Schizophrenia Research xxx (xxxx) xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Aberrant connectivity in auditory precision encoding in schizophrenia spectrum disorder and across the continuum of psychotic-like experiences

Kit Melissa Larsen [a,b,c,d,*], Ilvana Dzafic [a,b,e], Hayley Darke [e], Holly Pertile [f,g], Olivia Carter [e], Suresh Sundram [f,g], Marta I. Garrido [a,b,e,h]

[a] Queensland Brain Institute, The University of Queensland, Australia
[b] Australian Research Council of Excellence for Integrative Brain Function, Australia
[c] Danish Research Centre for Magnetic Resonance, Centre for Functional and Diagnostic Imaging and Research, Copenhagen University Hospital Hvidovre, Hvidovre, Denmark
[d] Child and Adolescent Mental Health Centre, Mental Health Services Capital Region Copenhagen, University of Copenhagen, Denmark
[e] Melbourne School of Psychological Sciences, University of Melbourne, Australia
[f] Department of Psychiatry, School of Clinical Sciences, Monash University, Clayton, VIC, Australia
[g] Monash Medical Centre, Monash Health, Clayton, VIC, Australia
[h] Centre for Advanced Imaging, The University of Queensland, Australia

ARTICLE INFO

Article history:
Received 19 February 2020
Received in revised form 11 May 2020
Accepted 27 May 2020
Available online xxxx

Keywords:
Posterior probability maps
Dynamic causal modelling
MMN
Schizophrenia
EEG
Schizotypy
Psychosis

ABSTRACT

Background: The ability to generate a precise internal model of statistical regularities is impaired in schizophrenia. Predictive coding accounts of schizophrenia suggest that psychotic symptoms may be explained by a failure to build precise beliefs or a model of the world. The precision of this model may vary with context. For example, in a noisy environment the model will be more imprecise compared to a model built in an environment with lower noise. However compelling, this idea has not yet been empirically studied in schizophrenia. Methods: In this study, 62 participants engaged in a stochastic mismatch negativity paradigm with high and low precision. We included inpatients with a schizophrenia spectrum disorder (N = 20), inpatients with a psychiatric disorder but without psychosis (N = 20), and healthy controls (N = 22), with comparable sex ratio and age distribution. Bayesian mapping and dynamic causal modelling were employed to investigate the underlying microcircuitry of precision encoding of auditory stimuli. Results: We found strong evidence (exceedance $P > 0.99$) for differences in the underlying connectivity associated with precision encoding between the three groups as well as on the continuum of psychotic-like experiences assessed across all participants. Critically, we show changes in interhemispheric connectivity between the two inpatient groups, with some connections further aligning on the continuum of psychotic-like experiences. Conclusions: While our results suggest continuity in backward connectivity alterations with psychotic-like experiences regardless of diagnosis, they also point to specificity for the schizophrenia spectrum disorder group in interhemispheric connectivity alterations.

1. Introduction

The ability to adapt to the ever changing environment and make inferences about future events is robustly reduced in people with schizophrenia (Adams et al., 2013; Fletcher and Frith, 2009; Kapur, 2003). This has been studied in a classical laboratory setting using auditory oddball paradigms where unpredictable ("oddball") sounds are interspersed in a stream of frequently occurring standard sounds. Such paradigms elicit a mismatch (MMN) response (Garrido et al., 2009b; Näätänen, 1995) or sensory prediction error. According to the predictive coding framework and the model-adjustment hypothesis for MMN (Winkler et al., 1996), this error response is caused by a violation to the regularities, arising when sensory input does not match the prediction according to a learnt model (Friston, 2005). The precision of this model varies according to the precision of context itself, such that a noisier environment will lead to the formation of more unreliable predictions than those formed in a stable environment (Mathys et al., 2011).

The MMN is robustly reduced in schizophrenia (Erickson et al., 2016; Umbricht and Krljes, 2005), first episode psychosis (Haigh et al., 2016) and in individuals with high risk for schizophrenia (Atkinson et al., 2012; Perez et al., 2014), hence suggesting that the ability to generate a precise model of the environment is reduced in schizophrenia and to some extent in the continuum of psychosis (Randeniya et al., 2017; van Os et al., 2009). Recent predictive coding accounts put forward

* Corresponding author at: Danish Research Center for Magnetic Resonance, Kettegårds Allé 30, 2650 Hvidovre, Denmark.
E-mail address: melissal@drcmr.dk (K.M. Larsen).

https://doi.org/10.1016/j.schres.2020.05.061
0920-9964/

that the range of psychotic symptoms in schizophrenia can be explained by a failure to build precise beliefs or a model of the world (Adams et al., 2013). The underlying processes of MMN generation involve both adaptation (neural habituation due to repeated standard sound stimuli) and prediction formation (guessing what might come next) (Garrido et al., 2009b; Larsen et al., 2019) It is unclear whether the consistent reductions of MMN in schizophrenia are caused by a failure of either adaptation or prediction, or both (Michie and Malmierca, 2016). Adaptation and prediction formation are hard to disentangle with classical oddball paradigms because they typically evoke both processes simultaneously. Effective connectivity modelling attempts (i.e. inferring the dynamic effect one brain region has on another (Friston et al., 2003)), point to both adaptive and predictive processes being affected in schizophrenia (Dima et al., 2012). In that study, dynamic causal modelling (DCM) was used to show that patients with schizophrenia have altered connectivity within the top-down connection from the right inferior frontal gyrus to the right superior temporal gyrus, as well as in the intrinsic connection (self-connection) within right primary auditory cortex. These two types of connections (intrinsic and top-down) are believed to reflect adaptation and prediction processes respectively, indicating that both processes were affected in that sample. We have further shown evidence that the same connections are altered in non-psychotic individuals with a genetic high risk for developing schizophrenia (Larsen et al., 2018). Such connectivity disruptions might explain the failure to build a precise (top-down) belief or model of the world.

While the majority of previous studies on MMN in schizophrenia have been case-control studies assessing group differences, recent results indicate that a continuum perspective of psychosis is more powerful in explaining real-world functioning rather than a categorical approach as proposed in the Diagnostic and Statistical Manual of Mental Disorders (DSM) (Hanlon et al., 2019; Owen, 2014; Owen and O'Donovan, 2017). According to the continuum view, the major clinical symptoms reflect the degree of alterations in brain function resulting in functional abnormalities (Owen and O'Donovan, 2017). Hence, while the categorical approach is very useful for diagnostic purposes, the behavioural and brain alterations may not always follow this dichotomy and its aetiology might be best aligned on a continuum. An evident manifestation of this is precisely the MMN attenuation over the psychosis continuum (Randeniya et al., 2017).

Here, we set out to investigate prediction errors with precision of the prediction manipulated to be either high or low in inpatients with a schizophrenia spectrum disorder (schizoaffective disorder or schizophrenia), inpatients with a psychiatric disorder but without psychosis, and healthy controls. We will adopt two approaches, a group comparison and a continuum approach along the dimension of psychotic-like experiences across all participants (N = 62, patients and controls) and parameterised by psychotic like experiences. The group approach will enable inferences on the specificity of connectivity changes in the schizophrenia spectrum group given our inpatient control group with a psychiatric diagnosis but without psychosis. The continuum approach will allow us to make inferences about how precision encoding and brain connectivity varies with the degree of psychotic-like symptoms irrespective of group membership. We use a stochastic MMN paradigm previously validated in healthy controls (Garrido et al., 2013) that allows us to tap into predictive processes while mitigating adaptive processes, as well as to manipulating precision levels in the auditory environment. We hypothesise that the ability to encode the level of precision is reduced in the schizophrenia spectrum group compared to the two (non-psychosis and healthy) control groups. We expect this will be present both at the scalp level as well as in the effective connectivity. In addition, we hypothesise that the ability to encode precision decreases over the continuum of psychotic-like experiences across the whole sample.

