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Dopamine-Induced Dysconnectivity Between Salience Network and Auditory Cortex in Subjects With Psychotic-like Experiences: A Randomized Double-Blind Placebo-Controlled Study

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Dopamine is involved in the pathophysiology of schizophrenia. Disrupted salience processing by the salience network (SN) may be a central link between dysregulated dopamine function and psychotic symptoms. However, dopaminergic influence on the SN and its presumed influence on psychotic and subpsychotic symptoms or psychotic-like experiences in healthy individuals remain unclear. Therefore, we investigated dopamine-induced changes in functional connectivity of the right anterior insula (rAI), a central SN hub, and their association with psychotic-like experiences. We enrolled 54 healthy, right-handed male subjects in a randomized, double-blind, cross-sectional placebo-controlled experiment. Psychotic-like experiences were assessed using the revised Exceptional Experiences Questionnaire (PAGE-R). They then received either placebo (n = 32) or 200 mg L-DOPA (n = 33), a dopamine precursor, orally and underwent resting-state functional magnetic resonance imaging. In a seed-to-voxel approach, we analyzed dopamine-induced changes in functional connectivity of the rAI and assessed the relationship between functional connectivity changes and PAGE-R score. L-DOPA reduced functional connectivity between the rAI and the left auditory cortex planum polare. In the placebo group, we found a strong negative correlation between PAGE-R score and rAI to planum polare functional connectivity; in the L-DOPA group, there was a strong positive correlation between PAGE-R score and functional connectivity between rAI and planum polare. The PAGE-R score explained about 30% of the functional connectivity variation between rAI and planum polare in the two groups. Our findings suggest that psychotic-like experiences are associated with dopamine-induced disruption of auditory input to the SN, which may lead to aberrant attribution of salience.

Key words: functional connectivity/resting-state functional magnetic resonance imaging/L-DOPA/exceptional experiences/salience/planum polare

Introduction

Schizophrenia is a disabling mental disorder affecting about 1% of the world's adult population.[1,2] It has been studied thoroughly and a few dominant theories of its pathophysiological underpinnings have emerged in the last decade. One of them is the concept of a psychosis continuum, where, at the one end, there are serious clinical psychotic syndromes and, at the other, there are mild psychotic-like experiences. The latter have been the subject of recent research, as they are thought to be representative of schizophrenia in its earliest pathophysiological stages.[3,4] Consistently, brief limited and intermittent psychotic symptoms appear to be an early indicator of psychosis onset.[5] While most studies on exceptional experiences do not specify schizophrenic subtypes, ie, positive, negative, or disorganized,[6] some research on predominantly "positive-like" experiences results from studies on exceptional experiences. These are defined as deviations from ordinary experiences or from experiences that are consistent with typical "reality models"—in the form of delusions, hallucinations, or odd beliefs.[7,8]

Dopamine plays a major role in the pathophysiology of schizophrenia and, especially, its positive symptoms.[9,10] It has been suggested that disrupted salience processing is a central link between dysregulated dopamine function and psychotic symptoms.[11] The imbalance of dopamine, as well as dopamine receptor hypersensitivity in psychosis,

may lead to an aberrant assignment of salience to the elements of one's experience.[12] Delusions might represent a cognitive effort to make sense of these aberrantly salient experiences, whereas hallucinations might reflect a direct experience of the aberrant salience.[13]

It has been postulated that two different kinds of salience exist: motivational salience, representing the assignment of a motivational value to the external object or internal representation once a stimulus is evaluated,[13] and proximal salience, referring to a momentary state generated by evaluation of external or internal stimuli in the context of interoceptive awareness, preceding subsequent choice of action.[14] Whereas the concept of motivational salience has been associated with the striatum, the concept of proximal salience has been associated with the right anterior insula (rAI) and anterior cingulate (ACC).[14]

