Schizophrenia Bulletin vol. 51 no. S2 pp. S173–S182, 2025
https://doi.org/10.1093/schbul/sbae171

SUPPLEMENT ARTICLE

Amygdala Function, Blood Flow, and Functional Connectivity in Nonclinical Schizotypy

Igor Nenadić[1,2,3,4,*], Jonas Hoffmann[1], Andrea Federspiel[5,6], Sebastian Walther[5,7], Ahmad Abu-Akel[8,9], Andreas Jansen[1,2,10], and Tina Meller[1,2]

[1]Cognitive Neuropsychiatry Laboratory, Dept. of Psychiatry and Psychotherapy, Philipps-Universität Marburg, Marburg 35039, Germany; [2]Center for Mind, Brain, and Behavior (CMBB), University of Marburg and Justus Liebig University Giessen, Gießen, Germany; [3]Marburg University Hospital – UKGM, Marburg, Germany; [4]LOEWE Center DYNAMIC, University of Marburg, 35032 Marburg, Germany; [5]Translational Research Center, University Hospital of Psychiatry and Psychotherapy, University of Bern, Bern, Switzerland; [6]Institute of Diagnostic and Interventional Neuroradiology, Inselspital, Bern University Hospital, and University of Bern, Bern, Switzerland; [7]Department of Psychiatry, Psychosomatics, and Psychotherapy, Center of Mental Health, University Hospital of Würzburg, Würzburg, Germany; [8]School of Psychological Sciences, University of Haifa, Haifa, Israel; [9]The Haifa Brain and Behavior Hub, University of Haifa, Haifa, Israel; [10]Core Facility BrainImaging, Medical School, Philipps-Universität Marburg, Marburg, Germany

[*]To whom correspondence should be addressed: Cognitive Neuropsychiatry Laboratory, Dept. of Psychiatry and Psychotherapy, Philipps-Universität Marburg, Rudolf-Bultmann-Str. 8, Marburg 35039, Germany; tel: +49 6421 58 65002, fax: +49 6421 58 68939, e-mail: nenadic@staff.uni-marburg.de

***Background and Hypothesis*: Schizotypy can be utilized as a phenotypic risk marker for schizophrenia and its spectrum and might relate to putative dimensional biological markers of the psychosis spectrum. Among these are amygdala function and structure, which are impaired in schizophrenia, but possibly also correlated with subclinical expression of schizotypy in nonclinical samples. We tested whether different parameters relating to amygdala function would be different in healthy subjects with relatively higher vs lower schizotypy traits. *Study Design*: Sixty-three psychiatrically healthy subjects (42 with higher vs 21 with lower schizotypy scores, selected on the basis of the Oxford-Liverpool Inventory of Feelings and Experiences positive schizotypy subscale) underwent a multimodal imaging protocol, including functional magnetic resonance imaging (fMRI) during a task-based emotional (fearful) face recognition paradigm, arterial spin labeling for measurement of regional cerebral blood flow (rCBF) at rest, and resting-state fMRI for functional connectivity (FC) analyses, as well as a T1-weighted structural MRI scan. *Study Results*: The high schizotypy group showed significantly higher right amygdala activation during viewing of fearful emotional images and lower resting-state FC of the left amygdala with a cerebellum cluster, but no differences in resting-state amygdala rCBF or volume. *Conclusions*: Our findings demonstrate a functionally relevant effect of schizotypy on amygdala activation in the absence of baseline rCBF or macroscopic structure. This suggests that while schizotypy might affect some functional or structural parameters in the brain, certain functionally relevant effects only emerge during cognitive or emotional triggers.**

Key words: arterial spin labeling/functional connectivity/functional magnetic resonance imaging/high risk/positive schizotypy/regional cerebral blood flow/resting-state fMRI/schizophrenia/schizotypal/schizotypy

Introduction

Amygdala function is central to the processing of emotionally relevant information, evaluations, and responses to stimuli; it is thus relevant to a range of affective and social functions that are impaired across several psychiatric disorders.[1] In the psychosis spectrum, aberrant amygdala activation has been reported in different tasks, including reward anticipation,[2] social functioning tasks,[3,4] and emotional processing or recognition tasks.[5–7] The latter are

Table 1. Sample Demographics and Characteristics

	High Schizotypy Group	Low Schizotypy Group	Group Difference
Number (female/male)	21 (14/7)	42 (24/18)	$P = .470$, $d = 0.091$
Mean age (SD)	23.67 (4.08)	22.86 (3.30)	$P = .571$, $d = 0.071$
Mean positive schizotypy (SD)	8.62 (2.50)	0.00 (0.00)	$P = 1.72\ e^{-14}$, $d = 0.994$
Mean negative schizotypy (SD)	5.10 (3.94)	3.55 (2.57)	$P = .166$, $d = 0.174$
Mean cognitive disorganization subscore (SD)	10.48 (4.52)	3.45 (3.79)	$P = 3.45\ e^{-07}$, $d = 0.642$
Mean impulsive nonconformity subscore (SD)	7.90 (2.84)	5.02 (2.01)	$P = 2.08\ e^{-4}$, $d = 0.353$
Mean IQ (SD)	108.62 (10.93)	117.05 (13.90)	$P = .010$, $d = 0.324$

of particular interest, since they seem to reflect difficulties of psychosis spectrum disorder patients to correctly identify, process, or appraise emotional information such as facial expressions, which bears direct relevance to social interactions and everyday functioning. While altered brain network activation to negative emotions such as fear might reflect cognitive-perceptual biases in schizophrenia,[8,9] earlier studies have argued for clinical state rather than genetic effects (at least in clinical cases).[10] Some subsequent studies have shown that amygdala activation in response to facial expressions, including fearful faces, in subjects with familial risk for psychosis is related to recognition of facial expressions,[11] yet recent meta-analyses of functional magnetic resonance imaging (fMRI) studies of at-risk individuals have not identified consistent amygdala activation differences in response to facial emotions.[12,13] It is thus unclear whether amygdala dysfunction reflects risk for schizophrenia/psychosis or expression of a clinical phenotype or both.

