# Children at Familial High risk of Schizophrenia and Bipolar Disorder Exhibit Altered Connectivity Patterns During Pre-attentive Processing of an Auditory Prediction Error

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*Background and Hypothesis*: Individuals with schizophrenia or bipolar disorder have attenuated auditory mismatch negativity (MMN) responses, indicating impaired sensory information processing. Computational models of effective connectivity between brain areas underlying MMN responses show reduced connectivity between fronto-temporal areas in individuals with schizophrenia. Here we ask whether children at familial high risk (FHR) of developing a serious mental disorder show similar alterations. *Study Design*: We recruited 67 children at FHR for schizophrenia, 47 children at FHR for bipolar disorder as well as 59 matched population-based controls from the Danish High Risk and Resilience study. The 11–12-year-old participants engaged in a classical auditory MMN paradigm with deviations in frequency, duration, or frequency and duration, while we recorded their EEG. We used dynamic causal modeling (DCM) to infer on the effective connectivity between brain areas underlying MMN. *Study Results*: DCM yielded strong evidence for differences in effective connectivity among groups in connections from right inferior frontal gyrus (IFG) to right superior temporal gyrus (STG), along with differences in intrinsic connectivity within primary auditory cortex (A1). Critically, the 2 high-risk groups differed in intrinsic connectivity in left STG and IFG as well as effective connectivity from right A1 to right STG. *Results* persisted even when controlling for past or present psychiatric diagnoses. *Conclusions*: We provide novel evidence that connectivity underlying MMN responses in children at FHR for schizophrenia and bipolar disorder is altered at the age of 11–12, echoing findings that have been found in individuals with manifest schizophrenia.

*Key words:* Familial high risk/EEG/MMN/DCM/Schizophrenia/Bipolar disorder/offspring

## Introduction

Being an offspring of parents with either schizophrenia or bipolar disorder is one of the largest known risk factors for developing either of these disorders.[1–3] Studying children born to parents with schizophrenia or bipolar disorder has the potential to identify abnormal developmental trajectories that are expressed before onset of clinical illness. This may help to identify mechanisms protecting against or leading to clinical manifestation.

One promising neurophysiological readout is the so-called mismatch negativity (MMN)[4–6] which can be readily detected with electroencephalography (EEG) when unpredictable deviant sounds are interspersed in a stream of frequently occurring standard sounds. Within the framework of predictive coding, the MMN reflects an error response caused by a mismatch between incoming sensory input and a predicted expectation formed by an internal model of the statistical regularities.[7] In this way, the MMN can be viewed as a measure of the ability to learn the underlying statistical sequence of sounds. MMN

amplitude reductions are highly replicated in schizophrenia,[4,8] first-episode schizophrenia,[9] first-degree relatives[10,11] as well as in clinical high-risk for psychosis[12–15] who subsequently convert to psychosis.[13,15–17] Likewise, it is found reduced in bipolar disorder albeit to a lesser extent and less replicated.[5,6,18] This suggests that MMN is reduced along the continuum of psychosis[19] and can be viewed as an index of psychopathology shared across those disorders. Studies on familial high-risk (FHR) are scarce and often include participants with a large age span., leaving a gap in the current literature.[2] Since a wide age range has the risk of obscuring results due to age effects on neurocognitive and brain maturation, this current gap can be minimized by introducing studies including participants with a narrow age range.[20]

The relationship between MMN alterations and psychopathology depends on the type of deviation in the acoustic sequence generating the MMN. The MMN evoked by deviants in the duration of the sound is altered along all clinical stages of psychosis, while the MMN elicited by a frequency deviant develops more gradually along illness progression.[21–25] Given the complexity of schizophrenia and bipolar disorder, impairments in either of these deviants may not be present in all patients and more research are needed considering combinations of markers in the quest to find a best predictor of illness stage.