2. Methods

2.1. Participants

62 participants took part in the study, with 20 inpatients with a schizophrenia spectrum disorder (SZS), 20 non-psychotic inpatients controls (NP), and 22 healthy controls (HC). Inpatients were recruited from the Monash Medical Centre, acute adult psychiatric inpatient facility. HC's were recruited through the Psychology Research Participation Scheme (SONA), using Gumtree, and flyers distributed around the Monash Medical Centre. Participants provided written informed consent before taking part in the study. The inpatients were clinically assessed by their case clinician with respect to their capacity to consent to participate, before referral to the research study. Participants received monetary reimbursement for their time. This research was approved by the Monash Health Human Research Ethics Committee.

The positive and negative syndrome scale (PANSS) (Kay et al., 1987) for schizophrenia was used to assess the symptoms of the two inpatient groups. In addition, the community assessment of psychic experience (CAPE) (Mossaheb et al., 2012) was administered to all participants in order to asses psychotic-like experiences across the continuum, including all three groups. The National Adult Reading Test (NART) (Nelson and W.J., 1991) was administered to get a proxy for IQ. Diagnoses for both groups of patients were made by the treating psychiatrist based on DSM-V criteria. Healthy controls were excluded if they had a history of a psychiatric or neurological disorder. Diagnoses within the NP group were: major depressive disorder; borderline personality disorder; post-traumatic stress disorder; or general/social anxiety. People in SZS group either had a diagnosis of schizoaffective disorder or schizophrenia. Groups were comparable with respect to sex ratio (HC: 12 males and 10 females, NP: 13 males and 7 females, SZS: 15 males and 5 females $\chi^2 = 1.92$, $P = 0.38$) and age distribution (HC: mean age = 34.09 years, standard deviation (SD) = 7.96 years; NP: mean age = 36.10 years, SD = 9.32 years; SZS: mean age = 34.30 years, SD = 7.33 years $F_{(2,61)} = 0.37$, $P = 0.69$). CAPE positive (CAPE+) scores differed overall between groups ($F_{(2,61)} = 3.049$, $P = 2.4 * 10^{-5}$). Post-hoc follow-up tests showed higher values for SZS than both NP ($P = 0.020$) and HC ($P = 1.4 * 10^{-5}$) but there was no difference between HC and NP ($P = 0.103$). The SZS group had greater positive ($t_{38} = -6.259$, $P = 3 * 10^{-7}$) and total ($t_{38} = -4.691$, $P = 3.5 * 10^{-5}$) PANSS scores compared to the NP group. There was no difference on the negative ($t_{38} = -1.422$ $P = 0.163$) and general ($t_{38} = -1.588$, $P = 0.120$) PANSS scores between NP and SZS. There was no difference in the approximation of IQ from the NART scores between the groups, see Table 1. However, years of education varied significantly between the groups, which is counterintuitive to the IQ results. This may be due to variance between groups as to English being their first language. Chlorpromazine equivalent doses were calculated for the two inpatient groups and correlated with connection strengths to rule out effects of antipsychotic medications on observed group and continuum results. A summary of the symptomatology and demographics can be seen in Table 1 and in Supplementary Fig. 1. Data relating to cigarette smoking and other substance use was collected as self-report data without any objective method of verification such as urine or blood sampling or family/carer confirmation. Unfortunately, we do not have data available for all participants. As such, it was determined that its reliability was too compromised to include in the analyses.

2.2. Stimuli

All participants engaged in a stochastic auditory paradigm in which participants listened to a stream of pure tones (Garrido et al., 2013). The tones were sampled from two different Gaussian distributions in log-frequency and centred at 500 Hz, see Fig. 1A. The two distributions had either low variance (0.5 octaves above mean) or high variance (1.5 octave above mean). Tones were presented every 500 ms with a

Please cite this article as: K.M. Larsen, I. Dzafic, H. Darke, et al., Aberrant connectivity in auditory precision encoding in schizophrenia spectrum disorder and across t..., Schizophrenia Research, https://doi.org/10.1016/j.schres.2020.05.061

Table 1
Summary of demographic data. Illness duration had missing data for 5 NP and 3 SZS. WAIS IQ scores are predicted from the National Adult Reading Test. Abbreviations: WAIS = Wechsler Adult Intelligence Scale; CAPE = community assessment of psychic experience; SD = standard deviation; substance use disorders = SUD; personality disorders = PD; depressive disorders = DD; anxiety disorders = AD; schizoaffective = SZA; schizophrenia = SZP; somatic symptom disorder = SSD. Note the DD and SSD in the SZS group is a comorbidity with SZP.

	HC (N = 22) Mean (SD)	NP (N = 20) Mean (SD)	SZS (N = 20) Mean (SD)	Statistic
Sex	Female: 10, Male: 12	Female: 7, Male: 13	Female: 5, Male: 15	$P = 0.380$
Age (years)	34.09 (7.96)	36.10 (9.32)	34.30 (7.33)	$P = 0.690$
WAIS-R IQ estimate (from NART)	102.29 (7.60)	103.47 (9.16)	101.79 (7.21)	$P = 0.800$
Years education	14.75 (2.31)	12.75 (2.34)	11.4 (2.11)	$P = 5 * 10^{-5}$
CAPE positive	27.05 (6.44)	32.15 (8.40)	38.95 (8.02)	$P = 2.4 * 10^{-5}$
PANSS positive	N/A	10.55 (3.85)	21.20 (6.57)	$P = 3 * 10^{-7}$
PANSS negative	N/A	11.40 (3.77)	13.65 (5.99)	$P = 0.163$
PANSS general	N/A	30.85 (3.51)	34.00 (8.14)	$P = 0.121$
PANSS total	N/A	52.80 (6.80)	69.35 (13.70)	$P = 3.5 * 10^{-5}$
Illness duration (years)	N/A	5.80 (6.08)	9.58 (8.47)	$P = 0.1627$
CPZE	N/A	125.83 (220.87)	583.70 (295.86)	$P = 2.4 * 10^{-6}$
Diagnoses (including comorbidities)	N/A	DD: 12 SUD: 8 PD: 6 AD: 4	SZA: 7 SZP: 13 DD: 1 SSD: 1	

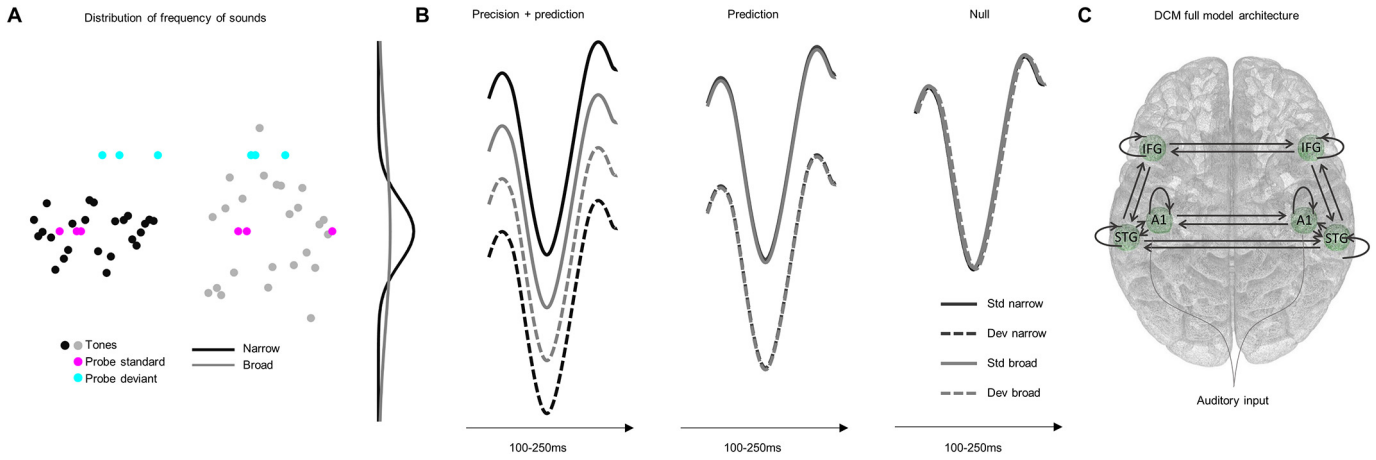


Fig. 1. Auditory paradigm, the three models for ERP scalp data and the DCM network architecture. A: The distribution of frequency of sounds are either following a narrow Gaussian distribution indicating high precision (black) or broad distribution indicating low precision (grey). Probe tones are indicated in turquoise for standards and magenta for oddballs. B: The precision + prediction model entails that both precision and prediction are encoded. The prediction model entails that a difference between standard and deviant tones are encoded but not the difference between broad and narrow context. Finally, the null model is representing that neither prediction nor precision is encoded. C: The full hierarchical DCM model, including bilateral inferior frontal gyrus (IFG), superior temporal gyrus (STG) and finally primary auditory cortex (A1). All connections are allowed to be modulated by the precision. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

duration each of 50 ms and a rise and fall time of 10 ms. Within the random frequency stream, probe tones of either frequency equal to the mean (500 Hz) or 2 octaves above the mean (2000 Hz) were embedded pseudo randomly 10% of the time. In what follows, we refer to the probe tone centred at the mean as the "standard" and the probe tone of 2000 Hz as the "deviant". For an extensive description of the paradigm see Garrido et al. (2013). Participants were asked to ignore the tones while performing a visual 1-back task, which entailed detecting repetitions of letters continuously presented, not coinciding with the sounds.

