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ORIGINAL ARTICLE

Auditory prediction errors and auditory white matter microstructure associated with psychotic-like experiences in healthy individuals

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Abstract

Our sensory systems actively predict sensory information based on previously learnt patterns, which are continuously updated with information from the actual sensory input via prediction errors. Individuals with schizophrenia consistently show reduced auditory prediction errors as well as altered fractional anisotropy (indicative of white matter changes) in the arcuate fasciculus and the auditory interhemispheric pathway, both of which are auditory white matter pathways associated with prediction errors. However, it is not clear if healthy individuals with psychotic-like experiences exhibit similar deficits. Participants underwent electroencephalography (EEG) recordings while listening to a classical two-tone duration deviant oddball paradigm ($n = 103$) and a stochastic oddball paradigm ($n = 89$). A subset of participants ($n = 89$) also underwent diffusion-weighted magnetic resonance imaging (MRI). Fractional anisotropy (FA), was extracted from the arcuate fasciculi and the auditory interhemispheric pathway. While prediction errors evoked by the classical oddball paradigm failed to reveal significant effects, the stochastic oddball paradigm elicited significant clusters at the typical mismatch negativity time window. Furthermore, we observed that FA of the arcuate fasciculi and auditory interhemispheric pathway significantly improved predictive models of psychotic-like experiences in healthy individuals over and above predictions made by auditory prediction error responses alone. Specifically, we observed that decreasing FA in the auditory interhemispheric pathway and reducing ability to learn stochastic irregularities are associated with increasing CAPE + scores. To the extent that these associations have previously been reported in patients with schizophrenia, the findings from this study suggest that both, auditory prediction errors and white matter changes in the auditory interhemispheric pathway, may have the potential to be translated into early screening markers for psychosis.

Keywords MMN · P300 · Prodromal · Diffusion-weighted imaging (DWI) · Schizophrenia · Electroencephalography (EEG) · Schizotypy

Introduction

Auditory prediction errors, particularly measured with electroencephalography (EEG), have gained headway in the search for biomarkers of schizophrenia. Mismatch negativity (MMN) is a component of prediction errors, evoked by stimuli that differ from a learnt pattern (Belger et al. 2012;

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Nagai et al. 2013; Näätänen 2014). Patients with schizophrenia consistently exhibit a robust attenuation of the auditory MMN (Todd et al. 2008; Horton et al. 2011; Erickson et al. 2016). Furthermore, MMN has also been shown to be attenuated in first-episode psychosis (Haigh et al. 2016a; Salisbury et al. 2016) and individuals at high risk for schizophrenia (Atkinson et al. 2012; Shaikh et al. 2012; Nagai et al. 2013; Perez et al. 2014; Solis-Vivanco et al. 2014). Critically, studies have shown that the MMN response predicts the development of schizophrenia in individuals at high risk (Bodatsch et al. 2011, 2015). The P300 component, a positive peak occurring 250–400 ms after stimulus onset (Sur and Sinha 2009), is a later component of the prediction error response elicited with auditory oddball paradigms. The P300 component has also been shown to be reduced in chronic schizophrenia (Ford et al. 2001; Winterer et al. 2003) and in first-episode schizophrenia (Qiu et al. 2014).

Findings in patients with schizophrenia can often be confounded by disease stage and medication use. Schizotypy is a construct that refers to healthy individuals with psychotic-like experiences, such as delusions and/or hallucinations, albeit to a lesser degree. To the extent that these psychotic-like experiences are not distressing for the individual and do not interfere with their daily living activities, schizotypy is thought to be a sub-clinical manifestation of schizophrenia in the general population (Ettinger et al. 2015). Studying psychotic-like experiences in healthy individuals has the advantage of avoiding the confounding factors present in many schizophrenia studies, such as medication effects and co-morbidities, and could therefore provide insights into the very early precursors of schizophrenia. Support for the contention that psychotic-like experiences in healthy individuals underlie the same neurophysiological abnormalities as psychotic symptoms in schizophrenia comes from the finding that prediction errors reduce with increasing delusional-like experiences in healthy populations (Corlett and Fletcher 2012). Furthermore, the trait phenotype social disorganization, which is shared by autism and schizotypy, has been linked to reduced fronto-temporal response to deviant tones in a magnetoencephalography study (Ford et al. 2017).

Auditory oddball paradigms have been tested comprehensively in schizophrenia and individuals at high risk for psychosis and revealed robust MMN attenuation to simple duration deviants (Erickson et al. 2016), as well as more complex paradigms with double deviants (Perez et al. 2014), tone omission deviants (Salisbury and McCathern 2016) and pattern violations (Haigh et al. 2016b). An fMRI study previously reported that psychotic-like experiences in healthy individuals were associated with changes to the frontal and striatal prediction error signal elicited by visual stimuli (Corlett and Fletcher 2012). Despite a vast body a literature showing MMN reduction in schizophrenia, only one other study has investigated a putative association between psychotic-like experiences in healthy individuals and auditory prediction errors using a classic oddball paradigm (Broyd et al. 2016). Here, we set out to employ simple and complex auditory oddball paradigms in the same sample of healthy individuals with varying degrees of psychotic-like experiences. Specifically, in addition to a simple duration deviant paradigm, which has consistently been reported to identify prediction error deficits in schizophrenia, we aimed to investigate a more complex, stochastic oddball paradigm (Garrido et al. 2013), whereby deviant tones are frequency outliers in a Gaussian distribution.