Resting-state functional magnetic resonance imaging (rs-fMRI) studies have revealed consistent functional brain networks of regions with correlated neural activity across time.[15] The salience network (SN) and the default mode network show disturbed functional connectivity along the whole psychosis continuum.[16–18] As part of the SN, the rAI is involved in the detection and processing of salient events[19–21] and its functional connectivity networks are regularly altered in schizophrenia.[14] There has been evidence of reduced gray matter, as well as of changes in functional connectivity in resting-state and during task-based fMRI.[18,22–24] The SN is also known for its critical role in modulating the default mode network during cognitively demanding tasks, which seems to be disturbed in various stages of the schizophrenic spectrum.[23,25] On the lower end of the continuum, even patients experiencing auditory hallucinations show altered connectivity within the SN.[26,27] In addition, rAI resting-state functional connectivity is correlated to symptom severity.[28] These reductions in network integrity may result in interrupted information processing. One consequence thereof has been suggested to be abnormal processing of external and internal sensory stimuli, which are perceived as abnormally salient.[29]

While converging evidence suggests that SN dysfunction in schizophrenia is likely to be associated with dopaminergic abnormality, no studies have examined the link between functional connectivity of the SN and dopamine in psychosis.[14,30] Some studies have shown a change in functional connectivity originating from the striatum after L-DOPA application.[31,32] The rAI and ACC are extrastriatal regions with high dopamine transporter concentration.[33] Further, dopaminergic activity in the striatum may directly influence SN connectivity.[30]

Here, we explored the effect of increased dopamine availability by L-DOPA administration on SN modulation and the development of subthreshold psychosis. We assessed exceptional experiences using the revised Exceptional Experiences Questionnaire (PAGE-R)[34] in 54 healthy, right-handed men and used a randomized, double-blind placebo-controlled design, in which we administered L-DOPA or placebo orally and, finally, analyzed changes in resting-state functional connectivity of the SN.

We hypothesized that (1) in the placebo group individuals with high PAGE-R scores would show a disruption of functional connectivity from the SN as has been reported in schizophrenia; that (2) SN connectivity would be disrupted by increased availability of dopamine after L-DOPA administration; and that (3) the L-DOPA induced changes in functional connectivity correlate with the PAGE-R score.

Methods

Subjects

As part of a larger project investigating exceptional experiences, 65 right-handed men (20–40 years old; Caucasian) were selected from a sample of 1580 persons representative of the Swiss population in terms of gender, age, and education.[34] Exclusion criteria were current intake of psychotropic drugs, own or first-degree family members' history of psychotic spectrum disorders (ie, psychosis or schizophrenia), as well as current disorders as assessed by the Mini-International Neuropsychiatric Interview,[35] acute or chronic disease of the nervous system, traumatic brain injury with lasting damage, and strong cigarette craving.

The study was approved by the canton of Zurich ethics committee (KEK-ZH-Nr. 2011-0423) and carried out according to the guidelines of Good Clinical Practice. Participation comprised two sessions (3 h each), and subjects received CHF 200 (approx. USD 200) after completion of the second visit. The canton of Zurich pharmacy carried out randomization and double-blinding procedures.

The L-DOPA group consisted of 33 subjects and the placebo group of 32 subjects. After rs-fMRI scanning, 11 of the original 65 participants were excluded from further analysis: three due to incomplete psychometric questionnaires, two because of a pathological Mini-International Neuropsychiatric Interview before testing, and six because of erroneous rs-fMRI sequence setup. According to protocol, the remaining 54 subjects stayed in their designated group. Groups did not differ significantly regarding age and intelligence (table 1).