2.3. EEG recordings and preprocessing

EEG data was recorded using a 64 channel Biosemi active two with electrodes arranged according to the 10-20 system and a sampling frequency of 1024 Hz. All offline preprocessing was performed using SPM 12 (http://www.fil.ion.ucl.ac.uk/spm/), which included high and low pass filtering with a 5th order Butterworth filter with a cut-off of 0.5 Hz and 40 Hz respectively. Data was epoched with a peristimulus interval of −100 ms to 400 ms, with baseline correction applied from −100 ms to −5 ms. Finally, artefact rejection was performed using a simple threshold technique rejecting trials if amplitudes exceed ± 100 μV, and finally the signals were referenced to the average of all electrodes.

2.4. Differences in MMN responses

Group differences in MMN responses were assessed using a one-way repeated measures ANOVA testing for differences in mean values across groups with the factor precision (broad and narrow) as within-subject factor. Mean amplitudes of MMN calculated as the mean values of ± 30 ms around the pooled group grand average peak were entered for each individual participant.

2.5. Posterior probability maps – modelling the encoding of precision at the scalp level

We used Bayesian posterior probability maps on EEG data (Harris et al., 2018; Rosa et al., 2010) (at the scalp level) to test three different models: 1) prediction is formed, 2) both prediction and precision are encoded, 3) none are encoded - the null model. Bayesian maps enable the comparison of an arbitrary number of hypotheses (or explanations for observed neural responses), at each and every brain voxel (fMRI,

or source level M/EEG) and/or in the scalp-time volume (scalp level), both within participants and at the group level. To compare the three models for event-related potentials (ERPs), we used Bayesian model comparison, on posterior probability maps (Harris et al., 2018; Rosa et al., 2010) as we have recently applied in Larsen et al. (2019). In this way, it is possible to infer across time and space which model is most likely. Epoched data were converted into scalp-map images of dimension 32×32 obtained using interpolation and smoothed using a Gaussian kernel specified by a FWHM of $8mm^2$ in the spatial dimension and 10 ms in the temporal dimension. Individual participant voxel-wise whole brain log-evidences were calculated using regressors describing the hypothesized relationship amongst the four conditions $standard_{narrow}$, $standard_{broad}$, $deviant_{broad}$, $deviant_{narrow}$ ([1 2 3 4] for the precision + prediction model, [1 1 2 2] for the prediction model and [1 1 1 1] for the null model), see Fig. 1B. We did not test for the model only including precision and not prediction, given previous work demonstrating that prediction is indeed encoded in this particular paradigm (Garrido et al., 2013, 2016). Note that a model precluding prediction encoding would correspond to the absence of MMN. The log-evidence for each model were estimated using the variational Bayes first-level model specification (Penny et al., 2005). Group level posterior probability maps were calculated using the random effects approach (RFX) for each model and each group. These probability maps can then be used to compare and select amongst the three different models for each voxel and time point.

2.6. Dynamic causal modelling

Next, we used dynamic causal modelling (DCM) to investigate the underlying microcircuitry of precision encoding in the three groups. We were here interested in what specific connections encoding precision are modulated by the individual expression of CAPE+ both on a continuum and across the three groups. The network architecture underlying MMN has previously been established (Garrido et al., 2009a; Larsen et al., 2018) to include bilateral primary auditory cortex, the superior temporal gyrus and the inferior frontal gyrus. We made a fully connected network comprising intrinsic, lateral, forward and backward connections at all levels. We modelled the modulatory effect of precision with the prediction error response in the broad condition as baseline (low precision) and the narrow condition (high precision) as 1. All connections within the network were allowed to be modulated and this full model was inverted for each individual participant, see Fig. 1C. Our models includes reciprocal lateral connections given their anatomical evidence (Karolis et al., 2019; Steinmann et al., 2014) and known alterations in schizophrenia (Steinmann et al., 2019) and further on the CAPE continuum (Oestreich et al., 2019). All reported results are from the B matrix, i.e. the matrix containing the connectivity modulated by precision.

2.7. Modelling group differences in connectivity

To look into which connections modulated by precision of prediction error responses are modulated by group membership, we used a hierarchical model over the parameters as implemented in the parametric empirical Bayes framework (Friston et al., 2016) in SPM12 (http://www.fil.ion.ucl.ac.uk/spm/). Here, we entered two regressors for the group membership, one modelling the main effect of being a patient (1 for the control group and −1 for both the NP and SZS group). The second regressor of interest modelled the difference between the two patient groups (0 for HC, 1 for the NP group and −1 for SZS group). Age and gender were entered as regressors of no interest and all regressors were mean centred. This design allowed us to tap into which connections were different overall between the controls and the two patient groups, and more specifically which connections were different between the two patient groups (i.e. specific to the schizophrenia spectrum). We report results that exceed 99% posterior probability, indicating very strong evidence that these connections are indeed modulated.

2.8. Modelling changes in connectivity associated with CAPE+

To estimate systematic variations in model parameters on the continuum of CAPE+ scores, we created another second level model over the parameters. In this second level model, we entered CAPE+ scores as a regressor of interest together with age and gender as regressors of no interest. All regressors were mean centred. With this design we can estimate what connections in our DCM network change as a function of CAPE+ scores. We report with 99% probability on connections that had an association with CAPE+ (given the model tested).