Effective connectivity studies of frequency MMN in healthy individuals have identified primary auditory cortex (A1), superior temporal gyrus (STG), and the inferior frontal gyrus (IFG) as key nodes in the generation of prediction errors (Garrido et al. 2008). Frequency oddball paradigms have shown that patients with schizophrenia have reduced connectivity within this network during auditory mismatch responses (Dima et al. 2012; Larsen et al. 2018). Interestingly, these effectively connected areas are also structurally connected via auditory white matter pathways. One such pathway is the auditory interhemispheric pathway, which is the part of the corpus callosum that connects bilateral A1, and the other is the arcuate fasciculus, an association tract which connects STG and IFG. In schizophrenia, altered white matter connectivity in the auditory interhemispheric pathway (Wigand et al. 2015) and the arcuate fasciculus (Geoffroy et al. 2014; McCarthy-Jones et al. 2015) have both been linked to auditory verbal hallucinations, which is the most prominent psychotic symptom. Specifically, evidence suggests that altered structural and functional connectivity between bilateral auditory areas, anatomically linked by the auditory interhemispheric pathway, may result in positive symptoms such as auditory verbal hallucinations (Steinmann et al. 2014) or unusual auditory perceptions in individuals at risk of schizophrenia (Rossell et al. 2001; Woodruff 2004; Kubicki et al. 2008), and more so in chronic schizophrenia patients with a history of auditory verbal hallucinations than in patients without a history of auditory verbal hallucinations (Wigand et al. 2015). Similarly, a meta-analysis reported more white matter connectivity disruptions within the arcuate fasciculus in schizophrenia patients with auditory verbal hallucinations relative to patients without hallucinations (Geoffroy et al. 2014). In healthy individuals, connectivity reductions in the arcuate fasciculus and the corpus callosum more broadly have been linked to psychotic-like experiences (Nelson et al. 2011; Oestreich et al. 2018).

Based on the robust findings of MMN attenuation in schizophrenia and high risk individuals who later transition, as well as known white matter reductions in auditory networks subserving prediction error generation, we set out to investigate whether these deficits could also be observed in healthy individuals with varying degrees of

psychotic-like experiences. Our first aim was to investigate whether a classical and/or a stochastic oddball paradigm (with the latter requiring context updating) are sensitive to less severe expressions of psychotic-like experiences in the general population. Our second aim was to identify if structural estimates of auditory white matter pathways can improve the prediction of psychotic-like experiences in the healthy population over and above predictions based on functional measures alone. Due to the supporting findings of MMN attenuation and altered auditory white matter connectivity associated with schizotypal traits, we hypothesized that (1) the prediction error amplitude would be attenuated as the number of psychotic-like experiences increased and (2) adding structural estimates of the arcuate fasciculus and the auditory interhemispheric pathway would further improve regression models of psychotic-like experiences in healthy individuals.

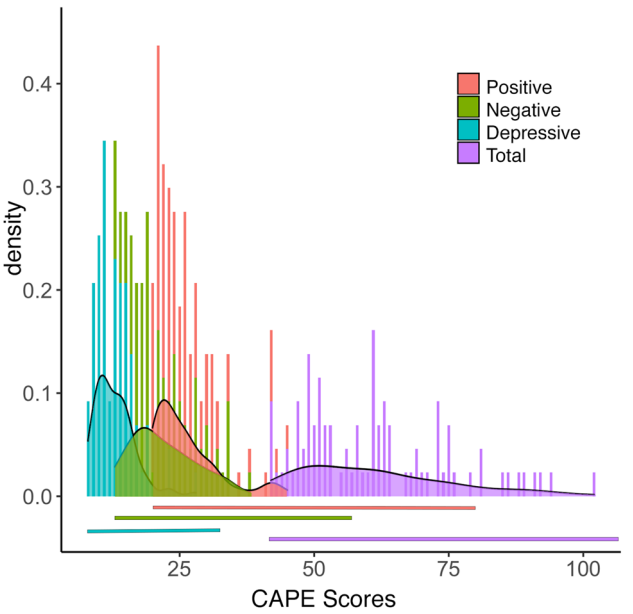

Fig. 1 Frequency and density distributions of participant's scores on the community assessment of psychic experiences (CAPE-42) questionnaire. Positive (red), negative (green) and depressive (blue) subscales and total (purple) scores are shown. The horizontal coloured bars below the distribution plot indicate the possible ranges for each sub-scale i.e. Total CAPE scores can range between 42 and 168, with positive dimension scores between 20 and 80, negative dimension scores between 14 and 56 and depressive dimension scores between 8 and 32 (Stefanis et al. 2002)

Methods

Participants

One-hundred and three participants were recruited via the University of Queensland (UQ) online recruitment system (SONA) and the UQ newsletter. Participants were between the ages 18 and 65 ($M = 24.67$, $SD = 9.77$) and 55.3% ($n = 57$) were female. Participants completed self-report questionnaires including demographic data, Beck's Anxiety Inventory (Beck et al. 1988), Beck's Depression Inventory (Beck et al. 1961), and the Community Assessment of Psychic Experience (CAPE) (Stefanis et al. 2002). The CAPE has three dimensions, namely positive (e.g. delusions, hallucinations), negative (e.g. avolition, affective flattening) and depressive experiences. Total CAPE scores can range between 42 and 168, with positive dimension scores between 20 and 80, negative dimension scores between 14 and 56 and depressive dimension scores between 8 and 32 (Stefanis et al. 2002). The distribution of CAPE scores in our sample is displayed in Fig. 1 and descriptive statistics of demographic data and psychometric scales are reported in Table 1. Participants were monetarily reimbursed for their time. Exclusion criteria were any diagnosis of psychiatric or neurological condition, or head injury with loss of consciousness. Three participants who were taking antidepressant medications during the time of the study were excluded from the analyses to rule out possible medication effects. Written informed consent was obtained from all participants. Ethical clearance for the study was obtained from the UQ Ethics Committee.