Subjects were instructed not to take drugs or drink alcohol 24 h before, not to eat 3 h before, and not to smoke for 1 h before the experiment. All scans were done in the afternoon, between 2 PM and 4 PM. Prior to subjects receiving either 200 mg L-DOPA and 50 mg Benserazide in a dual-release formulation (Madopar DR, Roche Pharma AG), a block of assessment tasks and questionnaires was administered. Twenty minutes after capsule ingestion, subjects received a standardized sandwich,[36]

Table 1. Demographic characteristics. Age, estimated intelligence, education, and psychometric ratings of the L-DOPA group and the placebo group are shown. All participants were male and right handed. Data are reported as mean ± SD or median (interquartile range). Premorbid intelligence was determined by extrapolating IQ values via Mehrfachwahl–Wortschatz Intelligence Test (MWT-B). Psychometric ratings are from the Revised Exceptional Experiences Questionnaire (PAGE-R) and its three subscores

	L-DOPA	Placebo	*P* value
n	30	24	
Age (years)	28.1 ± 4.9	27.4 ± 4.4	.54*
Estimated intelligence (IQ)	110.9 ± 13.4	113.7 ± 9.5	.59**
Education (years)	14.0 (12.0 to 15.0)	15.0 (13.3 to 16.5)	.25***
PAGE-R score	11.0 (4.8 to 29.3)	9.5 (4.0 to 27.8)	.50***
Odd beliefs subscore	7.5 (3.0 to 14.0)	4.0 (1.3 to 12.0)	.24***
Dissociative anomalous perceptions subscore	1.0 (0.0 to 3.0)	0.5 (0.0 to 3.0)	.63***
Hallucinatory anomalous perceptions subscore	2.0 (0.0 to 4.0)	2.0 (0.0 to 4.8)	.40***

Group difference assessed by *independent-samples *t* test, **Welch's *t* test, or ***Mann–Whitney *U* test.

followed by more behavioral testing. MRI scanning started after 100 min, commencing when the drug was at its estimated maximal serum concentration with stable levels thereafter for approximately 1 h.[37] The psychological, somatic, and motor (adverse) effects of the drugs were assessed through subjective ratings after the testing session ended.

Measurement of Psychotic-like Experiences

Exceptional experiences were assessed using the German "Revidierter Fragebogen zur Erfassung der Phänomenologie Aussergewöhnlicher Erfahrungen" (PAGE-R, English revised Exceptional Experiences Questionnaire).[34,38] Assessment took place before undergoing the fMRI scan and reflected on the participants' exceptional experiences in the time before the study. The PAGE-R assesses the frequency of 32 exceptional experiences on five-point Likert-scales ranging from 0 (*never*) to 4 (*very often*). Factor analysis of the PAGE-R has shown three subscales depicting: (1) odd beliefs, comprising experiences such as seeing meaning in coincidences or the anticipation of future events, (2) dissociative anomalous perceptions, encompassing, eg, the autonomous activity of body parts or the alienation to one's own personality, and (3) hallucinatory anomalous perceptions, referring to experiences such as hearing inexplicable noises or different hypnagogic perceptions.[8]

Resting-State Data Analysis

Details on the acquisition of the image data are available in supplementary appendix 1. After the first 10 frames were removed to allow for signal equilibration, the data were preprocessed using the CONN-fMRI functional connectivity toolbox v16 (http://www.nitrc.org/projects/conn; accessed October 3, 2016).[39] The steps included realignment, slice-timing correction, co-registration to structural T1-scan, spatial normalization to Montreal Neurological Institute (MNI) coordinates space, and spatial smoothing (6-mm Gaussian kernel). The structural scans were segmented per the unified segmentation approach that utilized Statistical Parametric Mapping (SPM8 Package) default values. None of the participants had to be excluded due to excessive head motion (linear shift <2.5 mm across and, on a frame-to-frame basis, rotation <2.5°). Frames with movement >0.5 mm or a global signal *z* score change >3 were identified with artifact detection, scrubbed, and excluded from analyses.[40] Residual data were band pass filtered (0.009–0.080 Hz). Further exclusion criteria were if >50% of the frames were contaminated by movement or if the mean framewise displacement exceeded 2 mm. No scans met these criteria. Spurious sources of noise, such as heart rate and respiration signals, were first estimated by the anatomical component base noise reduction (aCompCor) strategy and then included with the head movement parameters as nuisance regressors in a general linear model (GLM). The aCompCor algorithm does not rely on global signal regression, which can artificially introduce negative correlations.[41]