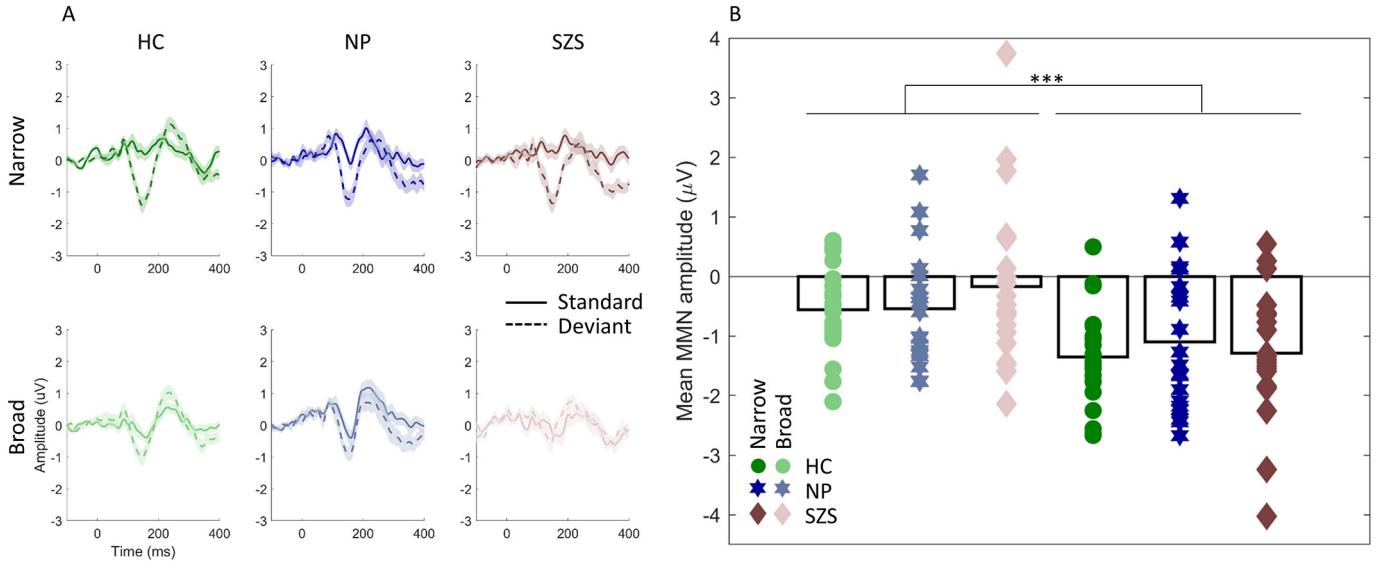


Fig. 2. A: Responses to standard and deviant tones in the narrow (first row) and broad (lower row) context, NT in green, NP in blue and SZS in brown. Dark colours represents narrow context and light colours represents broad context. B: Mean MMN amplitude for the three groups in the two contexts, dots represents individual participants and bars group means, colour-coding same as in A. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Please cite this article as: K.M. Larsen, I. Dzafic, H. Darke, et al., Aberrant connectivity in auditory precision encoding in schizophrenia spectrum disorder and across t..., Schizophrenia Research, https://doi.org/10.1016/j.schres.2020.05.061

3. Results

There was no overall difference in the performance on the 1-back task when comparing d′ and reaction times across groups, see Fig. 2 in Supplementary material. This rather easy task was intentionally chosen to keep participants engaged during the experiment, while avoiding potential confounds of task performance across groups.

3.1. Precision is encoded in all groups

To test for differences in MMN responses between the broad and the narrow context, we took the mean around the peak for the MMN response for each group, Fig. 2. MMN amplitudes differed between broad and narrow context across the three groups $F_{(1,59)} = 25.188$, $P = 5.1 * 10^{-6}$, showing a strong overall effect of precision. There was no difference in MMN responses between groups ($F_{(2,59)} = 0.421$, $P = 0.658$) as well as no interaction between group membership and the context (or precision) ($F_{(2,59)} = 0.954$, $P = 0.391$).

3.2. Patients with schizophrenia spectrum disorder encode precision, but to lesser extent than non-psychotic inpatients and healthy controls

To answer the question of which of the three models were employed by each of the three groups, we plotted the exceedance probability as a function of time, summed across electrodes, Fig. 3A. Overall, the null model expressing no difference between standards and deviants in the two contexts had highest exceedance probability in all time points except for the time window of the MMN response (100–200 ms), across the three groups. The model encoding precision (turquoise), as expected, showed highest probability in the time window of MMN, when prediction violations typically manifest. In that same window, HC and NP patients showed higher exceedance probability for the precision + prediction model than prediction only, whereas the SZS group showed equal probabilities across the two models. Hence, results indicate that during the time window of the MMN, HC's and NP inpatients encode precision of prediction, whereas the SZS group show this to a lesser extent. To test whether this effect was significant between the groups, we entered the regressors of the precision + prediction model as a contrast into the GLM at the scalp level, allowing us to test for specific group effects in the precision encoding, Fig. 3B. Hence, the contrast vector for HC < SZS would be $[1\ 2\ 3\ 4]_{HC} - [1\ 2\ 3\ 4]_{SZS}$. The SZS group showed reduced responses relatively to NT peaking at 248 ms in central-temporal channels, and at 104 ms in right fronto-central channels compared to the NP group. NP further showed an increased response compared to HC's at fronto-central channels peaking at 107 ms, see Fig. 3B. No significant effects were found for the reversed comparisons.

3.3. Brain connectivity is modulated by group membership

We asked which connections encoding precision differed between group membership. We found that the two patient groups overall had decreased lateral connectivity strength from left to right STG as well as top-down reductions from right IFG to STG when compared to the neurotypical control group. In comparison, the top-down connection from right STG to right A1 and the lateral connection from right to left STG was increased overall in the two patient groups compared to HC's, see Fig. 4A. Critically, we found that five lateral connections differed between the two patient groups, hence indicating specificity to the schizophrenia spectrum. Specifically, connections from left to right IFG and right to left A1 were decreased in the SZS group compared to the NP group. Lateral connections from the right to left IFG, as well as bi-directional connection between left and right STG, showed increased strength in SZS compared to the NP group, Fig. 4B. In order to rule out medication effects on connectivity parameters showing significant group effects we calculated Pearson correlations between CPZ scores and connectivity parameters. This revealed that greater connectivity from left to right STG for greater chlorpromazine equivalent scores ($\rho = 0.422$, $P = 0.034$ corr, $P = 0.0068$ uncorr). None of the other connections correlated with the medication dose. Years of education, as expected, varied between the three groups. To rule out the effect that this might have had on the connectivity differences we then conducted post hoc analyses including years of education as a covariate. All reported connections persisted as significant. However, one additional connection, from left STG to left A1, increased in the two patient groups compared to the neurotypical group. This connection was greater in the SZS compared to the NP group.

3.4. Brain connectivity is modulated by psychotic-like experiences CAPE+

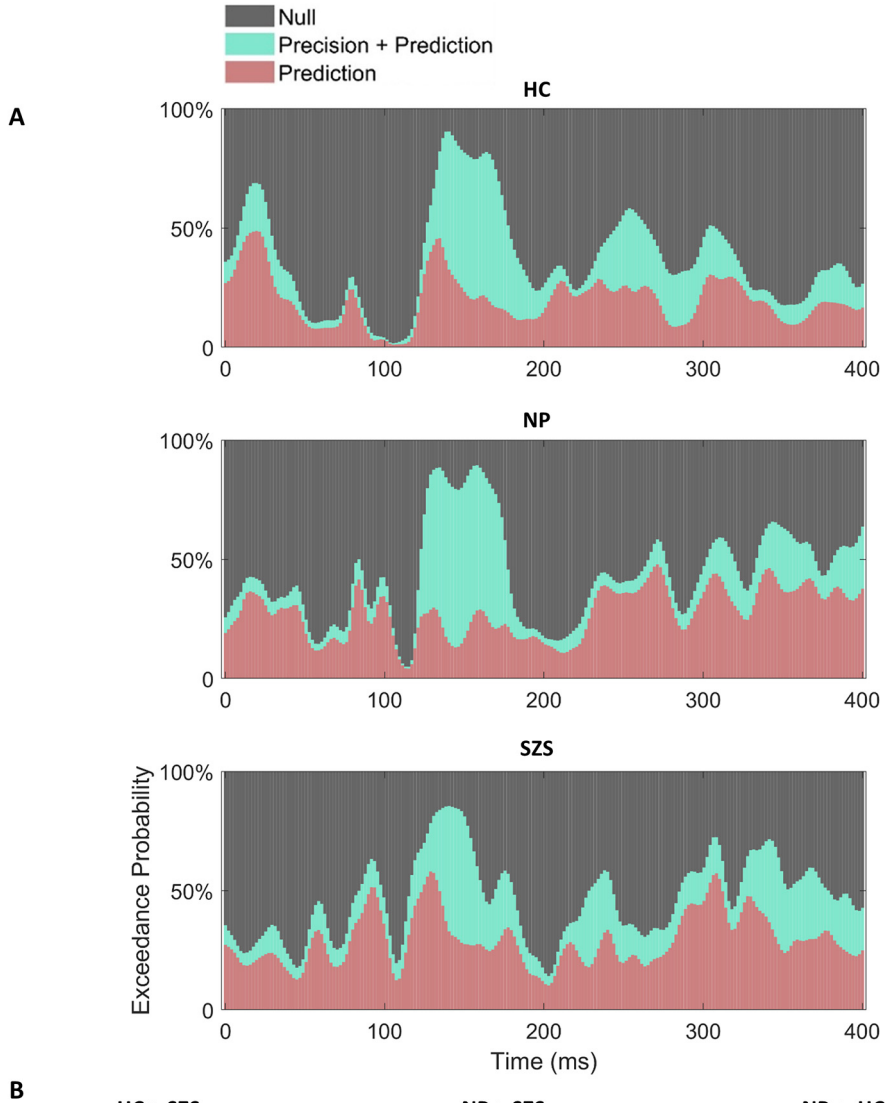
Most of the individuals in the SZS group, and in the NP group to some degree, had psychotic symptoms as measured by the PANSS. Across both patient groups there was a high correlation between CAPE+ and the PANSS positive symptoms score ($\rho = 0.488$, $P = 0.001$, see Fig. 1 in Supplementary material), indicating a high consistency between CAPE+ and PANSS positive symptoms. We therefore used the CAPE+ (instead of PANSS, which was only administered in the two patient groups) in order to align all participants on a continuum of psychotic-like experiences, including those in the healthy control group. By modelling the difference in contextual precision using the parametric empirical Bayesian framework in DCM, we were able to reveal which connections account for precision encoding and are modulated by the individual expression of CAPE+ across the whole sample. As mentioned previously, we report connections with associations above 99% exceedance probability. Lateral connections in both directions between IFG, as well as the top-down connection between right IFG and STG was negatively associated with CAPE+. The lateral connection from right to left STG as well as the bottom-up connection from right STG to right A1 were positively associated with CAPE+, see Fig. 5A. Hence, we see differences not only in the connectivity underlying precision encoding between the groups, but also individual connectivity alterations as a function of CAPE+ scores across the psychosis continuum. None of the connections associated with the CAPE+ scores were correlated with the chlorpromazine equivalent doses. In order to check whether group membership had an effect on the regression with CAPE+ scores, we repeated the analysis covarying out group membership, see Fig. 5B. The lateral connection from right STG to left STG disappears suggesting that changes in this connection can be explained by group membership more generally (rather than specifically CAPE). Two new connections become significant (right intrinsic A1 decreasing with CAPE and right STG to right IFG increasing with CAPE). Further, as in the group analysis above, we included years of education as a post hoc covariate where again all connection persisted but reciprocal lateral connections between left and right A1 became significant as well.