Table 1 Demographic information

Variable	Mean/category	SD	Range
Age	24.16	9.04	18–63
Gender (male/female)	44/56		
English as first language (yes/no)	47/56		
Handedness (left/right)	9/94		
Full scale IQ	111.07	8.20	87–127
Caffeine (number of units per day)	0.80	0.82	0–3
Nicotine[a]	96/2/2		
Alcohol[b]	77/14/6/3		
Becks anxiety score	7.18	8.15	0–42
Becks depression score	6.95	7.09	0–27
CAPE total score	62.68	15.81	42–112
CAPE positive symptom score	26.36	6.07	20–45
CAPE negative symptom score	23.26	6.10	14–39
CAPE depressive symptom score	13.06	3.64	8–28

[a]Nicotine categories: 1 = zero, 2 = one pack per week, 3 = more than one pack per week

[b]Alcohol categories: 1 = zero, 2 = 1–5 standard drinks per week, 3 = 6–10 standard drinks per week, 4 = more than 10 standard drinks per week

Experimental procedure

Classical oddball paradigm

All participants underwent a classical auditory duration oddball paradigm which consisted of two blocks. The long deviant block consisted of standard tones (500 Hz, 50 ms duration, 80% probability), and deviant tones (500 Hz, 100 ms duration, 20% probability). The short deviant block consisted of the reverse, i.e. standard tones—500 Hz, 100 ms duration, 80% probability. All tones were played at an inter-stimulus interval of 500 ms. The total number of tones in each deviant block was 1000 tones, of which 200 tones were deviants. The order of the blocks was counterbalanced across participants. In order to isolate prediction errors from effects due to attention to tones (Naatanen 2000), participants also engaged in a simultaneous 1-back task (Miller et al. 2009) that consisted of a stream of letters displayed on a screen and in different frames. The participants were asked to detect consecutive repetitions of any letter presented. All stimuli were delivered in Matlab using Psychtoolbox3 (Brainard 1997; Pelli 1997). This experimental component lasted for approximately 20 min.

Stochastic oddball paradigm

Participants also underwent a stochastic frequency oddball paradigm (Garrido et al. 2013) and a simultaneous 2-back task (Sweet 2011). Participants listened to a stream of tones with log-frequencies sampled from two Gaussian distributions with equal means (500 Hz) and different standard deviations (narrow: $\sigma_n = 0.5$ octaves; broad: $\sigma_b = 1.5$ octaves). All tones were played with a duration of 50 ms with 10 ms smooth rise and fall periods and inter-stimulus intervals of 500 ms. 10% of the tones were defined as standard tones, which were played at 500 Hz, i.e. the mean of both distributions and 10% of the tones were defined at deviant tones, which were played at 2000 Hz, i.e. as outliers to the two distributions. Standard and deviant tones were inserted into the sound stream at random time points. Participants were instructed to disregard the tones and to focus on the visual task instead. This experimental component lasted for approximately 30 min and was divided into four blocks. The narrow and broad distribution conditions were presented in separate blocks (two blocks per condition) and the order of the blocks was counter-balanced across participants. The total number of tones in each block was 900 (i.e. 1800 tones for each condition), resulting in approximately 180 deviant tones of each type per condition. The order of the stochastic and classical oddball paradigms was counterbalanced across participants.

EEG data

Acquisition and processing

Throughout the auditory oddball experiments, an electroencephalogram (EEG) was recorded using a 64 electrode-cap with BioSemi ActiView system at a sampling rate of 1024 Hz. Further electrodes were placed on the outer canthi of both eyes, as well as below and above the left eye to measure eye movements. Triggers were marked in the EEG data at the onset of each tone. The EEG raw data were pre-processed using SPM12 implemented in MATLAB version R2015b (MathWorks). Data were first referenced to the common average of all electrodes, down sampled to 200 Hz and filtered using a high-pass filter of 0.5 Hz. Topography-based correction (Berg and Scherg 1994) was used to correct for eye blinks. Next, EEG data were segmented into 500 ms intervals, consisting of 100 ms pre-, and 400 ms post-stimulus onset. Trials containing artefacts with voltages exceeding ± 50 μV, were rejected. The remaining artefact-free trials (classical oddball: 89%; stochastic oddball: 93%) were robustly averaged (Wager et al. 2005) to event-related potentials (ERPs) for each condition, low-pass filtered at 40 Hz, and baseline corrected using the 100 ms pre-stimulus interval.

Spatiotemporal analysis

Auditory prediction error studies typically report the main effect of surprise and the interaction effect (Peter et al. 2010; Garrido et al. 2013). While not the main focus of our study, we report these analyses to make the result of the present study comparable to previous studies. Using SPM12 ERPs were converted into 3D spatiotemporal volumes for each condition and participant, by interpolating and dividing the scalp data per time point into a 2-dimensional (2D) 32×32 matrix. One 2D image was obtained for each time bin and stacked according to their pre-stimulus temporal order. This resulted in a 3D spatiotemporal image volume with $32 \times 32 \times 81$ dimensions per participant. In order to test the effect of prediction, the 3D image volumes were modelled with a full-factorial general linear model using 2×2 ANCOVA designs, with Deviant Type (long/short) and Surprise (standards/deviants) in the classical oddball paradigm, and Variance (narrow/broad) and Surprise (standards/deviants) in the stochastic oddball paradigm, as within-subject factors. As it has previously been reported that MMN decreases with age (Cheng et al. 2013), age and age squared were included as covariates in order to model the non-linear effects of age.

We then investigated whether healthy individuals with increasing psychotic-like experiences showed reductions in mismatch responses (classical oddball paradigm) and

are less able to learn statistical regularities in a stochastic environment (stochastic oddball paradigm). To this end, we ran regression analyses for both paradigms with individually computed contrast images for the main effects of surprise and the interactions from the spatiotemporal analyses as outcome variables and CAPE positive dimension scores (CAPE +) as the predictor variable. Age and age squared were again added as a covariates. In order to isolate the effects of psychotic-like experiences on the MMN from other measures of psychopathology, we added Beck anxiety scores, CAPE depression, CAPE distress and CAPE negative symptom scores as covariates to the analysis. All statistical analyses were corrected for multiple-comparisons using a family-wise error (FWE) rate at an alpha level of 0.05. All *p*-values reported are cluster-FWE corrected.