In addition to the assessment of MMN responses at the ERP level, modeling the connectivity patterns that generate these responses can give additional insights by providing information on the mechanisms behind the responses. In dynamic causal modeling (DCM) of MMN responses, changes in forward connections (from lower to higher cognitive areas) is believed to reflect sensitivity to prediction errors, which is sent to higher levels. Computational models of effective connectivity between brain areas underlying MMN responses revealed an attenuated connectivity between fronto-temporal areas in individuals with schizophrenia[26–28] and individuals at genetically high risk for schizophrenia.[29,30] The intrinsic (self-connection) connection within right inferior frontal gyrus (IFG) and the backward connection from right IFG to superior temporal gyrus (STG) have been linked to the degree of psychopathology.[27,28,31,32] Within the framework of predictive coding, these 2 types of connections (intrinsic and top-down) have been attributed to adaptation and prediction processes, respectively. In this framework, increases in intrinsic connectivity may encode progressive increases in the estimated precision of top-down predictions, responsible for suppressing prediction error. These changes could be mediated by adaptation-like mechanisms in the auditory cortices to repeated sounds. Changes in forward connections may reflect changes in sensitivity to prediction error that is conveyed to higher levels. These higher levels form predictions so that backward connections can provide contextual guidance to lower levels. In this view, the MMN represents a failure to predict bottom-up input and consequently, a failure to suppress prediction error. The MMN changes associated with schizophrenia, therefore, suggest that both processes are affected by varying degrees of psychopathology. Although research within this area is growing, it is still unknown whether these alterations in connectivity underlying MMN responses, are reduced in children at FHR of either schizophrenia or bipolar disorder.

We have previously presented MMN data from a subgroup of the Danish High Risk and Resilience cohort, providing moderate evidence for higher MMN amplitudes for duration MMN responses in children at FHR of bipolar disorder compared to population-based controls.[33] Here, we take a step further, and investigate MMN responses from a slightly larger cohort (final sample from the Danish High Risk and Resilience study, VIA11) and specifically target the connectivity changes underlying MMN responses. This is the first study to assess the connectivity pattern underlying MMN responses in children at FHR of schizophrenia and bipolar disorder with a narrow age range.

## Methods

### Participants

A total of 173 children from the Danish High Risk and Resilience study,[34,35] participated in the current study. Of these, 67 children had at least one parent with a diagnosis of schizophrenia spectrum disorder (FHR-SZ), 47 children had either one or 2 parents with a diagnosis of bipolar disorder (FHR-BP), and finally 59 children with parents without any of these disorders (PBC).[34] The Danish High Risk and Resilience study is a longitudinal register-based cohort study starting when the children were age 7 years (the VIA7 study).[34] The EEG data presented here were collected at the first follow-up at age 11 years (the VIA11 study)[35] at the Danish Research Center for Magnetic Resonance, Copenhagen University Hospital Hvidovre.

### Clinical Variables

We used the child behavior checklist (CBCL) school-age version to assess problem behavior[36] and the Children's Global Assessment Scale (CGAS) to assess the level of general functioning in the previous month.[37]

Current or past presence of any axis-I disorder were identified through the semi-structured interview for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL),[38] see Gregersen et al. (2021) for a full description of procedures.[39] None of the participants in the present study met criteria for axis 1 psychotic disorder (DSM 298.9/298.8/297.1/292.30/295.90).

*Mismatch Negativity*

Participants were presented with a classic auditory odd-ball paradigm introducing 3 deviant types, frequency, duration, and a combined frequency and duration (referred to as combined deviant in the following). 1800 tones were binaurally presented through insert earphones (E-ARTONE 3A), at a sound pressure level of 75dB, using PsychToolbox3 running in Matlab. We used an external soundcard (RME Babyface 22-Channel, 192 kHz Bus-powered, Haimhausen, Germany). Standard tones (1000 Hz, 50 ms) were presented with a probability of 76% and the 3 deviant types each had a probability of 8%, see figure 1. Frequency deviants were 1200 Hz and 50 ms, duration deviants were 1000 Hz and 100 ms and finally, the combined deviants were 1200 Hz and 100 ms. The interstimulus interval were randomly jittered between 400 and 600 ms, resulting in a total duration of approx. 16 minutes. Children were seated in a comfortable adjustable chair in a quiet room and instructed to relax while ignoring the auditory stimuli they were presented with. While the tones were played, children watched a silent movie. On a few occasions, the parent stayed in the room during the EEG recordings to make the child comfortable. The testers were blinded towards high-risk status.