Schizotypy offers an additional valuable framework to study the wider schizophrenia/psychosis spectrum. It defines a phenotype associated with psychosis proneness that can be assessed along a spectrum (as opposed to health-disease dichotomies studied in case-control designs) and thus characterizes a general population risk marker.[14,15] Most schizotypy assessment inventories mirror the 3-factorial or 3-dimensional structure of clinical schizophrenia symptoms (ie, positive, negative, and disorganized), which have also been shown to relate to prodromal symptoms of schizophrenia in nonclinical populations.[16,17] On the behavioral level, recent years have seen accumulating evidence of schizotypy being linked to emotion processing deficits.[18] A most recent meta-analysis of facial emotion recognition in particular has linked schizotypal traits to multiple deficits in performance,[19] where positive schizotypy was specifically associated with lower accuracy and biases to both negative and neutral emotions. It is, however, unclear how this deficit associated with positive schizotypy is linked to amygdala function. For example, while a study contrasting high vs low subjects on negative schizotypy has linked reduced amygdala activation to both fearful and neutral facial emotion processing (as well as amygdala functional connectivity [FC] during fearful conditions),[20] a recent meta-analysis including 10 studies of emotion processing and schizotypy shows evidence for association with amygdala functioning, but no data on positive schizotypy.[21] Yet, recent literature on psychotic-like experiences, which refers mostly to positive symptoms in the (subclinical) psychosis spectrum, does indeed suggest links to amygdala activation during facial emotion processing,[22] as does a study of young adults with high vs low (subclinical) delusional beliefs.[23] Hence, although there is now good evidence of multiple facets of schizotypy in nonclinical cohorts to be linked to particular patterns of changes in (facial) emotion processing,[19] our understanding of links to brain mechanisms is poor, especially for positive schizotypy.[21]

In this study, we tested the hypothesis that schizotypy in nonaffected individuals (ie, without schizophrenia, psychosis, or another psychiatric diagnosis) would be associated with amygdala functioning, in particular during the processing of emotionally salient facial expressions. To this end, we selected subjects from an ongoing schizotypy study based on high vs low positive schizotypy profiles and applied a multimodal imaging approach, in which we characterize amygdala function on multiple levels, including (1) resting activity measuring regional cerebral blood flow (rCBF) using arterial spin labeling (ASL); (2) task-based amygdala activation (induced by processing socially salient vs nonsalient visual stimuli) using blood oxygenation level-dependent (BOLD) fMRI; (3) FC during resting-state BOLD fMRI (reflecting intrinsic variations in baseline and readiness prior to task-specific activation); and (4) amygdala volume.

Methods

Subject Cohort

A cohort of 63 psychiatrically healthy subjects (38 female, 25 male, mean age = 23.13, SD = 3.57) was studied, including 21 subjects with higher scores of positive schizotypy (14 female, 7 male, mean age = 23.67, SD = 4.08) and 42 subjects with low scores on positive schizotypy (18 male, 24 female, mean age = 22.86, SD = 3.30; for an overview of sample descriptives, see Table 1). Subjects were drawn from a larger study in which we analyzed psychometric properties of schizotypal traits based on a

community cohort.[16,24] All subjects were native German speakers.

All study participants had provided written informed consent to study protocols approved by the Ethics Committee of the Medical School of Philipps-Universität Marburg (protocols 61/18, 79/18) in accordance with the Declaration of Helsinki in its current version.[25] Inclusion criteria for this study were age 18–40 years and ability to give informed consent. Exclusion criteria were as follows: current or past psychiatric disorders, current or past substance dependence, current or past psychiatric treatments, psychotropic drug use, central nervous neurological disorders, uncontrolled medical illness (eg, hypertension or diabetes), and learning disability (conceptualized as IQ lower 80). In order to ascertain the absence of psychiatric history, we used the German SCID-I screening inventory prior to further data acquisition.[26,27] In order to exclude learning disabilities, we used the German MWT-B test for the estimation of IQ.[28,29] For self-assessment of handedness, we used the Edinburgh Handedness Inventory (EHI).[30]

Phenotyping

We used the Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE) for self-report characterization of trait schizotypy in participating individuals.[31,32] Data were obtained through an online platform (SoSci Survey: www.Soscisurvey.de[33]) with individualized access.

The O-LIFE assesses schizotypy through 104 categorical response (yes/no) items. Following previous factor analysis of the O-LIFE advocating a 4-factor model,[16,31] subscores for the 4 facets were calculated, that is, *Unusual Experiences* (*UnEx*; 30 items, reflecting the positive schizotypy facet), *Introvertive Anhedonia* (*IntAn*; 27 items, reflecting negative schizotypy), *Cognitive Disorganization* (*CogDis*; 24 items), and *Impulsive Nonconformity* (*ImpNon*; 23 items, a fourth category outside the conventional 3-factor models).

Based on a larger cohort ($N = 383$), for which psychometric data were available,[16,24] we drew 21 subjects (7 male/14 female) with highest O-LIFE *UnEx* scores, for which psychometric data and full multimodal MRI data (with task-based fMRI, resting-state fMRI, and ASL, as well as structural T1) were available and matched those (1:2) for age and gender with 42 subjects (18 male/24 female) with low positive schizotypy for which the same data were available. Group matching of 1:2 was done to increase the number of available subjects for analysis, which was limited by the group of high-scoring subjects (while low-scoring subjects were more available from the larger reference sample[16,24]). Groups did not differ significantly for age ($P = .400$) or gender distribution ($P = .474$).

Mean values for both positive schizotypy and other schizotypy facets are given in Table 1. The mean value for the *UnEx* (positive) schizotypy in our "high schizotypy" group is comparable with the mean value of a previously published German reference sample of 1228 participants of 7.11 (SD 5.51).[34] However, the mean was slightly lower than a British reference sample (cf. [31,34]) and considerably lower than the *UnEx* means in our larger reference sample: in our initially reported sample of $n = 376$ German subjects, *UnEx* mean was 2.28 (SD 3.5),[24] and 1.91 (SD 2.51) in our subsequent and slightly larger cohort of $n = 383$ subjects.[16]

MRI Data Acquisition

We used a Siemens Tim Trio 3 Tesla MRI system with a 12-channel head matrix Rx-coil (Siemens, Erlangen, Germany) in order to acquire a multimodal imaging dataset with structural and multiple functional scans.

First, we acquired a T1-weighted sequence for morphometric analyses (repetition time [TR] = 1900 ms; echo time [TE] = 2.26 ms; time of inversion [TI] = 90 ms; bandwidth = 200 Hz/Px; 176 slices with sagittal orientation, slice thickness of 1 mm and voxel resolution of $1 \times 1 \times 1$ mm^3; field of view 256×256 mm^2, flip angle of 9°, phase encoding direction: anterior-posterior; acquisition time 4 min and 26 s).

Second, we then acquired resting-state fMRI using a T2*-weighted sequence (TR = 2000 ms, TE = 30 ms, flip angle = 90°, transversal orientation, phase encoding direction = anterior-posterior, FOV = 210×210 mm^2, slice thickness = 3.8 mm, distance factor = 10%, slices number = 33, and voxel size = $3.3 \times 3.3 \times 3.8$ mm, for a total acquisition time of 8 min).

