective study examines developmental trajectories of subcortical volumes in adolescents with higher and lower levels of schizotypy traits during adolescence and will potentially reveal both a common endophenotype with CHR for psychosis states as well as potential protective factors in non-

clinical samples. Our primary hypothesis is that the developmental patterns of subcortical volumes of individuals expressing higher schizotypal features would follow that of community individuals expressing high schizotypy. Moreover, we expect that when common to developmental differences found in CHR-converters, subcortical regions alterations might convey a risk for psychosis. The value of such research question is to find the earliest cerebral signature of psychotic pathogenesis, an endeavour which might be very significant to psychopathology.

2. Materials and methods

2.1 Participants

The present study included a total of 297 MRI-scans from 110 typically developing (TD) adolescents (57 males) recruited as part of an ongoing longitudinal study. Adolescents were aged between 12 and 20 y.o at the first time of visit (mean(age)=16.0, sd= 1.5, n=110). From the 110 adolescents of the first time visit, 77 of them came back for a second visit (Mage=17.3, sd=1.8), 64 for visit 3 (Mage=18.5, sd=2.1) and 46 for visit 4 (Mage=21.1, sd=1.9, n=46), *see Figure 1*. In total, 26 participants were scanned once, 19 twice, 27 three times, 38 four times (see *supplementary Figure* 1 and *supplementary table 1* for the mean intervals between each scanning session). They were French-native speakers, community adolescents with normal or corrected to normal vision, recruited through word of mouth and advertisement in youth centres around the Canton of Geneva. They were screened for the absence of acute psychotic phase and estimated general intellectual functioning scoring below 1 standard deviation of the developmental norm (based on the Cubes and Vocabulary subtests of the Weschler Scales of Intelligence for children (WISC-IV)(Wechsler D. Wechsler, 2003) or for participants older than 18 y.o, the Wechsler Adult Intelligence Scale(Wechsler D., 1997) (WAIS-IV). Participants received a financial compensation for their time, and written consent was obtained from themselves or their parents (if they were under 18), under protocols approved by the local ethical commission (Commission Centrale d'éthique de la Recherche des Hôpitaux Universitaires de Genève). From the initial sample of 123 adolescents, 13 adolescents were excluded to ensure a psychologically and medically healthy sample, as they were diagnosed with: depression and anxiety disorders (n=8), attention-deficit hyperactivity disorder (ADHD, n=4) or schizoaffective disorder (n=1). None of our

participants was taking psychoactive treatment, see *supplementary material* for more information.

2.2 Psychological Measures

To isolate the effect of schizotypy on subcortical structures development, we covaried for potential effects of internalized and externalized maladaptive behaviors (Modinos et al., 2014). To do so we included the Youth Self Report and Adult Self Report (YSR/ASR) standardized subscale scores of externalizing and internalizing behaviors as covariates in the neuroimaging statistical analyses.

Schizotypal personality traits were evaluated with the SPQ, which define 3 dimensions (positive, negative and disorganized - see *supplementary material* for details on these measures).

2.3 Partition of participants in groups

Higher and Lower groups of participants were created based on their SPQ score at first time point for each dimension separately (positive, negative and disorganized) in order to assess the potential influence of each of them on the development of subcortical volumes. For each dimension, optimal k-means clustering for univariate data implemented in R (ck.means.1d.dp package) was conducted (see *supplementary material* for details). According to the Bayesian criterion the algorithm returned 2 clusters as the best option per dimension: one representing the adolescents with elevated scores and the second one concerning individuals with low scores on a dimension: high positive scorers (HPS) and low positive scorers (LPS), high negative scorers (HNS) and low negative scorers (LNS), high disorganized scorers (HDS) and low disorganized scorers (LDS).

2.4 MRI acquisition

Magnetic Resonance Imaging (MRI) scans were acquired on a 3-Tesla Siemens Trio scanner at the Hôpitaux Universitaire Genevois (HUG, n=228), or at the Brain Behavioral Laboratory at University of Geneva (BBL, n=81). Both sites used the same scanner and sequences of acquisition. A 3D volumetric pulse sequence was used, with the following parameters: TR =

2500 ms, TE = 3 ms, flip angle = 8°, acquisition matrix = 256 x 256, field of view = 22 cm, slice thickness = 1.1 mm, 192 slices.