*EEG Preprocessing*

EEG data were recorded using a 128-channel Biosemi active 2 system (BioSemi, Amsterdam, Netherlands) and a sampling frequency of 4096 Hz. All offline preprocessing was performed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/) running in Matlab. Preprocessing steps included high and low pass filtering with a fifth-order Butterworth filter with a cutoff of 0.5 Hz and 40 Hz, respectively. Data were epoched with a peristimulus interval of −100 ms to 400 ms, with baseline correction applied from −100 ms to 0 ms. Artifact rejection was performed using a simple threshold technique rejecting trials if amplitudes exceeded ±100 µV, and finally, the signals were referenced to the average of all electrodes. MMN responses were extracted by subtracting responses to the standard tones from responses to the deviant tones. The MMN peak value were identified at the group level (pooled across groups) and individual MMN amplitudes were extracted by taking the mean around the peak MMN (50 ms before and 50 ms after). Mean values were extracted in the following time windows; frequency MMN: 110–210 ms, duration MMN: 100–200 ms and finally the combined frequency and duration MMN: 95–195 ms.

*Assessing Group Differences in MMN Responses*

Group differences in the amplitudes of the MMN responses were assessed through 3 independent analyses of covariance models (ANCOVAs), one for each of the deviant types (frequency, duration, and combined frequency and duration). Since participants included are in a sensitive period regarding brain development,[40] potentially affecting maturation of auditory responses,[41] age is included in the models as covariates. Sex differences are commonly observed during brain development,[42] and we therefore also include sex is included as a covariate. We performed both a traditional frequentist statistical approach reporting *P*-values as well as a Bayesian approach reporting Bayes factors (BF₁₀). All statistical analyses were performed in R using the packages car and BayesFactor.

In addition to the traditional hypothesis-driven single-channel approach, we also performed an unbiased search over the full-time-sensor space. The epoched EEG data were converted into scalp-map images of dimension 32 × 32. These were obtained using interpolation followed by smoothing using a Gaussian kernel specified by a
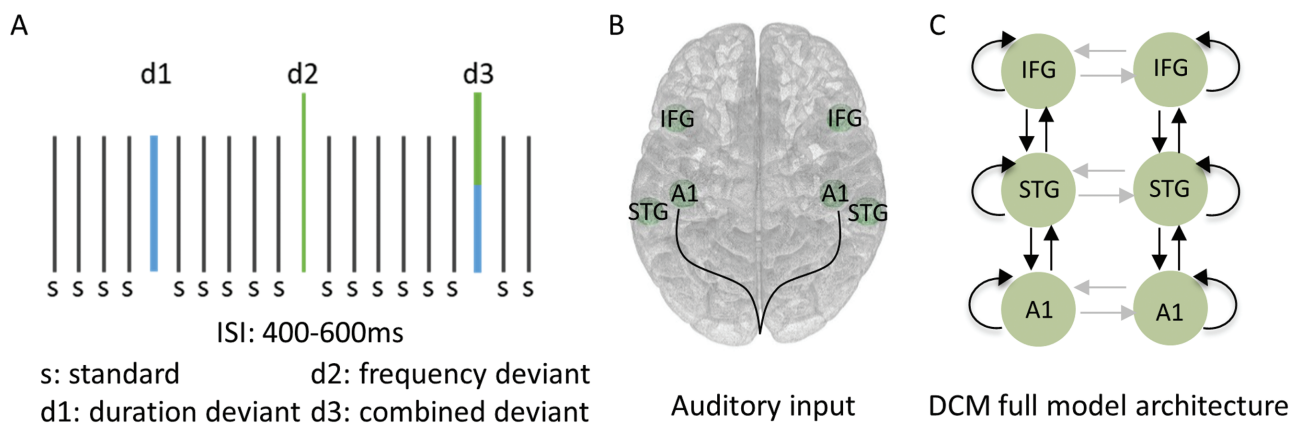