To compare our results with existing functional connectivity findings, we used a previously determined 8-mm radius sphere seed region of interest (ROI) of the rAI (MNI coordinates: $x = 38$ mm, $y = 22$ mm, $z = -10$ mm) based on earlier studies.[19,42–44] Accordingly, the SN consisted of the correlation with the rAI.[15,23,45] No other seeds were considered in this analysis.

A seed-to-voxel correlation map for each subject was computed using a weighted GLM for bivariate-weighted correlations. To investigate differences in functional connectivity from the rAI seed between the L-DOPA group and the placebo group, we processed the data via one-way ANCOVA, which controlled for covariation of total PAGE scores. Thus, the ANCOVA would be more sensitive particularly in cases where the variability associated with score differences might be large compared with the between-group differences. For further assessment of associations between L-DOPA-induced connectivity and PAGE scores, the analyses included only regions that showed significant differences in functional

connectivity between treatment groups (height threshold: *P*-uncorrected <.001, cluster threshold *P*-family-wise error rate (FWE) corrected <.05, two-sided statistics). The actual connectivity values for each subject within this supra-threshold cluster were then imported into a post hoc linear regression analysis. This enabled us to use a regression model to display absolute L-DOPA-induced alterations in functional connectivity and their Spearman's rank-order correlation to the PAGE-R as well as its subscores. Using the Fisher *r*-to-*z* transformation, we then assessed the significance of the difference between the two correlation coefficients. As the PAGE-R total score and three subscores are analyzed separately, a Bonferroni-adjusted *P* value of less than .0125 was considered to indicate statistical significance. The coordinates are presented in MNI space.

For the descriptive data and for the PAGE-R scores, normal distribution was assessed by Shapiro–Wilk test. Normally distributed data are presented as mean ± SD, otherwise as median (interquartile range). Group differences of normally distributed data were calculated with an independent-samples *t* test or Welch's *t* test, dependent on the *F* test for equality of variances. Group differences of nonnormally distributed data were assessed by Mann–Whitney *U* test. Blinding efficacy was assessed by chi-square test.

Results

Participants

Baseline patient characteristics, including age and estimated intelligence, were well balanced between L-DOPA and placebo groups. All recruited participants were male and right handed. In addition, the distribution of the PAGE-R score was similar (table 1). However, because our sample consisted of healthy subjects, the distribution of total PAGE-R scores and subordinate scores skewed to the left (supplementary figure 1).

To check the efficacy of the blinding, we then asked subjects to guess which substance they had received and found that 18 were correct (10 L-DOPA/8 Placebo group) and 31 were incorrect (15 L-DOPA/16 placebo group). Five subjects chose not to answer. Chi-square analysis revealed that this difference was not significant ($\chi^2(1) = 3.50$, $P > .05$).

Effect of L-DOPA Administration on SN

The one-way ANCOVA, controlled for covariation of the total PAGE-R score, was used to identify regions with L-DOPA vs placebo group differences in functional connectivity from the rAI. A significant decrease in functional connectivity was found between the rAI and a cluster corresponding to the left planum polare (−36, +0, −24 mm; cluster size = 234 voxels; cluster-size *P*-FWE = .003) (figure 1).