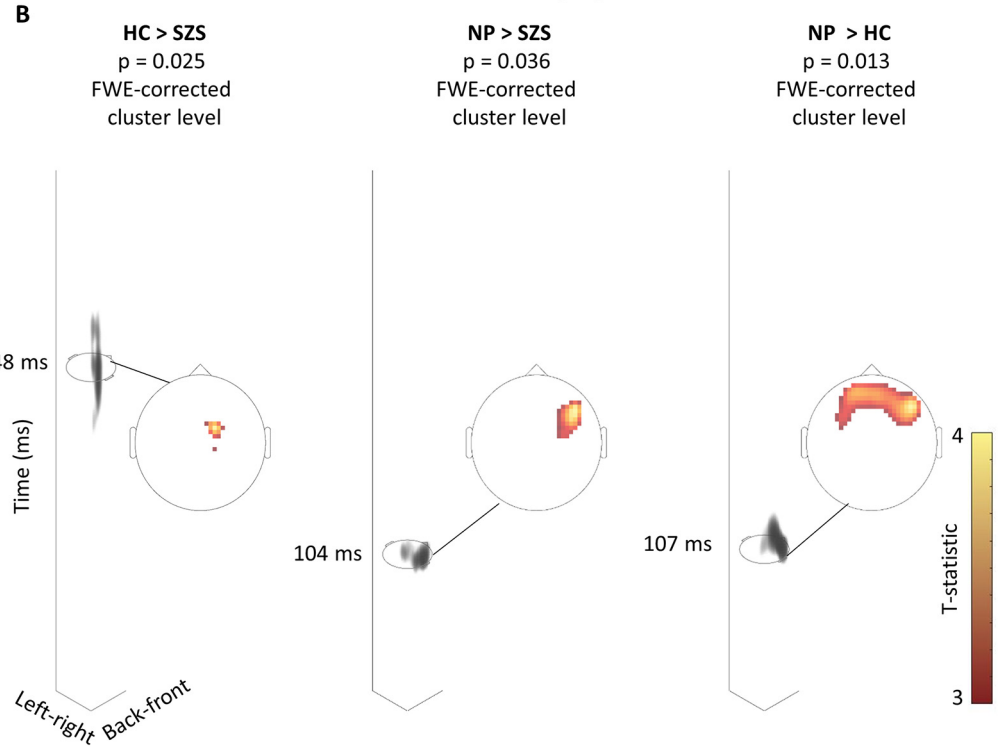
4. Discussion

Here we show that patients with schizophrenia spectrum disorder have alterations in the encoding of contextual precision that are associated with aberrant brain effective connectivity. Critically, we show that part of this connectivity alteration is specific to schizophrenia spectrum with the effect being present in the schizophrenia spectrum group but not the two control groups. We found not only group differences in the connectivity, but also connectivity changes across individuals on the continuum of CAPE+ scores. In addition, we showed that the schizophrenia spectrum group encodes both precision and prediction, albeit to a lesser extent than the respective non-psychotic patients and healthy controls. Medication effects were confined only to one connection linking left to right superior temporal gyrus.

We found group differences in the top-down connection from right IFG to STG. Further, this connection decreased with CAPE+. Perhaps not coincidently, this exact connection has previously been found to be

Please cite this article as: K.M. Larsen, I. Dzafic, H. Darke, et al., Aberrant connectivity in auditory precision encoding in schizophrenia spectrum disorder and across t..., Schizophrenia Research, https://doi.org/10.1016/j.schres.2020.05.061





Please cite this article as: K.M. Larsen, I. Dzafic, H. Darke, et al., Aberrant connectivity in auditory precision encoding in schizophrenia spectrum disorder and across t..., Schizophrenia Research, https://doi.org/10.1016/j.schres.2020.05.061