DWI data

Acquisition and pre-processing

A subsample of 89 (age $M = 24.69$; $SD = 10.13$) participants that underwent EEG recordings also underwent diffusion-weighted and T1-weighted MRI on a 3T Siemens Magnetom TrioTim system. Imaging parameters included TR = 8600 ms, TE = 116 ms, FOV = 220 mm, $2.0 \times 2.0 \times 2.0$ mm slice thickness and 15 min acquisition time. Diffusion data was acquired at b-value = 1000 s/mm^2 (32 directions) and b-value = 3000 s/mm^2 (64 directions). Three interspersed $b = 0$ images were obtained in addition to one phase-encoded $b = 0$. A T1-weighted image data set was acquired with the MP2RAGE sequence (Marques et al. 2010) with FoV 240 mm, 176 slices, 0.9 mm isotropic resolution, TR = 4000 ms, TE = 2.92 ms, TI1 = 700 ms, TI2 = 2220 ms, first flip angle = 6°, second flip angle = 7°, and 5 min acquisition time.

The diffusion-weighted volumes were pre-processed using FSL (Functional MRI of the Brain Software Library). Signal intensity inhomogeneities were removed (Zhang et al. 2001). Intra-scan misalignments due to head movements and eddy currents were removed using FSL TOPUP (Smith et al. 2004) and EDDY (Andersson and Sotiropoulos, 2016). Diffusion-weighted and T1-weighted images were co-registered using boundary-based registration (Greve and Fischl, 2009). The T1-weighted images were processed with the recon-all command in Freesurfer (http://surfer.nmr.mgh.harvard.edu/) (Dale et al. 1999). Five tissue-type segmentation of T1-weighted images was conducted and response functions were estimated from the diffusion data using the multi-shell, multi-tissue algorithm (Jeurissen et al. 2014) implemented in MRtrix3 (https://github.com/MRtrix3/mrtrix3).

Tractography

All tractography steps were undertaken in MRtrix3 (Tournier et al. 2012). Multi-tissue constrained spherical deconvolution was applied to obtain fibre orientation distributions for each voxel (Jeurissen et al. 2014). Probabilistic streamlines of the right arcuate fasciculus, left arcuate fasciculus and auditory interhemispheric tract (Fig. 2) were reconstructed using anatomically-constrained tractography (Smith et al. 2015). Regions of interest (ROIs) were first drawn in Montreal neurological institute (MNI) space in the MRtrix3 image viewer MRview (Tournier et al. 2012) (see Figure S1). ROIs were then warped into individual subject space. The protocol for the reconstruction of the arcuate fasciculi was adapted from the procedure described by Catani and Thiebaut de Schotten (2008). The arcuate fasciculus was seeded from Broca's area, with inclusion masks in Geschwind's territory and target ROIs in Wernicke's area. The protocol for the auditory interhemispheric pathway was adapted from the protocol by Steinmann et al. (2014). A ROI was drawn in the left primary auditory cortex with inclusion masks in the left and right Wernicke's region and a target ROI in the right primary auditory cortex. The tractography procedure was guided by 500,000 seeds, 4 mm minimum and 200 mm maximum track length, 1 mm step size, an angular threshold of 45° and a cut-off value for the FOD amplitude of 0.05. Spherical Deconvolution Informed Filtering of Tractograms (SIFT2) was used to ensure that the reconstructed white matter tracts reflected biologically meaningful connectivity, reducing inadequacies resulting from the reconstruction method (Smith et al. 2015). Individual binary label maps were generated for the arcuate fasciculi and the auditory interhemispheric pathway for each subject by labelling all voxels through which fibres traversed. Next, we calculated fractional anisotropy (FA) for each voxel in every subject's label map, and the mean FA of all voxels in the label map. The reproducibility of the arcuate fasciculi and auditory interhemispheric pathway were assessed with the intra-rater reliability on a subset of 10 randomly chosen participants with a 1-year interval between ratings. Reproducibility was quantified with the intraclass correlation coefficient (ICC) (Metzler-Baddeley et al. 2012). ICC values between 0.60–0.79 can be interpreted as representing substantial agreement between ratings and ICC values between 0.80 and 1.00 are generally interpreted as excellent agreement between ratings.

Regression model for predicting psychotic-like experiences

A secondary aim of this study was to investigate if structural estimates (i.e. FA) of auditory white matter pathways could improve predictions of psychotic-like experiences when