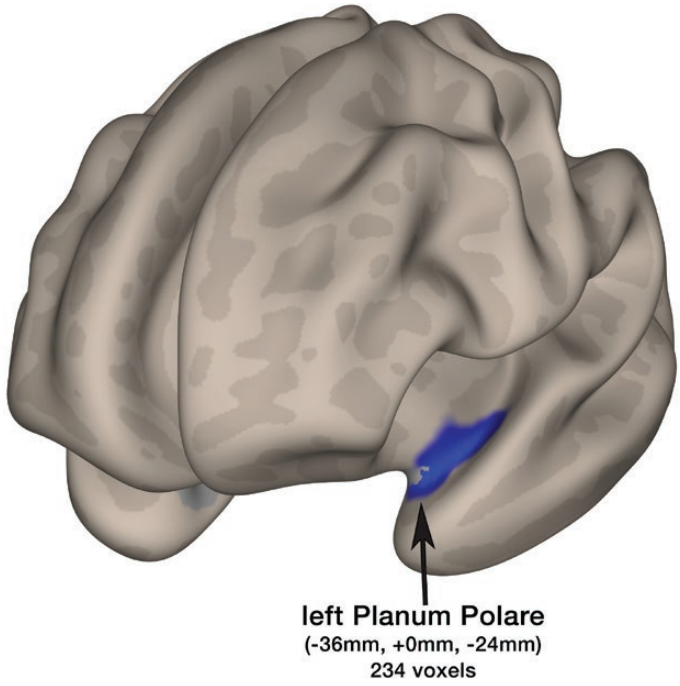

Fig. 1. Seed-to-voxel analysis from the right anterior insula to identify regions with L-DOPA vs placebo group differences in functional connectivity. A significant decrease in functional connectivity was found between the right anterior insula and a cluster corresponding to the left planum polare (−36, +0, and −24 mm; cluster size = 234 voxels; cluster-size *P*-FWE = .003).

Spearman's Correlation of Dopamine Modulated Connectivity and PAGE-R

A Spearman's rank-order correlation was run to assess the relationship between absolute rAI to planum polare connectivity values and PAGE-R scores in both the L-DOPA and placebo group. In the L-DOPA group, there was a statistically significant, moderate positive correlation between rAI to planum polare connectivity and total PAGE-R score, $r_s(98) = .514$, $P = .004$. In the placebo group, there was a statistically significant, moderate negative correlation between rAI to planum polare connectivity and total PAGE-R score, $r_s(98) = -.501$, $P = .012$. Fisher *r*-to-*z* transformation determined these correlation coefficients to be significantly different ($z = 3.85$, two-tailed $P < .001$; figure 2A).

The correlation of the PAGE-R odd beliefs subscores with rAI to planum polare connectivity presented itself in a similar manner, Bonferroni-adjusted, not significant, moderate negative correlation in the placebo group [$r_s(98) = -.452$, $P = .026$] and significant, moderate positive correlation in the L-DOPA group [$r_s(98) = .539$, $P = .002$], with a significant difference between the two correlation coefficients ($z = 3.75$, two-tailed $P < .001$; figure 2B).

The same relationship was shown for the correlation of the PAGE-R dissociative anomalous perceptions subscore and rAI to planum polare connectivity, with a significant,