2.5 MRI processing

To obtain an accurate three-dimensional cortical model, images were processed using *FreeSurfer* software version 6.0 (http://surfer.nmr.mgh.harvard.edu). Processing steps were conducted following the *Freesurfer* pipeline for fully automated preparation of images, including resampling of the surface into cubic voxels, skull stripping, intensity normalization, white matter segmentation, surface atlas registration, surface extraction and gyrus labeling. After preprocessing, each participant was registered to the spherical atlas *fsaverage* in *FreeSurfer*. For each individual, resulting white matter and pial surfaces were visually checked and manually corrected when necessary.

2.6 MRI Longitudinal processing

In order to reduce within subject variability between scan sessions, a longitudinal analysis methodological step was performed using FreeSurfer version 6.0. This method increases repeatability and statistical power (Reuter et al., 2012). All scans were processed using this procedure, including individuals with a single time point to ensure consistency of treatment for all scans (Bernal-Rusiel et al., 2013). An unbiased within-subject template and average image were created, using inverse consistent registration. This reduces the potential over-regularization of longitudinal image processing (Reuter et al., 2010).

2.7 Subcortical volumes extraction

Left and right thalamus, lateral ventricle, pallidum, accumbens, caudate, putamen, hippocampus, amygdala volumes as well as intra cranial volumes (ICVs) were obtained from the T1 pre-processed scans (see Figure 2), using Freesurfer and following the Enigma protocol for extraction of volumes' values (enigma.usc.edu) (Stein, Medland, (the Alzheimer's Disease Neuroimaging Initiative (ADNI) et al., 2012). For quality control, all regions of interest (ROIs), with a volume larger than or <1.5 times the interquartile range were identified and visually inspected by overlaying their segmentation on the subjects'

anatomical images. ROI data for which segmentation was judged accurate were included in statistical analyses (van Erp et al., 2016), no scans had to be excluded.

2.8 Statistical analyses: descriptive statistics

We performed descriptive analyses comparing participant within subgroups statistics as obtained with the schizotypy clustering methodology using Mann-Whitney U tests in SPSS version 24.0 to compare Age and cognitive variables (ASR/YSR internalized and externalized behaviors and WISC/WAIS-IV block design standardized scores). We used chi square tests to compare sex and scan locations between groups.

2.9 Statistical MRI analyses: Developmental trajectories

We performed mixed model regression analyses to examine developmental trajectories of subcortical volumes, the potential differences between high and low levels of each schizotypy dimensions, as well as the interaction between schizotypy dimensions and age. Following a previously published procedure (Mancini et al., 2019), we fitted random-slope models to our data to estimate optimal developmental trajectories considering both within-subject and between-subject effects. Briefly, the *nlmefit* function in MATLAB R2016b was used to estimate constant, linear, quadratic and cubic models. Then, the best model was selected based on the Bayesian Information Criterion (Peng & Lu, n.d.). All models included group, age, and their interaction as fixed effects. Finally, a likelihood ratio test was used to quantify significant between-group differences in the intercept and slope of resulting developmental trajectories. To perform these analyses we used in-house scripts that have been made available at https://github.com/danizoeller/myMixedModelsTrajectories.

For each analysis, sex, location of MRI scanner, ASR/YSR internalized and externalized behaviors score, ICVs, as well as Wechsler's WISC/WAIS-IV Block Design standardized score were entered as mean-centered (demeaned) covariates of no interest. We analyzed left and right hemisphere separately, and all retained results survived a threshold of $p<0.05$, corrected for multiple comparisons using False Discovery Rate FDR.

3. Results

3.1 Descriptive statistics

Are presented in Table 1 for each group of high and low scorers on the three dimensions of schizotypy. The low positive schizotypy group comprised 76 individuals and the high positive scorers consisted of 34 adolescents. The negative schizotypy groups included 68 low scorers and 42 high scorers. Lastly, the group based on the disorganized dimension consisted of 74 low scorers and 36 high scorers. All pair of groups (high VS low) differed in terms of schizotypy scores as well as internalized behaviors but not on age, block design and vocabulary subtest. Additionally, low and high positive and disorganized scorers differed on externalized mean scores.

3.2 Developmental trajectories

Significant results of the mixed models analyses for each ROI are shown in *supplementary Table 2* (all results can be found in *supplementary Tables 3 to 8*). No significant results were found when investigating the positive dimension. We observed differential linear developmental trajectories in four subcortical structures when comparing higher scorers on the disorganized and negative dimensions of schizotypy to their respective lower scorers. We showed trajectories of results that were significant at $p<.05$, corrected for multiple comparisons using the FDR criterion (see Figures 3&4).