**Fig. 1.** (A) The MMN paradigm. S are standard tones, where d1, d2, and d3 are the different deviant types. Interstimulus interval (ISI) was jittered between 400 and 600 ms. (B) Anatomical presentation of the prior locations of sources used in the dynamic causal modeling (DCM) analysis. The auditory input is received by the primary auditory cortex (A1: primary auditory cortex, STG: superior temporal gyrus, IFG: inferior frontal gyrus. (C) Hierarchical presentation of the full DCM architecture. The black connections are included in the B-matrix (can be modulated by prediction). The gray connections are present (in the A-matrix) but fixed across conditions (Bmatrix).

FWHM of 8 mm$^2$ in the spatial dimension and 10 ms in the temporal dimension ([8 8 10]). Group differences were assessed using a factorial design with factors group (FHR-SZ, FHR-BP, and PBC) and condition (standard and deviant). All *P*-values reported are thresholded using alpha = 0.05 FWE corrected at cluster level.

### Dynamic Causal Modeling

We used DCM to model the underlying microcircuitry of prediction in the 3 groups. The 3 different MMN types (frequency, duration, and combined frequency and duration) were modeled separately, and we were interested in what specific connections encoding prediction differed between groups. The architecture of the MMN has previously been established[31,43] to include bilateral primary auditory cortex, the STG and the IFG. In line with this, we made a fully connected network comprising intrinsic, lateral, forward, and backward connections at all levels. The prediction effect was modeled with the standards as baseline, 0 and deviants as 1. All connections except lateral, were modeled in the B matrix. Each full model (figure 1B and 1C) was inverted for each individual participant. Results reported are from the B matrix (ie, connections modulated by the MMN).

### Modeling Group Differences of Connectivity in the Network Underlying MMN Responses

We used a hierarchical model over the parameters as implemented in the parametric empirical Bayes framework in SPM12.[44] This framework allows to have regressors of interest as well as covariates. We added 2 regressors for group membership; one modeling the main effect of being at FHR (1 for PBC, -1 for FHR). The second regressor of interest modeled the difference between the FHR groups (0 for PBC, 1 for FHR-SZ, and -1 for FHR-BP). As covariates we added age and sex and all regressors were mean-centered. Using these regressors, we can tap into which connections are overall different between the FHR groups and the population-based controls as well as assess which connections are different between the 2 high-risk groups. For clarity, we show results exceeding 75% exceedance probability. We have marked all connections surviving the threshold of 99% exceedance probability in black, indicating very strong evidence that these connections are indeed modulated.

Following up on the main analysis which assessed group differences in the MMN network, we performed a post-hoc analysis to test how potential group effects within the connectivity network are related to the manifestation of past and present axis 1 disorder. In this way, we were able to test whether any group difference was statistically driven by those children that have a mental disorder. We created a separate model mirroring the model described above only now with an additional regressor added, coding for the presence of an axis 1 disorder. Axis 1 disorder was included as a binary variable without distinguishing whether one or 2-lifetime diagnoses were present. The follow-up analyses also put us in the position to examine which connections were modulated by the presence of an axis 1 disorder irrespective of high-risk status.

### Results

The mean age of the children was 12.1 at the time of examination (see table 1). The 3 groups of children were comparable regarding age and sex. CBCL total and externalizing problem scores were higher (indicating more problems) in both FHR groups compared to the PBC group, while CBCL internalizing problem scores showed no statistical difference across groups. Scores of general functioning as measured with CGAS were also lower in both FHR groups compared to PBC. The presence of any lifetime axis 1 diagnosis did not significantly differ between groups. table 1 lists the summary statistics for each group.