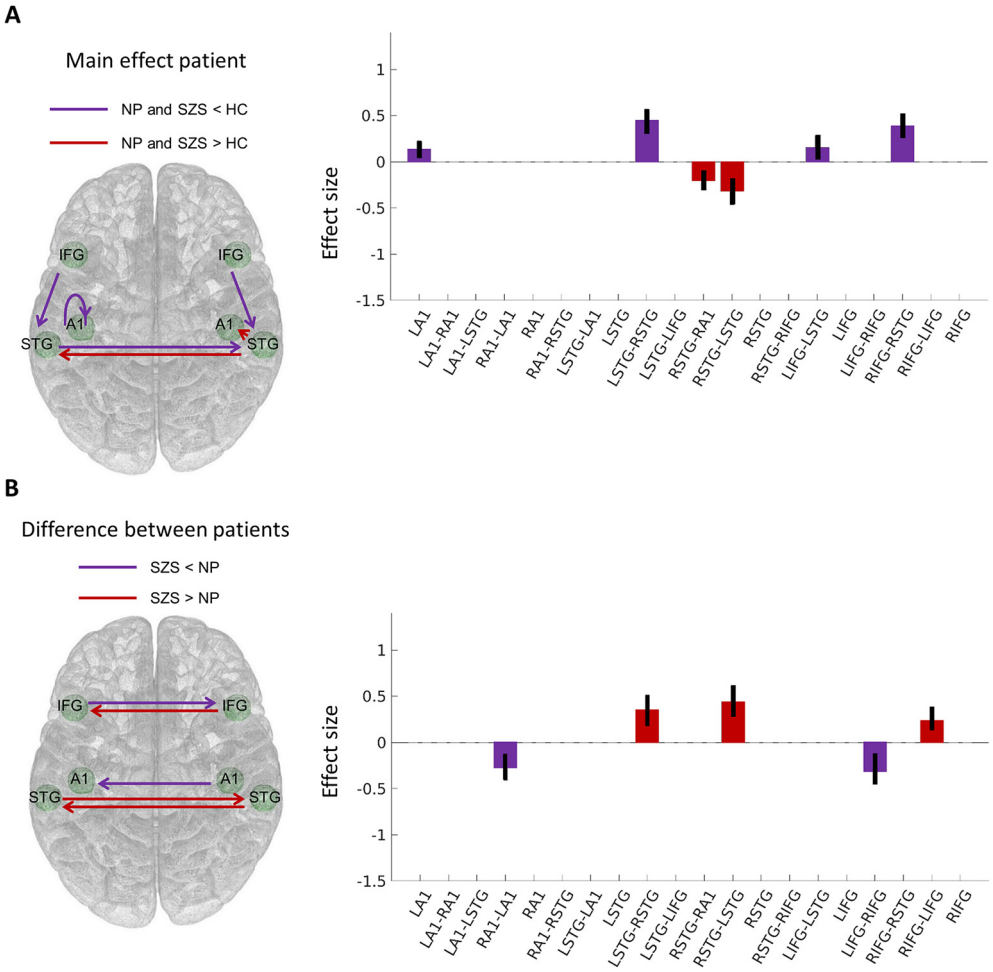


Fig. 4. Connections modulated by group membership (A and B) and CAPE+ scores (C) with an exceedance probability of at least 99% (very high evidence). A: main effect of patient, hence overall difference between HC and the two patient groups. Purple indicates connections where the two patient groups showed reduced connectivity when compared to HC, and red is where HC show less connectivity than the patient groups. B: connections showing differences between the two patient groups. Purple indicate connections where SZS show less connectivity than NP and red indicates SZS > NP. Note that the left to right STG connection is likely driven by medication effects. Dots correspond to individual participants in the HC group (green), NP (blue) and SZS (light red). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

weaker in schizophrenia (Dima et al., 2012) and in non-psychotic individuals with increased genetic risk for schizophrenia (Larsen et al., 2018). According to the predictive coding framework, top-down connections convey predictions, suggesting that as CAPE+ increases, distorted predictions are sent down the cortical hierarchy where precision is encoded. However, this connection did not show specificity to the schizophrenia spectrum group since no difference was found between this group and the NP group. In addition, we found that the two patient groups had decreased intrinsic connectivity within left A1, a connection thought to reflect adaptation (Kiebel et al., 2007). This connection was found exclusively in the patient groups, hence not specific to the SZS group nor modulated by CAPE+. Therefore, considering our findings we suggest that this connection is affected more generally across psychiatric disorders or may be medication related, although there was no correlation with antipsychotic dose. It is important to note that positive symptoms were grouped together, that is, not divided into hallucinations, delusions etc. And yet, different kinds of positive symptoms may carry with them vastly different signatures from a predictive processing standpoint, see Corlett et al. (2019). The CAPE-42 questionnaire used here has good validity in terms of lumped positive experiences/symptoms, but the same cannot be said for dividing the positive domain into further subdimensions. Future work with larger samples and targeting groups that fill in the gaps of the continuum will reveal whether such relationships are general to CAPE+ or specific to certain symptom subdimensions.

A limitation to the current study is that we do not have a control continuum. In this way we can only report on the observed results but cannot say if this is specific to psychosis.

The SZS group showed reduced connectivity in lateral connections from left to right IFG and from right to left A1 as compared to the NP patient group suggesting that such reductions are specific to schizophrenia spectrum disorders. This is in line with previous results as it is robustly found that schizophrenia is associated with an interhemispheric disconnection (Bleich-Cohen et al., 2012; Chang et al., 2015; Guo et al., 2014;

Fig. 3. Precision and prediction are less encoded in schizophrenia spectrum disorder. A: Exceedance probability as a function of time, summed across space for the precision + prediction model (turquoise), prediction model (red) and null model (black). B: Regressors from the prediction + precision model were entered into the second level GLM to test for group differences for this effect across time and space. To the left statistical T-maps for HC > SZS is shown, middle is NP > SZS and finally to the right NP > HC. On the time axis it can be seen where in time there is significant activity for the given contrast as indicated with grey shading. The significant areas (over electrodes) for a given contrast are visualised within the topographic plot. The colour indicates a correspondence with the T-statistic above significance, with yellow being the strongest, see also Taylor et al., 2019 (Taylor and Garrido, 2019) for further description on this visualisation method. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Please cite this article as: K.M. Larsen, I. Dzafic, H. Darke, et al., Aberrant connectivity in auditory precision encoding in schizophrenia spectrum disorder and across t..., Schizophrenia Research, https://doi.org/10.1016/j.schres.2020.05.061

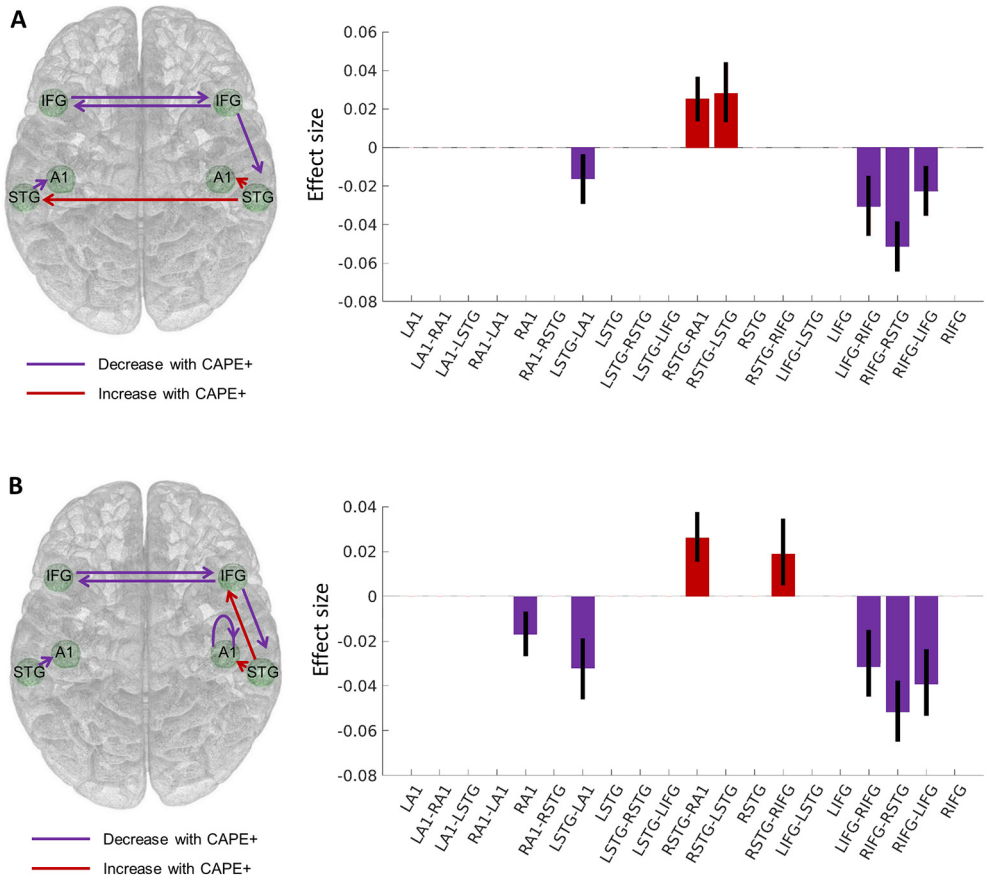


Fig. 5. A: Connections modulated by individual differences in CAPE+ scores, showing decreases with CAPE+ (purple) and increases (red). B: Same as in B with group membership added as a covariate. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Zhou et al., 2018). Previous results on functional connectivity have shown that interhemispheric connectivity can distinguish schizophrenia patients from patients with depression, indicating specificity for schizophrenia (Guo et al., 2013). Here we show evidence for specificity in the directed functional connectivity between hemispheres elicited by precision encoding in auditory stimuli. While we found reductions in connectivity that are specific to the schizophrenia spectrum, we also found some increases, namely in the lateral connections from the right to the left inferior frontal gyrus. An increase in the left to right superior temporal gyrus connections was found for the schizophrenia spectrum compared to the non-psychotic patient control group, although this (but not the former) appears to be driven by medication effects.

Years of education varied, as expected, between the three groups. Hence, we included this as a covariate in order to rule out a possible effect on the found connectivity patterns. In both the analysis concerning group modulations of connectivity as well as the CAPE+ continuum analysis, all connectivity patterns persisted when covarying for years of education. However, in both cases, additional connections emerged significant.