Third, we used perfusion images (ASL sequence) acquired with a pulsed arterial spin labeling sequence at rest, applying Siemens' Proximal Inversion with Control of Off-Resonance Effects (PICORE Q2T) protocol with 16 slices of 6 mm thickness each and a distance factor of 25% (TR = 3000 ms, TE = 11 ms, inversion time 2 TI2 = 2200 ms, TI1 = 700 ms, saturation stop time = 1600 ms, field of view of 230×230 mm^2, flip angle of 90°, 153 measurements, and a resulting voxel size of $3.6 \times 3.6 \times 6.0$ mm^3).

Finally, task-based fMRI was acquired with a T2*-weighted EPI sequence within a slab including the amygdala and early visual areas (TR = 1610 ms, TE = 36 ms, FoV = 256×256 mm^2, manually aligned to the individual's temporal and occipital poles based on the anatomical image. TA: 14:20, PAT: Off, number of slices = 18, slice thickness = 2.4 mm, distance factor = 15%, transversal orientation, phase encoding direction = anterior-posterior, voxel size: $2.0 \times 2.02 \times 2.4$ mm^3; field map parameters: FoV = 230×230 mm^2 with identical tilting as the EPI slab, TR = 400 ms, TE1 = 4.92 ms, TE2 = 7.38 ms, flip angle = 60°).

During the task-based (BOLD) fMRI experiment, participants performed an emotional 1-back face-matching task. Subjects were presented with a face localization

paradigm[35] with grayscale photographs of 30 faces with a neutral expression, 30 faces with a fearful expression (from the Karolinska Directed Emotional Faces database[36]), as well as 30 houses (images provided by Goh et al[37]). To induce sustained attention to the presented images, participants were asked to indicate the occurrence of 2 identical subsequent images (target) by pressing a response box button with their right index finger. We used a blocked design for stimulus presentation, with each block (~14 s in total, 300 ms stimulus duration, interstimulus interval of 383 ms) consisting of 20 images drawn from the respective dataset followed by a 5.6-s pause (showing a fixation cross), for a total of 14 blocks per each of the 3 conditions (42 blocks in total). Two to three targets were presented per block. After half of the blocks, there was a 30-s break during which the German word for break (Pause) was presented visually (see Figure 1 for a schematic depiction). We used the software package Presentation (Neurobehavioral Systems, San Francisco, CA, USA) to present stimuli on an MRI-compatible LCD screen placed behind the MRI machine and visible via a tilted mirror. The task paradigm scan lasted 14 min 42 s in total.

MRI Data Preprocessing

For preprocessing of T1-weighted structural images, we used CAT12 (version 12.8, build r2137; Christian Gaser, Structural Brain Mapping Group, Jena University Hospital, Jena, Germany, http://dbm.neuro.uni-jena.de/cat/) for SPM12 (version 7771, Statistical Parametric Mapping, Wellcome Centre for Human Neuroimaging, Institute of Neurology, London, UK) running under MATLAB (version 2021a, The MathWorks Inc., USA). All images were checked with the quality assurance protocol implemented in CAT12, following CAT12-recommended values and the default pipeline. We used the ICBM space brain template implemented in CAT12 for spatial registration and SPM12 tissue probability maps to segment the image into gray matter, white matter, and cerebrospinal fluid. GM images were then further segmented into Neuromorphometrics atlas regions of interests (ROIs), resulting in individual mean GM values for the right and left amygdala for each participant.

rCBF images were quantified using the first volume of the sequence (M0 image, ie, equilibrium brain tissue magnetization image) and underwent motion correction and realignment. CBF images, including mean CBF images, were coregistered with the individual anatomical T1 scans, normalized in MNI space, and smoothed with a Gaussian kernel of $6 \times 6 \times 6$ mm^3. We then used the MATLAB-based toolbox MarsBar[38] to again extract individual mean rCBF values for the right and left amygdala.

Functional resting-state images were preprocessed using the CONN toolbox with default options.[39] Functional images were realigned using the SPM12 realign & unwarp procedure.[40] Temporal misalignment was corrected through the standard SPM12 slice-timing correction procedure.[41] Functional and anatomical data were normalized into standard MNI space and segmented into gray matter, white matter, and CSF tissue classes using the SPM12 unified segmentation and

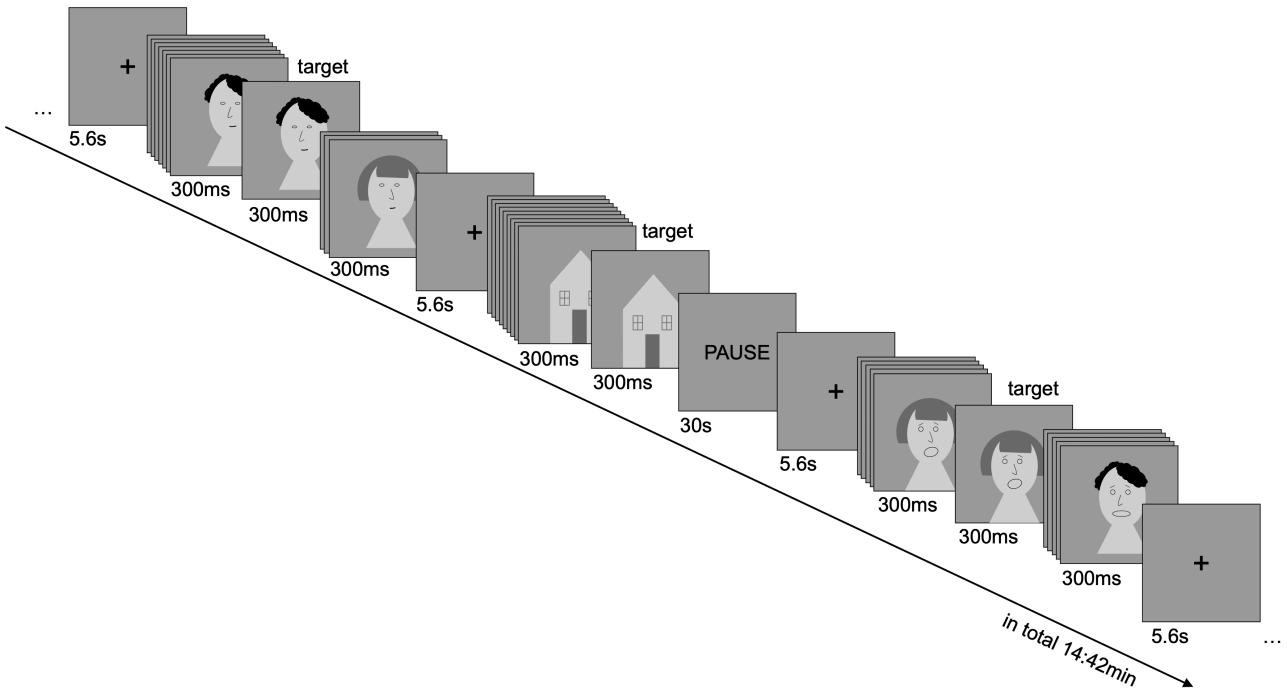

Figure 1. Schematic depiction of emotional face paradigm task.