3.2.1 Disorganized dimension (Figure 3)

Adolescents expressing higher levels of *disorganized* schizotypy (HDS) exhibited a steady developmental trajectory of bilateral hippocampus volumes, whereas LDS showed a linearly increasing volume trajectory. Notably, after 17 years of age LDS showed steeper increasing volumes trajectory of both right and left hippocampus when compared to HDS (R-hippocampus: p=0.049; L-hippocampus: p=0.023).

We found a similar pattern concerning the left pallidum with LDS showing a steeper increasing trajectory than HDS. Both trajectories followed a linear increase, however the enlargement trajectory was more pronounced in LDS (p=0.006).

Concerning the left lateral ventricle (p=0.025), we found the opposite pattern, with a steeper linearly increasing trajectory in adolescents who scored higher on disorganized schizotypy. Once again, the trajectories seem to cross at 17 years old, the LDS group followed a relatively constant trajectory, whereas after this age, the lateral ventricle in the HDS group showed a steeper enlargement.

3.2.2 Negative dimension (Figure 4)

Concerning the *negative* dimension of schizotypy, lower scorers presented a stronger linearly increasing trajectory of bilateral pallidum volumes (right-pallidum: p<0.000; left-pallidum: p=0.010) when compared to HNS. Once again, we observed a change around 17 years of age, where HNS exhibited lower rate of increasing volumes than LNS passed this age.

When looking at the right thalamus (group effect, p=0.006), we identified similar patterns of developmental volume trajectories. Both HNS and LNS had constant trajectories, and volumes were larger in HNS than LNS throughout the entire investigated age range.

4. Discussion

We investigated the developmental trajectory of subcortical brain structures in adolescents expressing higher schizotypal traits compared to matched adolescents without such traits. Importantly, with our adolescents coming on a voluntary basis from the general population, we measured a mild variant of schizotypal features less pronounced than in clinical samples. However, our strategy was to focus on the developmental antecedents of the clinical states that can ensue during adulthood. We observed differential linear trajectories in four different subcortical structures when comparing higher disorganized and higher negative dimension scorers to their corresponding lower scorers. Expression of higher level of disorganized schizotypy was associated with differential trajectories of the hippocampus bilaterally, the left pallidum and lateral ventricle. On the other hand, higher levels of negative schizotypy were associated with differences in trajectories within the pallidum bilaterally, and with globally reduced volumes over the entire age range in the thalamus. With the present longitudinal study, we sought out to characterize which subcortical volumes differences were associated with a vulnerability to develop schizophrenia spectrum disorders to those linked to inter-individual variability of the schizotypy trait and/or a compensatory process. Convergence with findings in clinical populations, notably CHR-converters may be indicative of processes

involved in pathogenesis, but divergence may be indicative of protective/resilience factors or variability in term of personality traits.

[Reduced volumes of hippocampus are observable in relation to disorganized schizotypy]
Previous research consistently reports that hippocampus volumes are significantly reduced in schizophrenia patients (Huang et al., 2015; Spoletini et al., 2011), as well as in their non-psychotic relatives (Bois et al., 2016). In addition, longitudinal studies have provided evidence for progressive reductions in the hippocampus of individuals at clinical high risk compared to controls, suggesting that alterations to this structure may form part of a general vulnerability to schizophrenia (Pantelis et al., 2003; Walter et al., 2012). In the present study, high scorers on disorganized schizotypy were lacking a developmental increase that was present in low scorers, leading to a tendency for reduced hippocampal volumes at the end of adolescence. This suggests a similarity with schizophrenia spectrum disorders, and notably with individuals at clinical high risk of developing psychosis, thus representing a potential vulnerability feature. Reinforcing this idea, CHR participants who subsequently convert to psychosis are reported to show hippocampal hypermetabolism which predicts hippocampal volume loss (Schobel et al., 2009). On the other hand, the increasing developmental trajectory observed in the lower scorers is in line with previous research indicating a robust maturational process in healthy individuals resulting in linear increase of hippocampal volumes along adolescence (Gogtay et al., 2004; Suzuki et al., 2004); (Giedd et al., 1996). As similar longitudinal abnormalities of hippocampal volumes are observable in CHR individuals, they could potentially represent an increased predictive risk to develop psychosis rather than being specific to illness-related mechanisms.