Somewhat unexpectedly, we found no evidence for MMN reductions in our SZS group. While reduced MMN in schizophrenia is very robust for duration oddballs, it is not the case for frequency deviants, as employed here. Indeed the effect size for MMN deficits in schizophrenia to frequency deviants are less than effect sizes for duration deviants (Avissar et al., 2018). In addition, the paradigm used in the present study is stochastic, meaning that it is not a sequence-based rule typically seen in auditory oddball paradigms. A recent meta-analysis suggested that effect sizes for MMN deficits in schizophrenia are reduced in auditory oddball paradigms with a more complex deviant type or pattern rule, as compared to standard oddball paradigms, where no complex rules are present (Avissar et al., 2018). Both the use of frequency (instead of duration) oddballs and the complexity of the paradigm might explain the absence of the typically observed MMN reductions in the schizophrenia spectrum group. However, the connectivity results mentioned above, indeed show evidence for group differences, as well as differences across the continuum of CAPE+ scores, showcasing the usefulness of multivariate approaches (DCM) and Bayesian mapping as more sensitive methods for detecting group differences in brain activity than the traditional univariate EEG single channel analysis.

Here we demonstrate that while contextual precision is encoded in individuals with schizophrenia spectrum disorder it is so to a lesser extent compared to both non-psychotic patients and neurotypical control groups. However, we cannot conclude from this data if prediction is impaired, since the univariate analysis did not show reduced MMN for the schizophrenia group. We have previously shown that adaptive but not predictive processes are impaired in non-psychotic individuals with increased genetic risk for schizophrenia(Larsen et al., 2019). Future studies are needed to elucidate whether the reduction of MMN in schizophrenia is caused by impaired adaption or impaired prediction.

Both volatility and precision (inverse variance) speak to the concept of uncertainty and, in that sense, our experimental paradigm has parallels with previous volatility manipulations (Mathys et al., 2011). Note, however, that volatility implies that statistical contingencies change over a period of time, which is not the case here as our sounds are sampled from a Gaussian with the same precision within a block and a between-block manipulation of precision.

In conclusion, we show that connectivity underlying precision encoding is altered across the continuum of psychotic-like experiences. Critically, we show alterations (decreases and increases) in interhemispheric connectivity that are specific to the schizophrenia spectrum

Please cite this article as: K.M. Larsen, I. Dzafic, H. Darke, et al., Aberrant connectivity in auditory precision encoding in schizophrenia spectrum disorder and across t..., Schizophrenia Research, https://doi.org/10.1016/j.schres.2020.05.061

group and top-down fronto-temporal connectivity reductions that align on the continuum of psychotic-like experiences across both patients and healthy individuals.

Role of funding body

The funding body had no role in conducting this study.

Contributors

MIG, SS, ID and OC contributed in the design of the study. ID, HD and HP collected the data. KML analysed the data and wrote the first draft of the manuscript. All authors contributed to the interpretation of the data, revised the manuscript and agreed with the final content of the manuscript.

Financial disclosures

All authors declare that there are no conflicts of interest in relation to this study.

Acknowledgements

We would like to thank all included participants for their time in this study as well as the nurses in the psychiatric ward at the Monash Medical Centre, Adult Inpatient Psychiatric Facility.

Funding

This work was funded by the Australian Research Council Centre of Excellence for Integrative Brain Function (ARC Centre Grant CE140100007), a University of Queensland Fellowship (2016000071), and a Women's Academic Fund Maternity funding from Queensland Government, to MIG. OC is supported by the Australian Research Council FFT40100807.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2020.05.061.

References

Adams, R.A., Stephan, K.E., Brown, H.R., Frith, C.D., Friston, K.J., 2013. The computational anatomy of psychosis. Front. Psychiatry 4, 47. https://doi.org/10.3389/fpsyt.2013.00047.

Atkinson, R.J., Michie, P.T., Schall, U., 2012. Duration mismatch negativity and P3a in first-episode psychosis and individuals at ultra-high risk of psychosis. Biol. Psychiatry 71, 98–104. https://doi.org/10.1016/j.biopsych.2011.08.023.

Avissar, M., Xie, S., Vail, B., Lopez-Calderon, J., Wang, Y., Javitt, D.C., 2018. Meta-analysis of mismatch negativity to simple versus complex deviants in schizophrenia. Schizophr. Res. 191, 25–34. https://doi.org/10.1016/j.schres.2017.07.009.

Bleich-Cohen, M., Sharon, H., Weizman, R., Poyurovsky, M., Faragian, S., Hendler, T., 2012. Diminished language lateralization in schizophrenia corresponds to impaired interhemispheric functional connectivity. Schizophr. Res. 134, 131–136. https://doi.org/10.1016/J.SCHRES.2011.10.011.

Chang, X., Xi, Y.-B., Cui, L.-B., Wang, H.-N., Sun, J.-B., Zhu, Y.-Q., Huang, P., Collin, G., Liu, K., Xi, M., Qi, S., Tan, Q.-R., Miao, D.-M., Yin, H., 2015. Distinct inter-hemispheric dysconnectivity in schizophrenia patients with and without auditory verbal hallucinations. Sci. Rep. 5, 11218. https://doi.org/10.1038/srep11218.

Corlett, P.R., Horga, G., Fletcher, P.C., Alderson-Day, B., Schmack, K., Powers, A.R., 2019. Hallucinations and strong priors. Trends Cogn. Sci. https://doi.org/10.1016/j.tics.2018.12.001.

Dima, D., Frangou, S., Burge, L., Braeutigam, S., James, A.C., 2012. Abnormal intrinsic and extrinsic connectivity within the magnetic mismatch negativity brain network in schizophrenia: a preliminary study. Schizophr. Res. 135, 23–27. https://doi.org/10.1016/j.schres.2011.12.024.

Erickson, M., Ruffle, A., Gold, J., 2016. A meta-analysis of mismatch negativity in schizophrenia: from clinical risk to disease specificity and progression. Biol. Psychiatry 79, 980–987.

Fletcher, P.C., Frith, C.D., 2009. Perceiving is believing: a Bayesian approach to explaining the positive symptoms of schizophrenia. Nat. Rev. Neurosci. 10, 48–58. https://doi.org/10.1038/nrn2536.

Friston, K., 2005. A theory of cortical responses. Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci. 360, 815–836. https://doi.org/10.1098/rstb.2005.1622.

Friston, K.J., Harrison, L., Penny, W., 2003. Dynamic causal modelling. Neuroimage 19, 1273–1302. https://doi.org/10.1016/S1053-8119(03)00202-7.

Friston, K.J., Litvak, V., Oswal, A., Razi, A., Stephan, K.E., van Wijk, B.C.M., Ziegler, G., Zeidman, P., 2016. Bayesian model reduction and empirical Bayes for group (DCM) studies. Neuroimage 128, 413–431. https://doi.org/10.1016/J.NEUROIMAGE.2015.11.015.

Garrido, M.I., Kilner, J., Kiebel, S., Friston, K., 2009a. Dynamic causal modeling of the response to frequency deviants. J. Neurophysiol. 101, 2620–2631. https://doi.org/10.1152/jn.90291.2008.

Garrido, M.I., Kilner, J.M., Stephan, K.E., Friston, K.J., 2009b. The mismatch negativity: a review of underlying mechanisms. Clin. Neurophysiol. 120, 453–463. https://doi.org/10.1016/j.clinph.2008.11.029.

Garrido, M.I., Sahani, M., Dolan, R.J., 2013. Outlier responses reflect sensitivity to statistical structure in the human brain. PLoS Comput. Biol. 9. https://doi.org/10.1371/journal.pcbi.1002999.

Garrido, M.I., Teng, C.L.J., Taylor, J.A., Rowe, E.G., Mattingley, J.B., 2016. Surprise responses in the human brain demonstrate statistical learning under high concurrent cognitive demand. npj Sci. Learn. 1, 16006. https://doi.org/10.1038/npjscilearn.2016.6.