normalization procedure.[42] Functional data were then smoothed with a Gaussian kernel of 4-mm full-width half maximum. We then used amygdala ROIs supplied by the standard atlas implemented into CONN (Harvard-Oxford atlas) to define the right and left amygdala as seeds for a seed-to-voxel analysis, creating a seed-based connectivity map representing the degree of FC between the seed and every brain voxel. Briefly, seed-based maps are computed as the Fisher-transformed bivariate correlation coefficients between the ROI BOLD time series and each individual voxel BOLD time series. Seed-to-voxel FC was examined through the standard random field theory (RFT) parametric statistics. Briefly, clusters of interest are initially defined through RFT (uncorrected $P < .001$), and then, an FDR-corrected $P < .05$ cluster-level threshold is used to select among the resulting clusters those significant.[39]

Task-based activation images were acquired with a slab-based scanning procedure. Due to slab-based acquisition, standard normalization was not satisfactory for a significant portion of the data. Therefore, based on contrast faces vs houses, manual identification of amygdala peak voxel localization per subject was conducted by experienced medical observers compared with a standard atlas (Neuromorphometrics). For our analysis, we selected the contrast image of fearful faces vs neutral faces to best isolate activation due to the emotional content of stimuli. At each individual peak localization, 6-mm spheres were placed and individual mean activation values for the right and left amygdala were extracted for each subject.

Statistical Analysis

To test our hypotheses of group-level differences for task-based amygdala activation, we used Wilcoxon signed-rank tests as implemented in the *stats* package of R[43] for extracted mean amygdala activations. For seed-based analysis of amygdala FC, we used the general linear model approach implemented in CONN, modeling a *t*-test–like group comparison for each voxel across the brain gray matter, using CONN-based FDR cluster-level correction for multiple comparisons. For extracted amygdala rCBF from ASL preprocessing and amygdala volumes, we again used Wilcoxon signed-rank comparisons of groups.

Results

Task-Based Functional MRI Results

The high schizotypy group showed significantly lower right amygdala activation (task condition: fearful faces vs neutral faces) compared with the low schizotypy group ($P = .047$, Cohen's $d = 0.516$), while there was no significant difference in left amygdala activation ($P = .466$, $d = 0.092$). Group-level differences are shown as box plots in Figure 2.

Amygdala rCBF/ASL

Testing low vs high schizotypy groups, we found no significant difference in rCBF as measured by ASL for either right amygdala ($P = .661$, $d = 0.058$) or left amygdala ($P = .341$, $d = 0.125$; see Table 2).

Amygdala Functional Connectivity

Seed-based analysis of amygdala FC showed 1 significant group difference with high positive schizotypy subjects showing lower FC compared with low positive schizotypy group between the left amygdala and a cluster in the cerebellum ($P_{\text{FDR-cluster}} = .048$; $d = 1.31$, $k = 51$ voxels, coordinates of maximum voxel: −2; −56; 54; covering parts of left and right cerebellum lobule 9). The results are shown in Figure 3. There were no significant group differences for seed-based FC from the right amygdala.

Amygdala Volume

Testing low vs high schizotypy groups, there was no significant difference in amygdala ROI volume for either right amygdala ($P = .145$, $d = 0.184$) or left amygdala ($P = .109$, $d = 0.202$; see Table 2).

Discussion

In this study, we used a multimodal imaging approach to characterize amygdala functioning in high vs low schizotypy subjects. The rationale and benefit of a multimodal imaging approach are to complement the core analysis, that is, amygdala activation during viewing of emotional/socially salient materials, with additional characterizations of its function and structure, and specifically its resting activity (ASL), FC, and volume.

Three main insights emerge from our analyses. First, our analyses provide support for an association of (positive) schizotypy with fear-based amygdala activation, even in the absence of psychotic pathology or manifest mental disorders. This can be interpreted as an effect of the schizotypy-associated risk for psychosis. Considering schizotypy as a personality feature that is distributed across the population, higher expressions are associated with increasing risk for schizophrenia/psychosis.[14,16] This is an interesting contrast to clinical studies, which have posited that amygdala dysfunction in schizophrenia is related to clinical symptom expression (as a state) rather than genetic liability (when comparing patients with nonaffected siblings).[10] In nonclinical subjects, Wang et al. did not find differences in subjects with high negative vs low negative schizotypy for fear and other emotions activating the amygdala,[20] and Modinos et al. found no amygdala activation difference in high overall vs low overall schizotypy[44] (although differences were found in other areas such as the caudate nucleus). Considering our results, these findings can be reconciled when considering