[Enlargement of lateral ventricle is associated with disorganized dimension of schizotypy]
Enlarged volume of left-lateral ventricle found in adolescents with HDS are concordant with large scale studies of schizophrenia (Naohiro Okada et al., 2018; van Erp et al., 2016), FEP (Ellison-Wright et al., 2008) patients, as well as in adolescents with SPEs (Naohiro Okada et al., 2018). However, in FEP patients, some contradiction exist, as longitudinal studies have showed a progressive enlargement occurring after the first episode and especially within the first years of illness (Kempton et al., 2010). Thus, the question arises whether ventricular dilation was a progressive change beginning in the prodromal phase of the illness, or an abnormal developmental process starting closer to birth with progressive changes through life. Our results lend support to the latter hypothesis suggesting that ventricular enlargement seems

to be progressive, and present at the earliest stages of the spectrum as it is already observable in adolescents expressing higher levels of disorganized schizotypy. Opposite findings in favor of the prodromal-start to enlargement could be explained in terms of modulation of trajectories by psychotic episodes, periods of remission and antipsychotic treatment (Garver & Kingsbury, 2000).

[Decreased volume of the pallidum was found in relation to disorganized and negative dimension]

The pallidum, enlarged in chronic schizophrenia (N Okada, 2016) was found to be decreased in our study in HDS (left-pallidum) as well as in HNS (bilateral pallidum) when compared to their respective low scorers. However, normal pallidal volumes were demonstrated in drug-naïve (Spinks et al., 2005) schizophrenia patients, FEP (Lang et al., 2001) and CHR (Harrisberger et al., 2016b). Our results concerning the trajectory of low scorers on both dimensions follow a linearly increasing trajectory that resemble the first part of the typical inverted U shaped trajectory found in healthy adolescents (Wierenga et al., 2014a). Therefore, we could suggest that the subtle volumetric decrease exhibited in higher scorers may only reflect inter-individual variability. Moreover, pallidum alterations did not seem to be specifically linked with the negative or disorganized dimension of schizotypy, whereas they were found to be associated with processing speech alterations and negative symptoms in patients with schizophrenia (Mwansisya et al., 2013).

[Increased thalamic volumes are observable in high negative schizotypy]

Studies involving typical adults have observed a trend (no correction for multiple comparison) of negative association between schizotypy total score and thalamic volumes (Kühn et al., 2012b), compatible with reports of thalamic volume reductions in samples of individuals with schizophrenia (Ettinger et al., 2001), FEP (Adriano et al., 2010) and antipsychotic-naïve CHR (Harrisberger et al., 2016b). In contrast, in the present study, adolescents expressing higher level of negative schizotypy presented increased volumes of the thalamus when compared to lower scorers, consistent with the inverted U-shaped developmental trajectory observable in typically developing children and adolescents (Wierenga et al., 2014b) (7 to 24y.o). Those differences may be explained in terms of age, as our population included only adolescents, as well as by the fact that we studied the dimensions separately. Moreover, it is not clear whether reduced thalamic volumes documented by imaging studies pertains to any specific nuclei of the thalamus. In the literature the question also arises whether thalamic reductions may

represent an intermediate phenotype of presumed inherited vulnerability to schizophrenia (Allen et al., 2009). Thalamic structural volume decreases are observable early in the CHR population, but not in typical adolescents expressing higher level of negative schizotypal traits. Thus, we could also hypothesize that structural abnormalities of the thalamus might be subsequent to negative symptoms expression.

[Limitations]
Some limitations should be acknowledged. First, we looked at the whole volume of the different subcortical structures, rather than the substructures that compose them. Secondly, we included the whole period of adolescence, however, pubertal stages are known to greatly influence the development of subcortical structures, and therefore it could be promising to consider only the prepubertal stage. Secondly, we used a self-rated instrument (SPQ) to measure schizotypy; future studies should include an observer rater (i.e. interviews). While longitudinal schizotypal traits studied in the general population are still a burgeoning field, further research using larger cohorts is required. We contend that enhanced longitudinal characterization (with more time points or following the converters to psychosis) will prove fruitful grounds for replication and for discovering developmental processes that may be used as risk markers of impending disorders.

[Conclusion]
We described developmental trajectories of a number of subcortical structures using mixed model regression longitudinal analyses in a population of typically developing adolescents. Moreover, we identified disorganized personality traits of schizotypy associated with developmental trajectories of subcortical volumes and found similar pattern than those identified along the schizophrenia spectrum, notably the hippocampus and lateral ventricle. Higher levels of disorganized schizotypy identified during adolescence seemed to be linked to subtle developmental changes reflecting a neural signature at the non-clinical level. We additionally identified differences in trajectory patterns to those seen along the spectrum, notably decreased pallidum and increased putamen volumes which should be further investigated in clinical population to be interpreted as potential protective compensatory factors.

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Contributors

Author Melodie Derome designed the study and managed the literature search, statistical analyses and wrote the manuscript. Author Daniela Zöller developed the script for mixed models regression analyses. All authors contributed to and have approved the final manuscript.

Conflicts of interest

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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