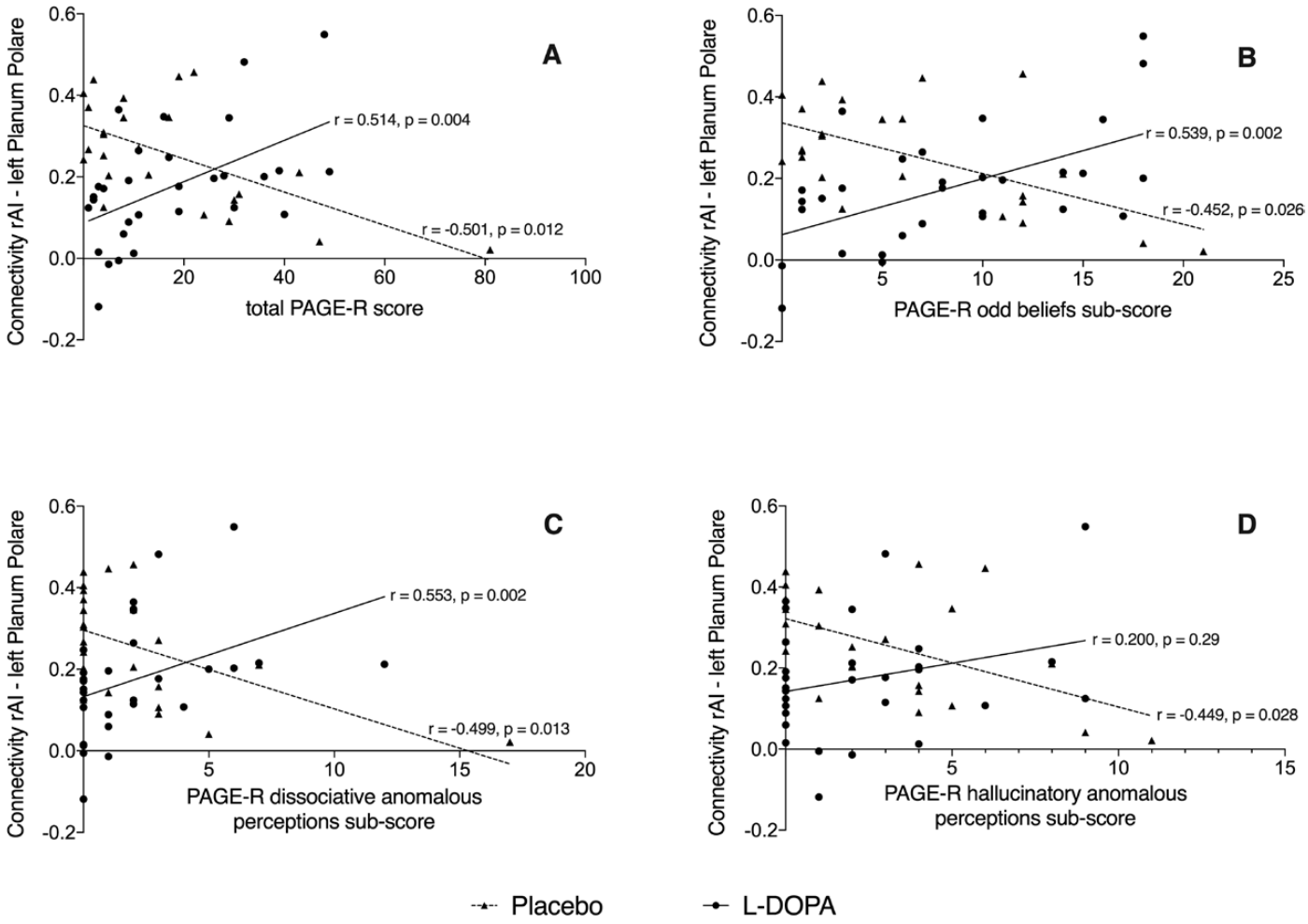

Fig. 2. Spearman's rank-order correlation was run to assess the relationship between individual rAI to planum polare connectivity values and Revised Exceptional Experiences Questionnaire (PAGE-R) scores in both the L-DOPA and placebo group. (A) The total PAGE-R score (max. possible score = 128), (B) the PAGE-R odd beliefs subscores (max. possible score = 44), (C) the PAGE-R dissociative anomalous perceptions subscore (max. possible score = 36), and (D) the PAGE-R hallucinatory anomalous perceptions subscore (max. possible score = 44).

moderate negative correlation in the placebo group [$r_s(98) = -.553$, $P = .002$] and a Bonferroni-adjusted, not significant, moderate positive correlation in the L-DOPA group [$r_s(98) = .499$, $P = .013$]. Consequently, there was also a significant difference between the L-DOPA and the placebo group correlation coefficients ($z = 3.80$, two-tailed $P < .001$; figure 2C).