Guo, S., Kendrick, K.M., Zhang, J., Broome, M., Yu, R., Liu, Z., Feng, J., 2013. Brain-wide functional inter-hemispheric disconnection is a potential biomarker for schizophrenia and distinguishes it from depression. Neuro. Image Clin. 2, 818–826. https://doi.org/10.1016/J.NICL.2013.06.008.

Guo, W., Jiang, J., Xiao, C., Zhang, Z., Zhang, J., Yu, L., Liu, J., Liu, G., 2014. Decreased resting-state interhemispheric functional connectivity in unaffected siblings of schizophrenia patients. Schizophr. Res. 152, 170–175. https://doi.org/10.1016/J.SCHRES.2013.11.030.

Haigh, S.M., Coffman, B.A., Salisbury, D.F., 2016. Mismatch negativity in first-episode schizophrenia: a meta-analysis. Clin. EEG Neurosci. https://doi.org/10.1177/1550059416645980.

Hanlon, F.M., Yeo, R.A., Shaff, N.A., Wertz, C.J., Dodd, A.B., Bustillo, J.R., Stromberg, S.F., Lin, D.S., Abrams, S., Liu, J., Mayer, A.R., 2019. A symptom-based continuum of psychosis explains cognitive and real-world functional deficits better than traditional diagnoses. Schizophr. Res. https://doi.org/10.1016/J.SCHRES.2019.01.024.

Harris, C.D., Rowe, E.G., Randeniya, R., Garrido, M.I., 2018. Bayesian model selection maps for group studies using M/EEG data. Front. Neurosci. 12, 598. https://doi.org/10.3389/fnins.2018.00598.

Kapur, S., 2003. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. Am. J. Psychiatry 160, 13–23.

Karolis, V.R., Corbetta, M., Thiebaut de Schotten, M., 2019. The architecture of functional lateralisation and its relationship to callosal connectivity in the human brain. Nat. Commun. 10, 1–9. https://doi.org/10.1038/s41467-019-09344-1.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276.

Kiebel, S.J., Garrido, M.I., Friston, K.J., 2007. Dynamic causal modelling of evoked responses: the role of intrinsic connections. Neuroimage 36, 332–345. https://doi.org/10.1016/j.neuroimage.2007.02.046.

Larsen, K.M., Mørup, M., Birknow, M.R., Fischer, E., Hulme, O., Vangkilde, A., Schmock, H., Baaré, W.F.C., Didriksen, M., Olsen, L., Werge, T., Siebner, H.R., Garrido, M.I., 2018. Altered auditory processing and effective connectivity in 22q11.2 deletion syndrome. Schizophr. Res. https://doi.org/10.1016/j.schres.2018.01.026.

Larsen, K.M., Mørup, M., Birknow, M.R., Fischer, E., Olsen, L., Didriksen, M., Baaré, W.F.C., Werge, T.M., Garrido, M.I., Siebner, H.R., 2019. Individuals with 22q11.2 deletion syndrome show intact prediction but reduced adaptation in responses to repeated sounds: evidence from Bayesian mapping. Neuro. Image Clin. 22, 101721. https://doi.org/10.1016/J.NICL.2019.101721.

Mathys, C., Daunizeau, J., Friston, K.J., Stephan, K.E., 2011. A Bayesian foundation for individual learning under uncertainty. Front. Hum. Neurosci. 5, 39. https://doi.org/10.3389/fnhum.2011.00039.

Michie, P.T., Malmierca, M.S., 2016. The neurobiology of MMN and implications for schizophrenia. Biol. Psychol. 116, 90–97. https://doi.org/10.1016/J.BIOPSYCHO.2016.01.011.

Mossaheb, N., Becker, J., Schaefer, M.R., Klier, C.M., Schloegelhofer, M., Papageorgiou, K., Amminger, G.P., 2012. The Community Assessment of Psychic Experience (CAPE) questionnaire as a screening-instrument in the detection of individuals at ultra-high risk for psychosis. Schizophr. Res. 141, 210–214. https://doi.org/10.1016/j.schres.2012.08.008.

Näätänen, R., 1995. The mismatch negativity. Ear Hear. 16, 6–18. https://doi.org/10.1097/00003446-199502000-00002.

Nelson, H.E., W.J., 1991. National Adult Reading Test (NART). NFER-NELSON.

Oestreich, L.K.L., Randeniya, R., Garrido, M.I., 2019. Auditory prediction errors and auditory white matter microstructure associated with psychotic-like experiences in healthy individuals. Brain Struct. Funct. 224, 3277–3289. https://doi.org/10.1007/s00429-019-01972-z.

van Os, J., Linscott, R.J., Myin-Germeys, I., Delespaul, P., Krabbendam, L., 2009. A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness–persistence–impairment model of psychotic disorder. Psychol. Med. 39, 179. https://doi.org/10.1017/S0033291708003814.

Owen, M.J., 2014. New approaches to psychiatric diagnostic classification. Neuron 84, 564–571. https://doi.org/10.1016/j.neuron.2014.10.028.

Owen, M.J., O'Donovan, M.C., 2017. Schizophrenia and the neurodevelopmental continuum:evidence from genomics. World Psychiatry 16, 227–235. https://doi.org/10.1002/wps.20440.

Penny, W.D., Trujillo-Barreto, N.J., Friston, K.J., 2005. Bayesian fMRI time series analysis with spatial priors. Neuroimage 24, 350–362. https://doi.org/10.1016/J.NEUROIMAGE.2004.08.034.

Perez, V.B., Woods, S.W., Roach, B.J., Ford, J.M., McGlashan, T.H., Srihari, V.H., Mathalon, D.H., 2014. Automatic auditory processing deficits in schizophrenia and clinical high-risk patients: forecasting psychosis risk with mismatch negativity. Biol. Psychiatry 75, 459–469. https://doi.org/10.1016/j.biopsych.2013.07.038.

Randeniya, R., Oestreich, L.K.L., Garrido, M.I., 2017. Sensory prediction errors in the continuum of psychosis. Schizophr. Res. https://doi.org/10.1016/j.schres.2017.04.019.

Please cite this article as: K.M. Larsen, I. Dzafic, H. Darke, et al., Aberrant connectivity in auditory precision encoding in schizophrenia spectrum disorder and across t..., Schizophrenia Research, https://doi.org/10.1016/j.schres.2020.05.061

Rosa, M.J., Bestmann, S., Harrison, L., Penny, W., 2010. Bayesian model selection maps for group studies. Neuroimage 49, 217–224. https://doi.org/10.1016/j.neuroimage.2009.08.051.

Steinmann, S., Leicht, G., Mulert, C., 2014. Interhemispheric auditory connectivity: structure and function related to auditory verbal hallucinations. Front. Hum. Neurosci. https://doi.org/10.3389/fnhum.2014.00055.

Steinmann, S., Leicht, G., Mulert, C., 2019. The interhemispheric miscommunication theory of auditory verbal hallucinations in schizophrenia. Int. J. Psychophysiol. https://doi.org/10.1016/j.ijpsycho.2019.02.002.

Taylor, J.A., Garrido, M.I., 2019. Porthole and Stormcloud: Tools for Visualisation of Spatio-temporal M/EEG Statistics. bio Rxiv, p. 534784. https://doi.org/10.1101/534784.

Umbricht, D., Krljes, S., 2005. Mismatch negativity in schizophrenia: a meta-analysis. Schizophr. Res. 76, 1–23. https://doi.org/10.1016/j.schres.2004.12.002.

Winkler, I., Karmos, G., Näätänen, R., 1996. Adaptive modeling of the unattended acoustic environment reflected in the mismatch negativity event-related potential. Brain Res. 742, 239–252.

Zhou, Y., Zeidman, P., Wu, S., Razi, A., Chen, C., Yang, L., Zou, J., Wang, G., Wang, H., Friston, K.J., 2018. Altered intrinsic and extrinsic connectivity in schizophrenia. NeuroImage. Clin. 17, 704–716. https://doi.org/10.1016/j.nicl.2017.12.006.

Please cite this article as: K.M. Larsen, I. Dzafic, H. Darke, et al., Aberrant connectivity in auditory precision encoding in schizophrenia spectrum disorder and across t..., Schizophrenia Research, https://doi.org/10.1016/j.schres.2020.05.061