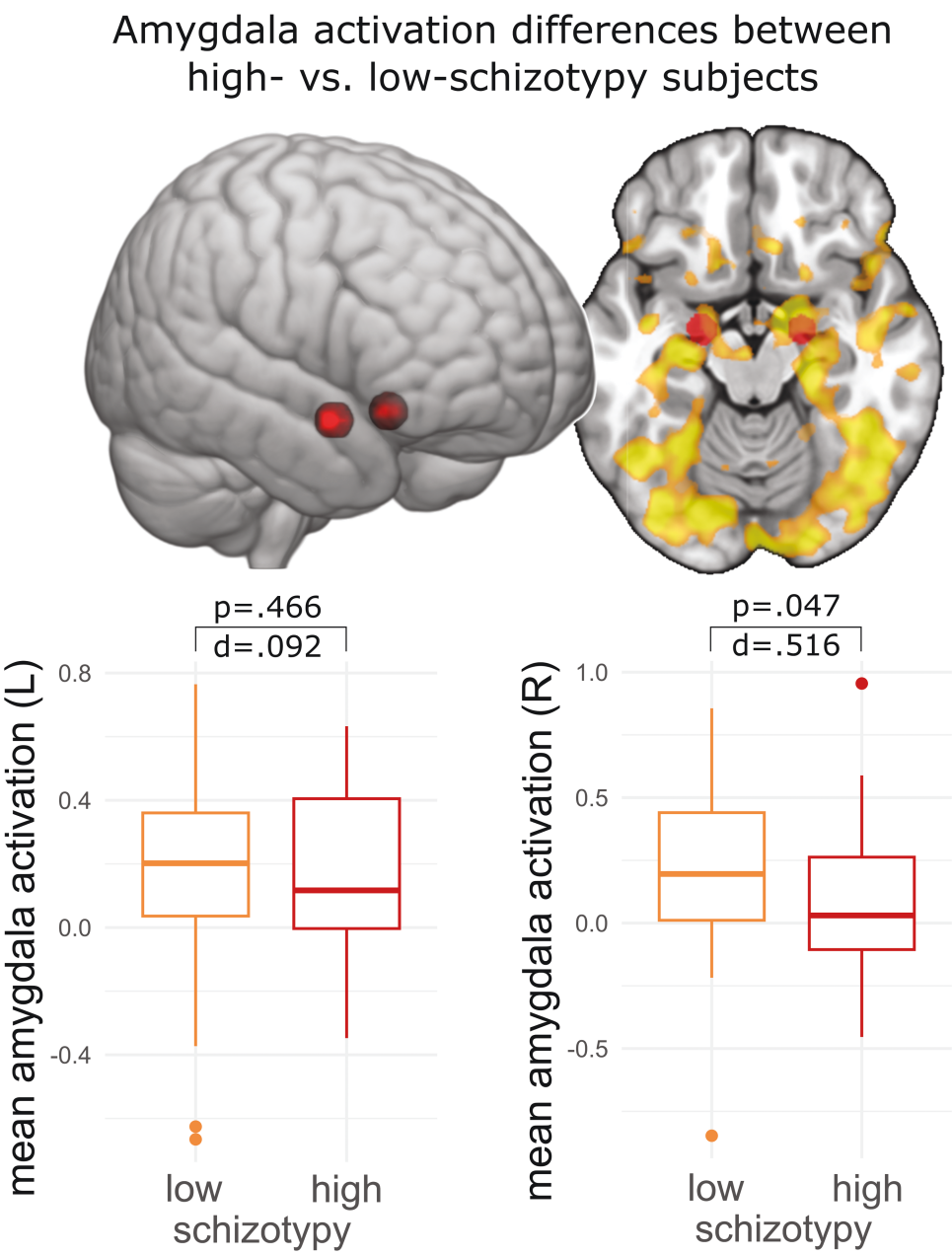

Figure 2. Group differences in amygdala activation (fearful faces vs neutral faces condition) of low positive schizotypy vs high positive schizotypy subjects (n = 42 vs n = 21, respectively): upper images show position of amygdala spheres (6 mm diameter) superimposed on 3D brain reconstruction and single transversal slice with exemplary first level activation results of a single subject; lower part of the images shows box plots of mean individual amygdala activations for left and right amygdala, respectively.

Table 2. Mean Values and Group Differences for Amygdala Volume and rCBF

	High Schizotypy Group	Low Schizotypy Group	Group Difference
Mean right amygdala volume (SD)	0.92 (0.08)	0.96 (0.10)	P = .145, d = 0.184
Mean left amygdala volume (SD)	0.93 (0.10)	0.97 (0.10)	P = .109, d = 0.202
Mean right amygdala rCBF (SD)	29.52 (12.71)	31.17 (16.82)	P = .661, d = 0.058
Mean left amygdala rCBF (SD)	29.50 (10.10)	32.39 (13.74)	P = .341, d = 0.125

Abbreviation: rCBF, regional cerebral blood flow.

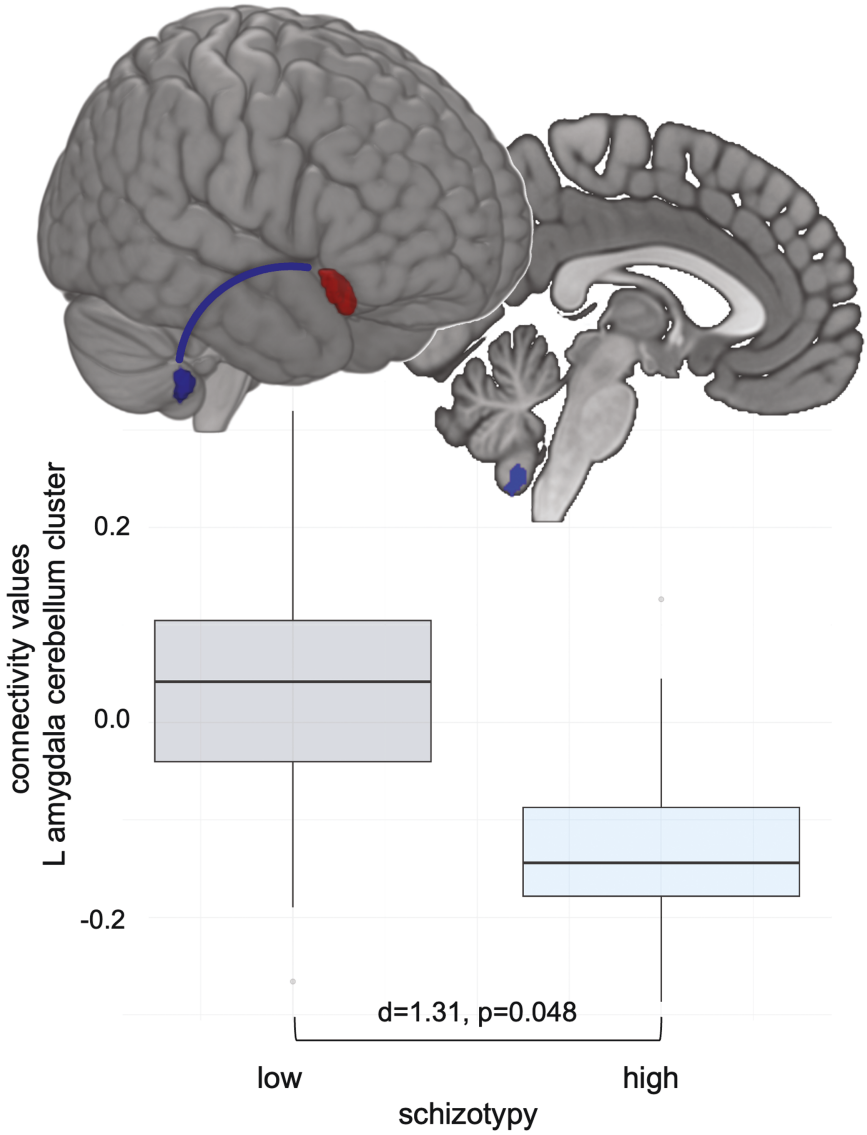

Figure 3. Group differences in amygdala functional connectivity: high schizotypy subjects show lower functional connectivity (compared with the low schizotypy group) between left amygdala (seed region) and a lower cerebellum cluster ($P_{\text{FDR-cluster}}$ = .048; d = 1.31, k = 51 voxels, maximum significance voxel at coordinates: −2; −56; 54).