In the placebo group, there was a Bonferroni-adjusted, not statistically significant, moderate negative correlation between rAI and planum polare connectivity and total PAGE-R hallucinatory anomalous perceptions subscore, $r_s(98) = -.449$, $P = .028$. However, no statically significant relationship was observed in the L-DOPA group for the correlation of the PAGE-R hallucinatory anomalous perceptions subscore, $r_s(98) = .200$, $P = .29$. Fisher r-to-z transformation determined the two correlation coefficients not to be significantly different on a Bonferroni-adjusted level ($z = 2.36$, two-tailed $P = .018$; figure 2D).

Discussion

Here, we explored the role of the SN under dopamine stimulation and its association with exceptional experiences within a healthy population. We applied seed-to-voxel connectivity analysis to rs-fMRI data to investigate abnormalities in functional connectivity of the SN after a dopaminergic challenge and its interaction with psychometrically assessed exceptional experiences. Compared to placebo, we found a significant reduction in functional connectivity from the rAI to the left planum polare after L-DOPA administration. The left planum polare is part of the superior temporal gyrus corresponding to the auditory cortex.[46] More importantly, we found that changes in functional connectivity correlated with increased exceptional experience scores: a negative correlation in the placebo group and a positive correlation in the L-DOPA group. In the placebo group, subjects with low exceptional experience scores showed functional connectivity

between the rAI and the left planum polare, which deteriorated with increasing exceptional experiences scores. After L-DOPA, subjects with low exceptional experiences scores showed connectivity between the rAI and the planum polare, but the functional connectivity increased with larger exceptional experience scores. Subgroup analysis of the three PAGE-R subscores yielded heterogenous significance after Bonferroni adjustment. However, with consistently medium to strong effect sizes and uniform association tendencies, this primarily implies an insufficient power of our sample for multiple subgroup analyses. While strong, significant correlation is shown for the total PAGE-R score, the associations in the subscores seem to be more nuanced and warrant further investigation.

To our knowledge, no studies have examined the influence of dopamine on functional connectivity of the SN in healthy subjects in association with exceptional experiences. One study has shown that striatal dopaminergic availability influences SN connectivity in healthy subjects, where greater striatal dopamine release capacity was associated with weaker SN functional connectivity.[30]

Although the positive, negative, and disorganized symptoms of schizophrenia are thought to be represented in psychotic-like experiences,[3] exceptional experiences primarily reflect aspects of delusions and hallucinations or "positive symptoms."[8] A study investigating a form of exceptional experiences (ie, auditory hallucinations) examined resting-state functional connectivity of the rAI and the ACC and showed changes in functional connectivity from these regions to left-hemisphere auditory and language regions, such as the superior temporal gyrus.[47] In auditory hallucinations, it has already been suggested that they may be originating in an abnormal modulation of the auditory cortex by resting-state networks like the SN.[48] Changes in SN functional connectivity have also been observed during the occurrence of other nonauditory hallucinations.[27] The nature of auditory and other hallucinations is particularly similar to the exceptional experiences represented in the hallucinatory anomalous perceptions subscore. However, while the association of functional connectivity and severity of exceptional experiences scores was weaker for the hallucinatory anomalous perceptions subscore in the placebo group, there was no correlation in the L-DOPA group. This implies that, while hallucinatory anomalous perceptions may be similarly correlated to functional connectivity as the PAGE-R total score and the other subscores, they react differently to a dopaminergic challenge.