**Table 1.** Demographic Data of the Cohort.

| | Total | FHR-SZ | FHR-BP | PBC | *P*-value |
|---|---|---|---|---|---|
| Children, *N* | 173 | 67 | 47 | 59 | — |
| Females, *N* (%) | 85 (49) | 31 (46) | 23 (49) | 31 (53) | .823 |
| Age, mean (SD) | 12.10 (0.28) | 12.10 (0.29) | 12.11 (0.28) | 12.11 (0.28) | .794 |
| CBCL, mean (SD) | | | | | |
| CBCL, Total | 17.58 (17.58) | 21.94 (20.76) | 19.98 (15.23) | 13.26 (14.39) | .006 |
|   CBCL, internalizing | 6.00 (6.11) | 6.91 (6.67) | 5.89 (4.99) | 5.09 (6.23) | .100 |
|   CBCL, externalizing | 3.85 (5.06) | 5.06 (6.24) | 3.85 (4.56) | 2.50 (3.49) | .005 |
| CGAS | 70.34 (15.72) | 65.91 (15.46) | 70.11 (14.88) | 75.41 (15.41) | <.001 |
| Lifetime Axis 1 disorder, excl. elimination disorders, *N* (%) | 75 (43) | 33 (49) | 22 (47) | 20 (34) | .178 |

Note: FHR, familial high risk; CBCL, Child Behavior Check List; CGAS, Children's Global Assessment Scale. Group Differences in Sex and Presence of Axis 1 Disorder was Performed Using a Kruskal–Wallis Test. Group Differences in Age, CBCL and CGAS was Performed With One-Way ANOVA.

*Event-Related MMN Responses*

We have reported on the MMN responses using a simple single-channel approach elsewhere in a slightly smaller sample than presented in the current article,[33] see supplementary table 1 for demographics on the original sample. For the sake of completeness, we show the MMN responses here since the present cohort is slightly larger, see figure 2A and 2B. Across deviant types, MMN amplitudes were comparable across groups (frequency MMN: $F_{(2,167)} = 1.920$, $P = .150$, $BF_{10} = 0.299$; duration MMN: $F_{(2,167)} = 2.057$, $P = .131$, $BF_{10} = 0.341$, combined frequency duration MMN: $F_{(2,167)} = 0.687$, $P = .505$, $BF_{10} = 0.111$). Bayes factors indicated anecdotal to moderate evidence against differences among groups, in line with a previous study.[45] This result differs from our previous MMN analysis which only included 131 individuals of the final sample and yielded a moderate evidence in favor of a group difference in MMN responses between children at FHR when compared to PBC children.[45] This shift in the sign of evidence indicates that the degree of uncertainty is too high to reliably infer whether or not the MMN amplitude is affected in children at FHR of severe mental illness.

Results from the assumption-free spatiotemporal analysis revealed a main effect of group for the duration deviant at mid-central channels at 234 ms, see figure 2C. This group effect was driven by FHR-BP having a larger response across conditions in this time period. The same was observed at 162 at mid-central as well as left-lateralized occipital channels. At the reported thresholds, no results were significant for the frequency MMN and the combined duration and frequency MMN, although present when lowering the threshold.

*Effective Connectivity Underlying MMN Responses is Modulated by Group Membership.* Compared to children without parental risk, the 2 high-risk groups showed decreased effective connectivity from left STG to left IFG (100%). This decrease was present across all 3 MMN types. At 78% exceedance probability increased effective connectivity was observed from right IFG to right STG along with increased intrinsic connectivity within right primary auditory cortex (A1, 85%) in the FHR groups compared to the PBC group (figure 3, left column). This between-group difference in effective connectivity was again consistent across MMN types, although with subtle differences in probabilities.