that different facets of schizotypy (and similar symptoms in clinical psychosis) might be associated with different activation patterns. This would be consistent with previous behavioral studies on schizotypy in nonclinical cohorts[18,19] and to some extent with some imaging studies of individuals a high risk for psychosis.[13] Synthesizing these studies in clinical and nonclinical populations would also lead to a reconsideration and reassessment of recent meta-analyses on the usefulness of emotional images for endophenotype identification in schizophrenia,[12] where categorical diagnostic effects might obscure dimensional effects such as those related to schizotypy. Although there are studies of amygdala reactivity in persons with schizotypal personality disorder, showing no adaptation changes of amygdala activity to repeated emotional picture viewing (in contrast to healthy controls), these studies are not directly comparable with our experimental paradigm.[45,46]

While our findings add to the understanding of emotion-related amygdala activation across the psychosis spectrum, we need to consider limitations such as sample size and effects related to other personality markers/phenotypes. This includes not only the higher degree of some cognitive disorganization features (which are sometimes conceptualized as a third schizotypy factor outside the positive-negative schizotypy dichotomy[14,16]) but also features not assessed in this and other schizotypy-related cohorts, such as neuroticism or markers of affective disorder liability. Nevertheless, our findings provide an important additional clue to indicate that positive vs

negative schizotypy might differentially impact amygdala reactivity.[20]

Second, the activation difference in the 2 groups is accompanied by neither a change in baseline rCBF nor the volume of the amygdala. As groups did not differ in either of these markers, we can infer that at least based on the available structural/functional markers, there is no underlying enduring amygdala deficit. This also makes it unlikely for amygdala reactivity to reflect a potential artifact of either elevated persisting activity (ie, ceiling effects during activation) or gray matter concentration.

Comparing our findings with those of rCBF studies in schizophrenia, it is worth noting that most studies overall find no group-level difference in amygdala rCBF between schizophrenia or schizophrenia spectrum disorder patients and healthy controls[47,48]; however, there are significant findings in those studies associating amygdala rCBF with symptom dimensions or patterns, in particular altered affectivity leading to elevated amygdala rCBF in schizophrenia spectrum disorders.[49] A previous study had found elevated left amygdala rCBF in actively paranoid schizophrenia individuals as compared with either healthy controls or nonparanoid patients.[50] These findings would be in line with the notion that altered baseline rCBF is related to clinical expression of a phenotype or disease-related alterations.

Finally, our FC analyses indicate that amygdala-cerebellum connectivity might be related to levels of nonclinical schizotypy. Cerebellum node 9 (or IX) in recent studies has been associated with nonmotor functions. For example, Guell and Schmahmann have suggested, on the basis of fMRI studies, that these lower parts of the cerebellum seem to be linked to default-mode/"task-negative" or possibly also attentional functions.[51] This model is also based on large fMRI analyses from the Human Connectome Project that also discuss the involvement of lobule 9/IX in social processing.[52] Yet, it does not specifically link the cerebellar area to the paradigm applied in our study. It is also unclear whether this involvement reflects a specific link to emotion processing or a more general involvement in nonmotor cognitive functions, which is a general matter of debate on cerebellar functional segregation.[53] In contrast to FC patterns, a multidomain task analysis of fMRI activation studies showed little cerebellar activation to faces, although some activation to sad faces was noted (fearful faces were not tested).[54]

There have been several recent reports relating FC of different cerebellar regions to schizotypy. However, these were related to FC to ventral striatal regions and reward functions,[55] autobiographical memory/"mental time travel,"[56] and cerebellar FC with hippocampus and prefrontal areas.[57,58] Only the study of Wang et al. implicated FC correlations specifically during emotional information processing, although this was related to negative schizotypy.[20] Notably, researchers have recently provided the first evidence of a functional cerebellum-amygdala pathway that could advance understanding of the cerebellum's role in emotion processing.[59] Notwithstanding, the interpretation of our finding on FC is, therefore, less straightforward and requires not only replication by other leads to integrate the potential role of the inferior cerebellum. This might be particularly the case since current models of paranoia have focused on altered amygdala to hippocampal connectivity.[60]

In addition to the limitations already discussed above, we need to address the drawbacks of the overall study design. While our study chose an "extreme" group comparison similar to that of previous schizotypy imaging studies,[20,44,58] this approach, while simple and straightforward, is not only limited to 1 facet (by which subgroups are typically divided), it might also have drawbacks in considering confounding variables such as other personality traits (either assessed or not assessed in a given cohort). Additional studies on clinical cases and nonclinical higher scoring subjects are also needed, not the least, since our cohort (like others) is typically drawn from the general public and is not enriched for ultra-high schizotypy subjects.

Taken together, our findings show schizotypy, as a phenotypic marker of psychosis proneness, to be related to amygdala reactivity to fearful (compared with neutral) faces, but not baseline blood flow/activity or volume of the amygdala. These findings extend the current literature to additional facets of schizotypy and provide a comparison across multiple imaging modalities (within 1 cohort) to characterize amygdala neurobiology in the psychosis spectrum. Our findings also make a case for future multimodal characterization of brain function/structure, as effects of schizotypy might emerge on single but not all levels of observation (eg, baseline activity/perfusion vs FC vs task-induced activation). Overcoming limitations of unimodal analyses could thus facilitate a better understanding of brain correlates of schizotypy and their link to findings in schizophrenia.

Funding

This study was supported in part by research grants of the University Hospital Giessen and Marburg (UKGM), grants 11/2017 MR (to I.N.) and 05/2018 MR (to Sarah Grezellschak and I.N.), as well as partially through Forschungscampus Mittelhessen (FCMH) FlexiFunds grants 2017_2_1_5 (to I.N. and Philipp Grant) and 2018_2_1_1 (to I.N.). I.N. received support from the Deutsche Forschungsgemeinschaft (DFG), grants NE2254/1-2, NE2254/2-1, NE2254/3-1, NE2254/4-1, and NE2254/6-1. I.N. is a PI of and supported by the DYNAMIC center, which is funded by the LOEWE program of the Hessian Ministry of Science and Arts (Grant Number: LOEWE1/16/519/03/09.001(0009)/98).