While we found a negative correlation between rAI to planum polare connectivity and total PAGE-R score in the placebo group, the L-DOPA group showed a positive correlation. In schizophrenia, the dopaminergic system has been shown to be dysfunctional, which may imply that the effects of L-DOPA on functional connectivity in people with psychotic-like traits are likely to differ from those seen in people with low PAGE-R score with a normal dopaminergic system.[49] Thus, depending on the baseline level of available dopamine, the administration of L-DOPA in persons with a low PAGE-R score may decrease connectivity between these areas, whereas, in persons with higher PAGE-R scores, L-DOPA could increase the connectivity. Understanding the exact relationship between exceptional experiences and baseline endogenous as well as exogenous dopamine, and subsequent processes, may not be straightforward because the relationship between dopamine and psychotic-like traits might be nonlinear. Further, seed-to-voxel analyses do not allow for interpretation of directional connectivity and causality modeling. It may be that the increase of connectivity with the PAGE-R in the L-DOPA group reflects a directional connectivity, inverse of the connectivity in the placebo group. Similar directional fMRI connectivity from the auditory cortex to the default mode network has been shown.[50] Our findings may imply an analogous relationship to the SN. It has been suggested that the auditory cortex may act as both a feedforward and feedback station in sensory processing that influences salient discrimination of sounds.[51–53] Thus, our study highlights a novel focus of investigation, making further research into the specific effect of dopamine on directional SN connectivity necessary.

Apart from its main hub, ie, the rAI, the SN also includes striatal regions as part of the dopaminergic system.[45] Striatal regions are important in assigning novelty and significance to sensorimotor and mental events.[12] Previously, we found that L-DOPA induces change in functional connectivity from the striatum to the fusiform gyrus in a way similar to that induced by schizotypal traits.[31] Thus, it is intriguing that both seeds, the striatal and the insular, which are both involved in salience processing, are aberrantly coupled to regions that lie in sensory areas, the planum polare, as part of the auditory cortex in the current study, and the fusiform gyrus, as part of the visual cortex in the earlier study.[31] This suggests that dopamine induces changes to functional connectivity between the salience and striatal network and sensory cortices in subjects on the healthy end of the psychosis spectrum. Our results support the dopamine hypothesis of schizophrenia, where dopaminergic regulation of salience is pathophysiologically essential to the development of schizophrenia spectrum disorders.[9] Palaniyappan et al[54] suggest that disturbance of proximal salience could play a major role in the generation of prodromal symptoms in schizophrenia. The generation of proximal salience, as opposed to motivational salience, is assumed to be prompted by the rAI.[14] Thus, hallucinatory associated perceptions as represented by the hallucinatory anomalous perceptions subscore may be experienced due to false allocation of proximal salience to primary sensory regions.[55] The aberrancy of subjects scoring high on psychometric

exceptional experiences in coupling due to dopaminergic stimulation in our study, thus, supports the proximal salience theory.[14,23]

It has been suggested that the SN is responsible for switching between the default mode network and the task-positive network.[56] It has also been shown in rs-fMRI that these two usually anticorrelated networks lose their anticorrelation in subjects at risk for psychosis.[23] The role of the rAI has been summarized in the insular modulation hypothesis, which postulates that functional and structural deficits in the insula induce the occurrence of hallucinations by wrongfully switching between the default mode network and the central executive network. This could then lead to perturbance between the attention to the inner and the outer state, leading to aberrant salience processing.[21,56,57]

Our study has limitations. We included male subjects only, which increases internal but limits external validity. Further, the PAGE-R scores represent composites of frequency (by rating) and intensity (by description of the experiences). Although quality and frequency of psychotic-like experiences can be discussed separately on a conceptual level and would be interesting to analyze as such, it is more challenging to truly separate them psychometrically. Furthermore, we utilized only one seed representing the SN to minimize the number of seed-based correlational analyses. This restricted our investigation to functional connectivity between one seed representing the SN and the rest of the brain. However, and in return, this allowed us to test our hypotheses without inflating the number of false positives. Future research should involve longitudinal, higher-powered studies with within-subject designs to assess changes in functional connectivity over time as sporadic exceptional experiences might consolidate into more severe symptoms or transition into schizophrenia.[58,59]

In conclusion, our study supports the importance of sensory input to the SN: dopamine-related dysfunctional SN to sensory cortex functional connectivity might lead to excessive salience attribution to internal experiences. This could consequently result in exceptional experiences, a consequence of which could be the development of delusions and hallucinations as observed in schizophrenia.[60,61]

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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Conflict of interest

The authors declare no conflicts of interest in relation to the subject of this study.

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