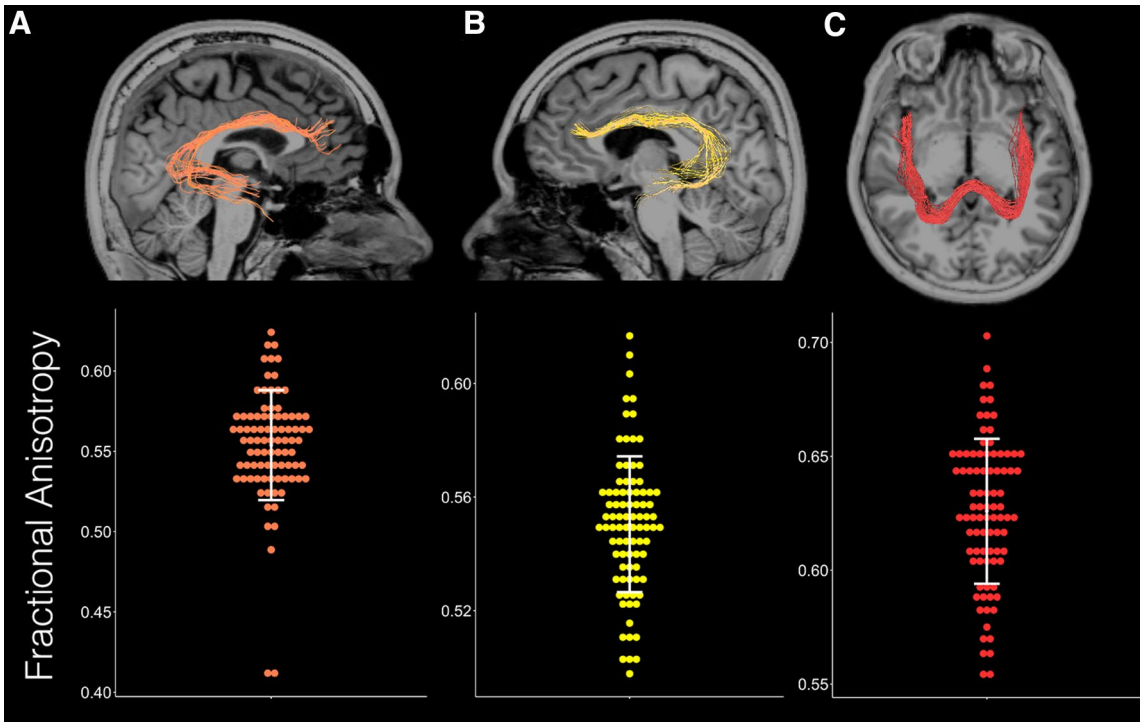

Fig. 2 *Auditory white matter pathways.* **a** The right arcuate fasciculus, **b** left arcuate fasciculus and **c** the auditory interhemispheric pathway from three participants. **d** FA of the three white matter pathways for the whole sample ($N = 89$ individuals). Each dot represents one participant and the error bar represents the standard error of the mean

added to ERP estimates (i.e. auditory prediction error responses). As the surprise*variance interaction in the stochastic oddball paradigm was significantly associated with CAPE + scores, we extracted the significant field intensity values (FIV) that were found to be associated with CAPE + scores. In a first step, FIV were added as predictor variables in the linear regression analysis with CAPE + scores as the outcome variable. In a second step, FA of each tract (left arcuate fasciculus, right arcuate fasciculus, auditory interhemispheric pathway) were added. In order to investigate if FA of the auditory pathways explained a significant amount of variance of CAPE + scores over and above the variance explained by the prediction error response alone, R^2_{change} was calculated.

Results

Spatiotemporal analysis

Classical oddball paradigm

Prediction error waveforms (deviants > standards) for each block are shown in Fig. 3a, b. In line with previous studies using classical oddball paradigms (Peter et al. 2010), an ANCOVA revealed a significant main effects of surprise and a significant interaction of surprise*deviant type (Fig. 3 and Table 2).

Regression analyses with the main effect of surprise or the surprise*deviant type interaction as outcome variables and CAPE + scores as the predictor variable, controlling for age and other measures of psychopathology did not reveal any significant clusters. We therefore conducted further separate regression analyses with the long deviant type condition and the short deviant type condition as outcome variables, which revealed a significant negative relationship between CAPE + scores and the long duration mismatch response ($t(97) = 4.10$, $R^2 = 0.148$, $p_{\text{cluster-FWE}} = 0.044$) at 380 ms. This is indicative of increasing attenuation of the mismatch response as the number of psychotic-like experiences increases, in the long deviant type condition only.

Stochastic oddball paradigm

Prediction error waveforms (deviants > standards) for each variance condition (narrow and broad) are displayed in Fig. 4a, b. An ANCOVA revealed a significant main effect of surprise (Fig. 4, Table 3), which is in line with previous prediction error findings in the mismatch negativity (100–250 ms) and P300 (250–500 ms) time-windows (Garrido et al. 2013). A significant surprise*variance interaction (Fig. 4, Table 3) also confirms previous findings whereby the

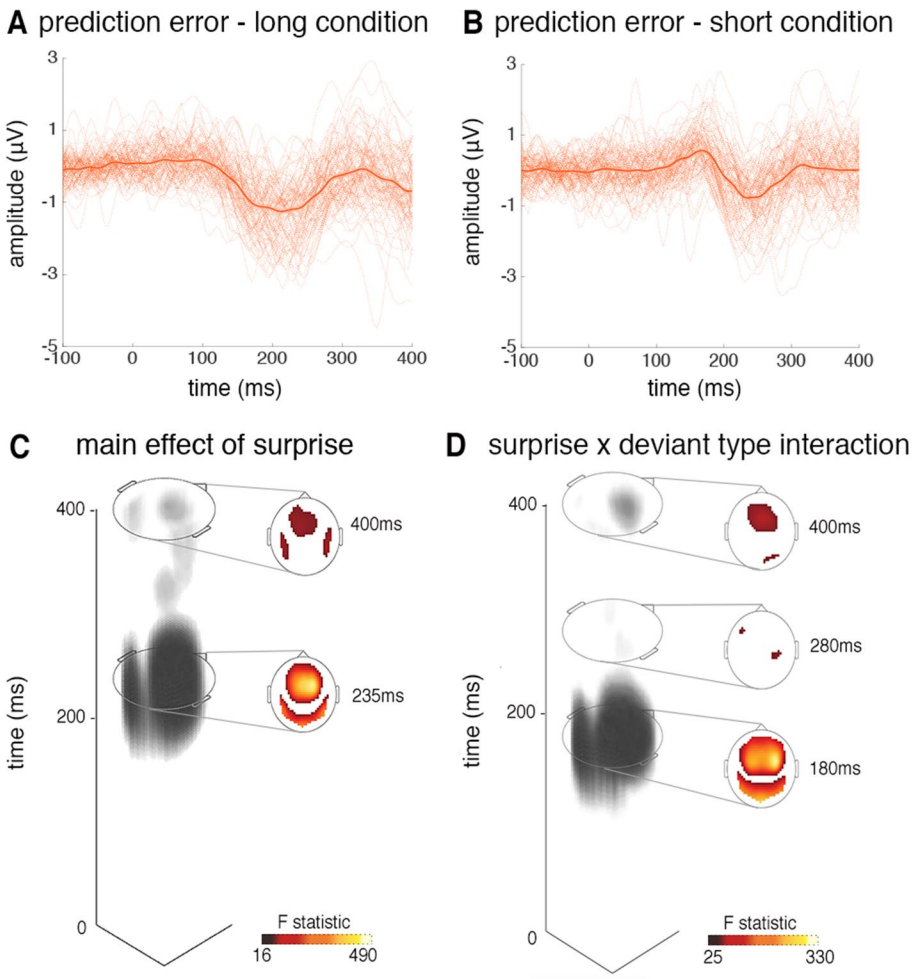

Fig. 3 Prediction errors to classical oddball stimuli. Prediction error waveforms at the Fz channel for **a** long duration deviants and **b** short duration deviants for each participant (dotted lines), with grand mean across all participants (solid lines). Spatiotemporal statistical analysis revealed a significant **c** main effect of surprise and a **d** surprise*deviant type interaction, with a greater surprise effect for long duration deviants. **c**, **d** are 3D *t*-statistic maps demonstrating significant spatiotemporal clusters where spatial dimensions are on the *x*–*y* plane and time is on the *z*-axis. The 2D scalp maps are cross-sections of the 3D maps, denotating the time points of interest. Maps are displayed at $p < 0.05$ FWE corrected for the whole space–time volume