Conflicts of Interest

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

Author Contributions

I.N.: Fundingacquisition, Methodology, Conceptualisation, Project administration, Resources, Software, Supervision, Validation, Writing – original draft J.H.: Data curation, Formal analysis, Methodology, Visualisation, Writing – review & editing A.F.: Data Curation, Formal analysis, Methodology, Resources, Validation, Software, Writing – review & editing S.W.: Methodology, Resources, Validation, Software, Writing – review & editing A.A.-A.: Methodology, Resources, Validation, Software, Writing – review & editing A.J.: Methodology, Resources, Validation, Software, Writing – review & editing T.M.: Data curation, Formal analysis, Software, Methodology, Project administration, Supervision, Visualisation, Validation, Writing – review & editing.

References

1. McTeague LM, Rosenberg BM, Lopez JW, et al. Identification of common neural circuit disruptions in emotional processing across psychiatric disorders. *Am J Psychiatry.* 2020;177:411–421.
2. Zeng J, Yan J, Cao H, et al. Neural substrates of reward anticipation and outcome in schizophrenia: a meta-analysis of fMRI findings in the monetary incentive delay task. *Transl Psychiatry.* 2022;12:448.
3. Vucurovic K, Caillies S, Kaladjian A. Neural correlates of theory of mind and empathy in schizophrenia: an activation likelihood estimation meta-analysis. *J Psychiatr Res.* 2020;120:163–174.
4. Stegmayer K, Bohlhalter S, Vanbellingen T, et al. Limbic interference during social action planning in schizophrenia. *Schizophr Bull.* 2018;44:359–368.
5. Dugre JR, Bitar N, Dumais A, Potvin S. Limbic hyperactivity in response to emotionally neutral stimuli in schizophrenia: a neuroimaging meta-analysis of the hypervigilant mind. *Am J Psychiatry.* 2019;176:1021–1029.
6. Dong D, Wang Y, Jia X, et al. Abnormal brain activation during threatening face processing in schizophrenia: a meta-analysis of functional neuroimaging studies. *Schizophr Res.* 2018;197:200–208.
7. Delvecchio G, Sugranyes G, Frangou S. Evidence of diagnostic specificity in the neural correlates of facial affect processing in bipolar disorder and schizophrenia: a meta-analysis of functional imaging studies. *Psychol Med.* 2013;43:553–569.
8. Garcia-Leon MA, Fuentes-Claramonte P, Valiente-Gomez A, et al. Altered brain responses to specific negative emotions in schizophrenia. *Neuroimage Clin.* 2021;32:102894.
9. Lee SC, Lin GH, Shih CL, et al. Error patterns of facial emotion recognition in patients with schizophrenia. *J Affect Disord.* 2022;300:441–448.
10. Rasetti R, Mattay VS, Wiedholz LM, et al. Evidence that altered amygdala activity in schizophrenia is related to clinical state and not genetic risk. *Am J Psychiatry.* 2009;166:216–225.
11. Pulkkinen J, Nikkinen J, Kiviniemi V, et al. Functional mapping of dynamic happy and fearful facial expressions in young adults with familial risk for psychosis – Oulu Brain and Mind Study. *Schizophr Res.* 2015;164:242–249.
12. Fiorito AM, Aleman A, Blasi G, et al. Are brain responses to emotion a reliable endophenotype of schizophrenia? An image-based functional magnetic resonance imaging meta-analysis. *Biol Psychiatry.* 2023;93:167–177.
13. Lukow PB, Kiemes A, Kempton MJ, Turkheimer FE, McGuire P, Modinos G. Neural correlates of emotional processing in psychosis risk and onset – a systematic review and meta-analysis of fMRI studies. *Neurosci Biobehav Rev.* 2021;128:780–788.
14. Grant P, Green MJ, Mason OJ. Models of schizotypy: the importance of conceptual clarity. *Schizophr Bull.* 2018;44(suppl 2):S556–S563.
15. Taylor JH, Calkins ME, Gur RE. Markers of psychosis risk in the general population. *Biol Psychiatry.* 2020;88:337–348.
16. Pfarr JK, Meller T, Evermann U, Sahakyan L, Kwapil TR, Nenadic I. Trait schizotypy and the psychosis prodrome: current standard assessment of extended psychosis spectrum phenotypes. *Schizophr Res.* 2023;254:208–217.
17. Racioppi A, Sheinbaum T, Gross GM, Ballespi S, Kwapil TR, Barrantes-Vidal N. Prediction of prodromal symptoms and schizophrenia-spectrum personality disorder traits by positive and negative schizotypy: a 3-year prospective study. *PLoS One.* 2018;13:e0207150.
18. Giakoumaki SG. Emotion processing deficits in the different dimensions of psychometric schizotypy. *Scand J Psychol.* 2016;57:256–270.
19. Zouraraki C, Karamaouna P, Giakoumaki SG. Facial emotion recognition and schizotypal traits: a systematic review of behavioural studies. *Early Interv Psychiatry.* 2023;17:121–140.
20. Wang Y, Li Z, Liu WH, et al. Negative schizotypy and altered functional connectivity during facial emotion processing. *Schizophr Bull.* 2018;44(suppl 2):S491–S500.
21. Zouraraki C, Karamaouna P, Giakoumaki SG. Cognitive processes and resting-state functional neuroimaging findings in high schizotypal individuals and schizotypal personality disorder patients: a systematic review. *Brain Sci.* 2023;13:615.
22. Assaf R, Ouellet J, Bourque J, et al. Neural alterations of emotion processing in atypical trajectories of psychotic-like experiences. *Schizophrenia (Heidelb).* 2022;8:1–8.
23. DeCross SN, Farabaugh AH, Holmes AJ, et al. Increased amygdala-visual cortex connectivity in youth with persecutory ideation. *Psychol Med.* 2020;50:273–283.
24. Nenadic I, Meller T, Evermann U, et al. Subclinical schizotypal vs. autistic traits show overlapping and diametrically opposed facets in a non-clinical population. *Schizophr Res.* 2021;231:32–41.
25. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA.* 2013;310:2191–2194.
26. Wittchen H-U, Wunderlich U, Gruschwitz S, Zaudig M. *SKID-I. Strukturiertes Klinisches Interview Für DSM-IV*. Hogrefe; 1997.
27. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed., text rev. Washington, DC: American Psychiatric Association; 2000.
28. Lehrl S. *Mehrfachwahl-Wortschatz-Intelligenztest: MWT-B*. 5th ed. Testzentrale; 2005.
29. Lehrl S, Triebig G, Fischer B. Multiple choice vocabulary test MWT as a valid and short test to estimate premorbid intelligence. *Acta Neurol Scand.* 1995;91:335–345.

30. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia.* 1971;9:97–113.
31. Mason O, Claridge G. The Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE): further description and extended norms. *Schizophr Res.* 2006;82:203–211.
32. Mason O, Claridge G, Jackson M. New scales for the assessment of schizotypy. *Pers Individ Differ.* 1995;18:7–13.
33. Leiner D. SoSci Survey (Version 3.2.01-i) [Computer Software]. https://www.soscisurvey.de
34. Grant P, Kuepper Y, Mueller EA, Wielpuetz C, Mason O, Hennig J. Dopaminergic foundations of schizotypy as measured by the German version of the Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE)—a suitable endophenotype of schizophrenia. *Front Hum Neurosci.* 2013;7:1.
35. Hildesheim FE, Debus I, Kessler R, et al. The trajectory of hemispheric lateralization in the core system of face processing: a cross-sectional functional magnetic resonance imaging pilot study. *Front Psychol.* 2020;11:507199.
36. Lundqvist D, Flykt A, Öhman A. *The Karolinska Directed Emotional Faces – KDEF, CD ROM from Department of Clinical Neuroscience, Psychology Section, Karolinska Institutet*. 1998, ISBN 91-630-7164-9.
37. Goh JO, Leshikar ED, Sutton BP, et al. Culture differences in neural processing of faces and houses in the ventral visual cortex. *Soc Cogn Affect Neurosci.* 2010;5:227–235.
38. Brett M, Anton J-L, Valabregue R, Poline J-B. Region of interest analysis using an SPM toolbox. In: 8th International Conference on Functional Mapping of the Human Brain, June 2–6, 2002, Sendai, Japan. Vol 16. Vol Available on CD-ROM in NeuroImage; 2002.
39. Whitfield-Gabrieli S, Nieto-Castanon A. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain Connect.* 2012;2:125–141.
40. Andersson JL, Hutton C, Ashburner J, Turner R, Friston K. Modeling geometric deformations in EPI time series. *Neuroimage.* 2001;13:903–919.
41. Henson RNA, Buechel C, Josephs O, Friston KJ. The slice-timing problem in event-related fMRI. *Neuroimage.* 1999;9:125.
42. Ashburner J, Friston KJ. Unified segmentation. *Neuroimage.* 2005;26:839–851.
43. R Core Team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing; 2022.
44. Modinos G, McLaughlin A, Egerton A, et al. Corticolimbic hyper-response to emotion and glutamatergic function in people with high schizotypy: a multimodal fMRI-MRS study. *Transl Psychiatry.* 2017;7:e1083.
45. Hazlett EA, Zhang J, New AS, et al. Potentiated amygdala response to repeated emotional pictures in borderline personality disorder. *Biol Psychiatry.* 2012;72:448–456.
46. Hazlett EA, Goldstein KE, Haznedar MM, et al. Hyperreactivity and impaired habituation of startle amplitude during unpleasant pictures in borderline but not schizotypal personality disorder: quantifying emotion dysregulation. *Biol Psychiatry.* 2022;92:573–582.
47. Percie du Sert O, Unrau J, Gauthier CJ, et al. Cerebral blood flow in schizophrenia: a systematic review and meta-analysis of MRI-based studies. *Prog Neuropsychopharmacol Biol Psychiatry.* 2023;121:110669.
48. Boisvert M, Lungu O, Pilon F, Dumais A, Potvin S. Regional cerebral blood flow at rest in schizophrenia and major depressive disorder: a functional neuroimaging meta-analysis. *Psychiatry Res Neuroimaging.* 2023;335:111720.
49. Stegmayer K, Strik W, Federspiel A, Wiest R, Bohlhalter S, Walther S. Specific cerebral perfusion patterns in three schizophrenia symptom dimensions. *Schizophr Res.* 2017;190:96–101.
50. Pinkham AE, Liu P, Lu H, Kriegsman M, Simpson C, Tamminga C. Amygdala hyperactivity at rest in paranoid individuals with schizophrenia. *Am J Psychiatry.* 2015;172:784–792.
51. Guell X, Schmahmann J. Cerebellar functional anatomy: a didactic summary based on human fMRI evidence. *Cerebellum.* 2020;19:1–5.
52. Guell X, Gabrieli JDE, Schmahmann JD. Triple representation of language, working memory, social and emotion processing in the cerebellum: convergent evidence from task and seed-based resting-state fMRI analyses in a single large cohort. *Neuroimage.* 2018;172:437–449.
53. Diedrichsen J, King M, Hernandez-Castillo C, Sereno M, Ivry RB. Universal transform or multiple functionality? Understanding the contribution of the human cerebellum across task domains. *Neuron.* 2019;102:918–928.
54. King M, Hernandez-Castillo CR, Poldrack RA, Ivry RB, Diedrichsen J. Functional boundaries in the human cerebellum revealed by a multi-domain task battery. *Nat Neurosci.* 2019;22:1371–1378.
55. Carruzzo F, Giarratana AO, Del Puppo L, Kaiser S, Tobler PN, Kaliuzhna M. Neural bases of reward anticipation in healthy individuals with low, mid, and high levels of schizotypy. *Sci Rep.* 2023;13:9953.
56. Ye JY, Qin XJ, Cui JF, et al. Neural correlates of mental time travel in individuals with high level of schizotypy. *Prog Neuropsychopharmacol Biol Psychiatry.* 2023;124:110734.
57. Wang Y, Yan C, Yin DZ, et al. Neurobiological changes of schizotypy: evidence from both volume-based morphometric analysis and resting-state functional connectivity. *Schizophr Bull.* 2015;41(suppl 2):S444–S454.
58. Waltmann M, O'Daly O, Egerton A, et al. Multi-echo fMRI, resting-state connectivity, and high psychometric schizotypy. *Neuroimage Clin.* 2019;21:101603.
59. Jung SJ, Vlasov K, D'Ambra AF, et al. Novel cerebello-amygdala connections provide missing link between cerebellum and limbic system. *Front Syst Neurosci.* 2022;16:879634.
60. Walther S, Lefebvre S, Conring F, et al. Limbic links to paranoia: increased resting-state functional connectivity between amygdala, hippocampus and orbitofrontal cortex in schizophrenia patients with paranoia. *Eur Arch Psychiatry Clin Neurosci.* 2022;272:1021–1032.