Table 2 Spatiotemporal results: classical oddball paradigm

	Df	*F*-statistic	*p*-value	Time (ms)	Location
Main effect of surprise	1, 96	476.00	< 0.001	235	Frontocentral
	1, 96	72.40	< 0.001	395	Temporoparietal
	1, 96	73.41	< 0.001	400	Temporoparietal
Surprise * deviant type interaction	1, 96	328.76	< 0.001	180	Frontocentral
	1, 96	27.99	< 0.001	280	Temporoparietal
	1, 96	70.42	< 0.001	400	Temporoparietal

All effects are family-wise error corrected at the cluster level

df - degrees of freedom

prediction error response is greater in the narrow than the broad condition (Garrido et al. 2013).

A regression analysis with the main effect of surprise as outcome variable and CAPE + scores as the predictor variable, controlling for age and other measures of psychopathology did not reveal any significant clusters. A regression analysis with the surprise*variance interaction as outcome variable and CAPE + scores as the predictor variable, controlling for age and other measures of psychopathology revealed significant clusters over left temporoparietal channels at 155 ms ($t(80) = 5.28$, $R^2 = 0.258$, $p_{\text{cluster-FWE}} = 0.002$) and medial frontocentral channels at 145 ms ($t(80) = 4.84$, $R^2 = 0.227$, $p_{\text{cluster-FWE}} = 0.008$). This indicates that as the number of psychotic-like experiences increases, the sensitivity for learning and detecting violations to regularities in a stochastic environment decreases.

Structural and functional predictors of psychotic experiences

Intra-rater reliability was very good for FA of all white matter pathways ($ICC_{\text{left arcuate fasciculus}} = 0.88$, $ICC_{\text{right arcuate fasciculus}} = 0.91$, $ICC_{\text{auditory interhemispheric pathway}} = 0.83$).

For the Gaussian paradigm, FIV at 145 ms and 155 ms were found to be significantly associated with CAPE + in the previous regression analysis and were therefore extracted and added to the model as predictor

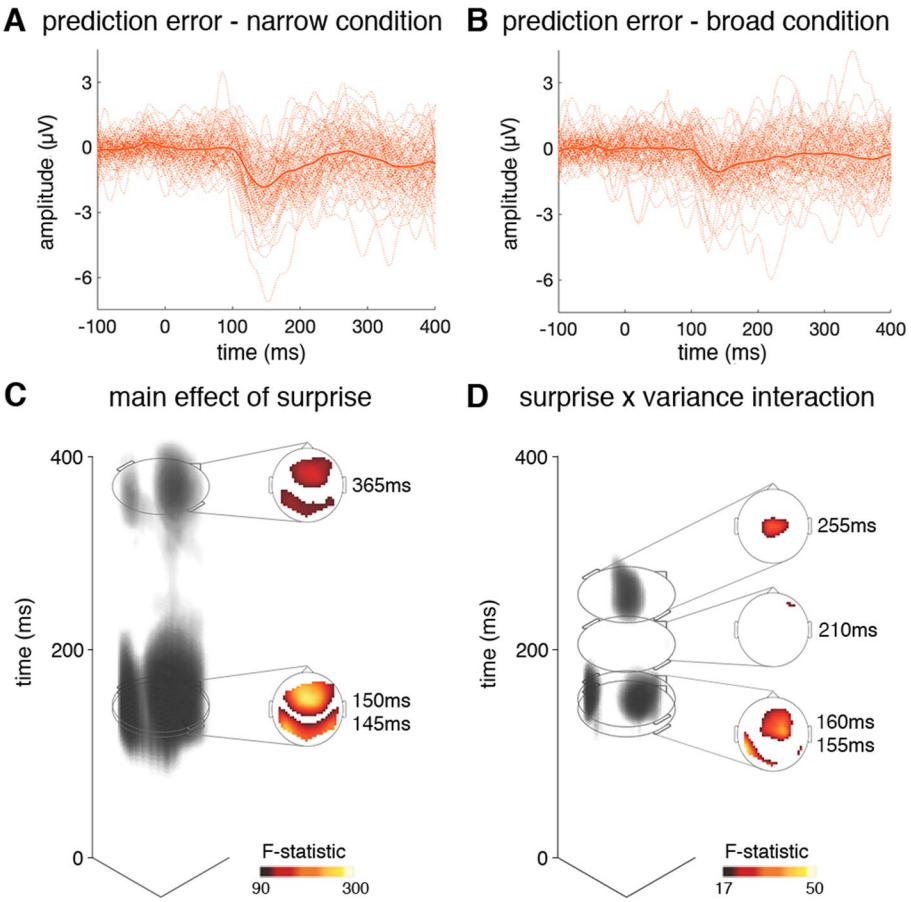

Fig. 4 Prediction errors to stochastic oddball stimuli. Prediction error waveforms at the Fz channel for **a** narrow and **b** broad conditions for each participant (dotted lines), with grand mean across all participants (solid lines). Spatiotemporal statistical analysis revealed significant **c** main effect of surprise and **d** surprise*variance interaction. As before, (**c**, **d**) are 3D *t* -statistic maps demonstrating significant spatiotemporal clusters where spatial dimensions are on the *x*–*y* plane and time is on the *z*-axis. The 2D scalp maps are cross-sections of the 3D maps, denotating the time points of interest. Maps are displayed at $p < 0.05$ FWE corrected for the whole space–time volume

Table 3 Spatiotemporal results: stochastic oddball paradigm

	df	*F*-statistic	*p*-value	Time (ms)	Location
Main effect of surprise	1, 83	295.51	< 0.001	150	Frontocentral
	1, 83	259.66	< 0.001	145	Parietal
	1, 83	91.66	< 0.001	365	Frontocentral
Surprise * variance interaction	1, 83	49.23	< 0.001	155	Temporoparietal
	1, 83	42.73	< 0.001	155	Frontocentral
	1, 83	35.70	< 0.001	260	Frontocentral

All effects are family-wise error corrected at the cluster level

df - degrees of freedom

variables. In a second step, we added FA of the left arcuate fasciculus, the right arcuate fasciculus and the auditory interhemispheric pathway to investigate if the model improved significantly. All VIFs were below 1.9, indicating that multicollinearity was small. Prediction errors alone explained 11% of the variance in CAPE + scores ($F(4,82) = 3.644$, $R^2_{adj} = 0.11$, $p = 0.009$), but when FA of the three white matter tracts were added to the model the variance explained increased to 17.8% ($F(7,79) = 3.665$, $R^2_{adj} = 0.178$, $p = 0.002$). This significant increase in explained variance ($F_{change}(3,79) = 3.286$, $R^2_{change} = 0.094$, $p = 0.025$), indicates that mismatch responses and FA in auditory white matter pathways together better predict psychotic-like experiences in psychologically healthy individuals than mismatch responses alone. This regression analysis revealed that FA of the auditory interhemispheric pathway ($t(79) = -2.959$, $r = -0.345$, $p = 0.004$) and the FIV for the surprise*variance interaction at 145 ms ($t(79) = -3.266$, $r = -0.316$, $p = 0.002$) were significant independent predictors of CAPE + scores. To illustrate the relationship between CAPE + and the significant predictors (when controlling for the other independent variables) we show the partial correlation plots in Fig. 5. In Fig. 5a we show the CAPE + residuals (computed from regressing CAPE + against all independent variables except FIV at 145 ms) and the FIV at 145 ms residuals (computed from regressing the FIV for the surprise*variance interaction at 145 ms against the remaining independent variables). Similarly, in Fig. 5b we display the partial correlation for the CAPE + residuals (now regressing CAPE + without auditory interhemispheric FA) and the residuals of FA of the auditory interhemispheric pathway. This finding indicates that psychotic experiences increase as both FA of

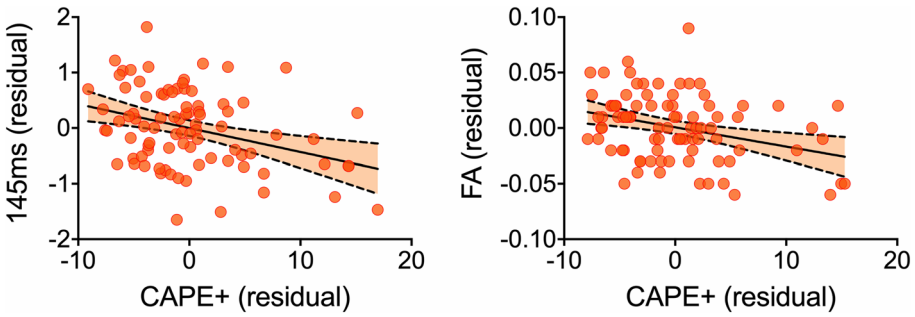

Fig. 5 Partial correlation plots for the two significant independent predictors derived from the regression analysis with positive psychotic experiences (CAPE+) as outcome variable and field intensity values (145 ms/155 ms) and fractional anisotropy (auditory interhemispheric pathway/left arcuate fasciculus/right arcuate fasciculus) as independent variables. The plot on the left displays the partial correlation between CAPE+residuals and the residuals of the field intensity values for the surprise*variance interaction at 145 ms. The plot on the right displays the partial correlation between CAPE+residuals and the residuals of fractional anisotropy (FA) of the auditory interhemispheric pathway. Error bands represent 95% confidence interval

the auditory interhemispheric pathway and the sensitivity to learn regularities in a stochastic environment decrease.

Discussion

The aims of the present study were (1) to investigate if auditory prediction error responses commonly reported in schizophrenia, are also associated with psychotic-like experiences in the healthy population and (2) to explore if structural estimates of auditory white matter pathways, thought to be altered in schizophrenia and previously associated with auditory prediction errors, could improve regression models of psychotic-like experiences in the healthy population over and above predictions made by auditory prediction error responses alone. We found that reduced auditory prediction error responses were associated with increasing positive psychotic-like experiences in healthy individuals, specifically in a stochastic context. These findings indicate that as the number of psychotic-like experiences increases the mismatch response and the ability to learn and detect violations to statistical regularities in a stochastic environment decrease. Critically, we found that models based on auditory prediction error responses in a stochastic environment significantly improved when fractional anisotropy of auditory white matter pathways were added to predict psychotic-like experiences.

The classical oddball paradigm failed to reveal significant effects with CAPE+scores within the MMN or P300 time windows, which is in line with findings by Broyd et al. (2016), who did not find group differences between high and low schizotypy groups. The stochastic oddball paradigm however, found clusters that fall within the typical MMN time-window (Sams et al. 1985). This is in line with MMN attenuation consistently observed in chronic schizophrenia, first-episode psychosis, and individuals at high risk for schizophrenia (Todd et al. 2008; Näätänen et al. 2015; Erickson et al. 2016). It should be noted that the classical and stochastic oddball paradigms are dissimilar in several ways which may explain the discrepancy of our results in the two paradigms. Specifically, the two paradigms differ on (1) the deviants used (frequency vs. duration), (2) deviant probabilities (simple vs. stochastic), and (3) the cognitive load of the incidental task (i.e. one back vs. two back). It is not possible to directly compare the two paradigms since MMN varies with both deviant type (Nagai et al. 2013) and deviant probabilities (Javitt et al. 1998), which are both different in the classical and stochastic paradigms used here. It is also worth pointing out that while it has been reported that increasing cognitive load does not decrease prediction error amplitude in healthy individuals (Otten et al. 2000; Garrido et al. 2016), it does so in people with schizophrenia (Rissling et al. 2013). Nonetheless, the finding that the stochastic, but not the classical oddball paradigm, demonstrated a differential association between MMN attenuation in the two contexts with increasing psychotic-like experiences. This suggests that complex oddball paradigms with abstract rules may be more sensitive for detecting prediction error deficits associated with psychotic-like experiences in healthy individuals.

Here we demonstrate that MMN amplitudes identified with the stochastic oddball paradigm in combination with strucutral measures of auditory white matter tracts are associated with psychotic-like experiences in healthy individuals, which are subtler than psychotic symptoms experienced by patients diagnosed with schizophrenia. Specifically, we observed that reducing fractional anisotropy of the auditory interhemispheric pathway and decreasing ability to learn stochastic irregularities are associated with increasing psychotic-like experiences in healthy individuals. A study investigating the association between the auditory interhemispheric pathway and psychotic symptoms in schizophrenia

observed decreased fractional anisotropy (indicative of white matter changes) and increased radial diffusivity (indicative of myelin changes) in patients with auditory verbal hallucinations compared to patients without auditory verbal hallucinations and healthy controls (Wigand et al. 2015). Similarly, our findings suggest that fractional anisotropy of the auditory interhemispheric pathway might be associated with psychotic-like experiences in the healthy population.

Contrary to findings in schizophrenia whereby reduced fractional anisotropy of the arcuate fasciculus has recurrently been linked to psychotic symptoms such as auditory verbal hallucinations (Geoffroy et al. 2014; McCarthy-Jones et al. 2015), we did not observe the arcuate fasciculi to be independent predictors of psychotic-like experiences in healthy individuals. Fractional anisotropy has been reported to deteriorate gradually with illness duration from early to chronic stages of schizophrenia (Friedman et al. 2008; Di Biase et al. 2017) and previous studies failed to observe fractional anisotropy changes of the arcuate fasciculus in first-episode schizophrenia (Peters et al. 2008) or individuals at high-risk for schizophrenia (Munoz Maniega et al. 2008). It is therefore possible that white matter changes associated with psychotic-like experiences are initially localized to auditory pathways in the corpus callosum and then advance to association tracts like the arcuate fasciculus with symptom development and prolonged illness duration. It is furthermore possible that other white matter tracts are implicated in psychotic experiences that were not included in our analyses. Indeed, in a recent structural connectome analyses, we reported widespread white matter reductions with increasing psychotic experiences in healthy individuals (Oestreich et al. 2018). More specifically, the cingulum bundle and the uncinate fasciculus have previously been linked to psychotic symptoms in schizophrenia (Kawashima et al. 2009; Whitford et al. 2014). However, both of these white matter connections are limbic association tracts that have specifically been implicated in delusions as opposed to auditory hallucinations (Fitzsimmons et al. 2014; Oestreich et al. 2016). While we restricted our analysis to auditory white matter pathways related to auditory prediction errors in this study, future prediction models may benefit from the inclusion of other white matter tracts.

We calculated fractional anisotropy estimates by averaging values across all voxels traversed by fibres of interest. It is possible that some voxels contain only few, potentially spurious, streamlines and could therefore be weighted less heavily when extracting fractional anisotropy values than voxels traversed by a large quantity of streamlines. The fact that we did not account for streamline density therefore represents a limitation of our study. Another limitation is the two-step approach we took to identify predictors of CAPE + scores. We first used CAPE + dimension scores as a predictor variable with spatiotemporal contrasts as an outcome variable. This allowed us to isolate spatiotemporal clusters significantly associated with CAPE + scores. In our final regression analysis, we entered these clusters together with the fractional anisotropy values of the auditory interhemispheric pathway and arcuate fasciculi as predictor variables, and psychotic experiences as outcome variable. In doing so, we reversed the regression model by using the field intensity values as outcome (used as predictor variables in the first regression step). The rationale behind this approach was to investigate whether structural estimates of auditory white matter tracts can improve predictions of psychotic experiences over and above predictions based on functional ERP measures alone. While the first regression therefore served the purpose of identifying clusters that are associated with psychotic experiences, the second regression analyses was conducted to explore if this association could be strengthened by including structural measures. Furthermore, the range of scores on the positive dimension of the CAPE in our study (i.e. 20–45) seems relatively low, given that the highest possible score is 80. However, a study by (Mossaheb et al. 2012) assessed a clinical, help-seeking population with the CAPE and established cut-off scores to identify individuals at ultra-high risk for developing psychosis. In this study, dimension scores were calculated by dividing the total score within a dimension by the number of questions on that dimension. The resulting cut-off score for ultra-high risk individuals was 2.8. When calculated according to this procedure, the range of scores in our study was 0–0.2.5 with an average of 1.32. Given that our participants were drawn from a healthy population and we excluded participants with a psychiatric disorder and individuals taking antidepressant medication, we believe that the distribution of positive scores in our sample reflects that of a healthy population. The lack of a clinical schizophrenia group limits the extent to which the findings of the present study might be informative for the identification of psychosis biomarkers. Future studies including clinical cohorts will be key in determining whether the structural and functional predictors of psychotic-like experiences identified in the present study are valuable psychosis symptom predictors. In the future, comparing healthy individuals with psychotic-like experiences to individuals at high risk for psychosis, first-episode schizophrenia patients and chronic schizophrenia patients longitudinally will reveal whether the observed changes can provide prognostic clues about illness progression.

In conclusion, we found that reducing sensitivity to auditory regularities in a stochastic environment and decreasing fractional anisotropy of the auditory interhemispheric pathway are associated with psychotic-like experiences in healthy individuals. To the extent that these structural and functional brain connectivity changes have previously been reported in patients with schizophrenia, the findings of this study suggest that both MMN and white matter changes in

the auditory interhemispheric pathway may have a translational potential as early screening markers for psychosis.

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