The effective connectivity patterns of the 2 high-risk groups differed in 4 connections. The right-hemispheric connection from right A1 to right STG and left-hemispheric connection from IFG to STG as well as in intrinsic connections in left STG and left IFG were relatively attenuated in FHR-SZ children compared to
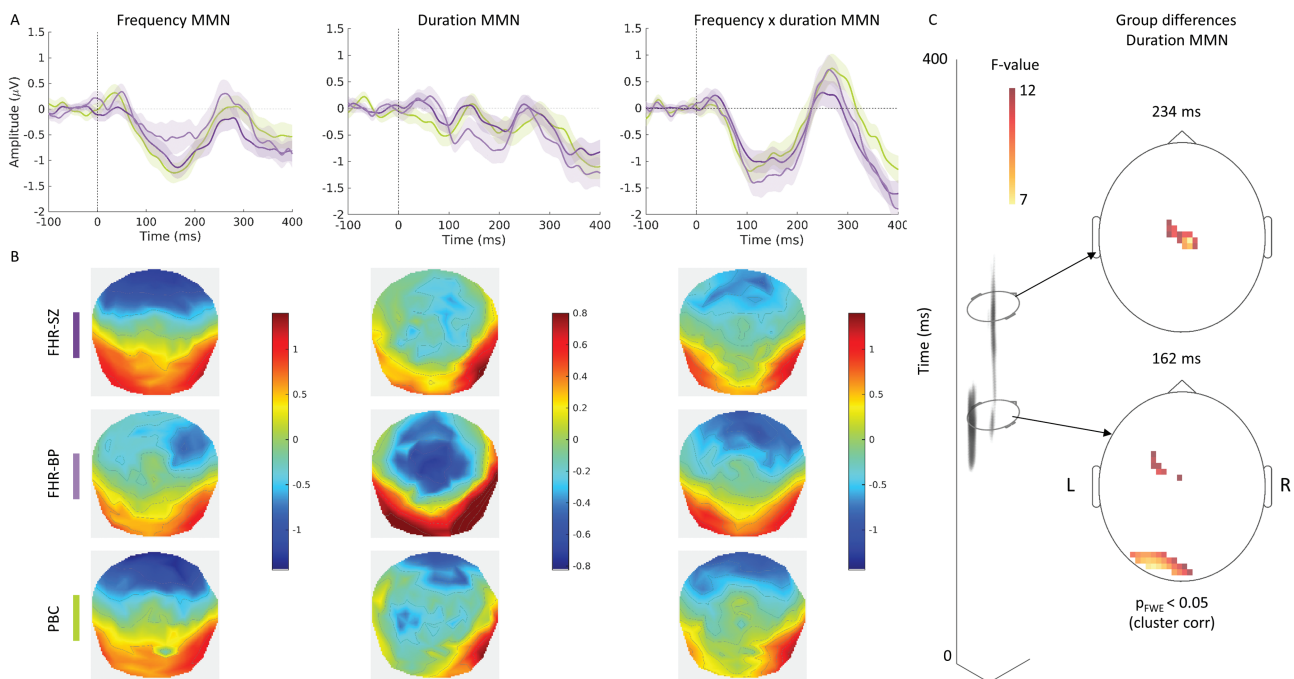


**Fig. 2.** (A) MMN responses for the 3 different deviant types, frequency, duration, and combined frequency and duration, all from channel Fz. . (B) Topographical distribution of MMN responses in the time period of the MMN, for each of the MMN types and each of the 3 groups. Color bar represents amplitude intensity averaged across the MMN window. (C) Main effect of group for the spatiotemporal analysis, here shown for the duration deviant. The time axis displays the timing of significant activity for the contrast, as indicated with gray shading. The significant areas (over electrodes) for a given contrast are visualized within the topographic plot. The color indicates the T-statistic above significance. Group differences are observed at 162 ms as well as 234 ms.
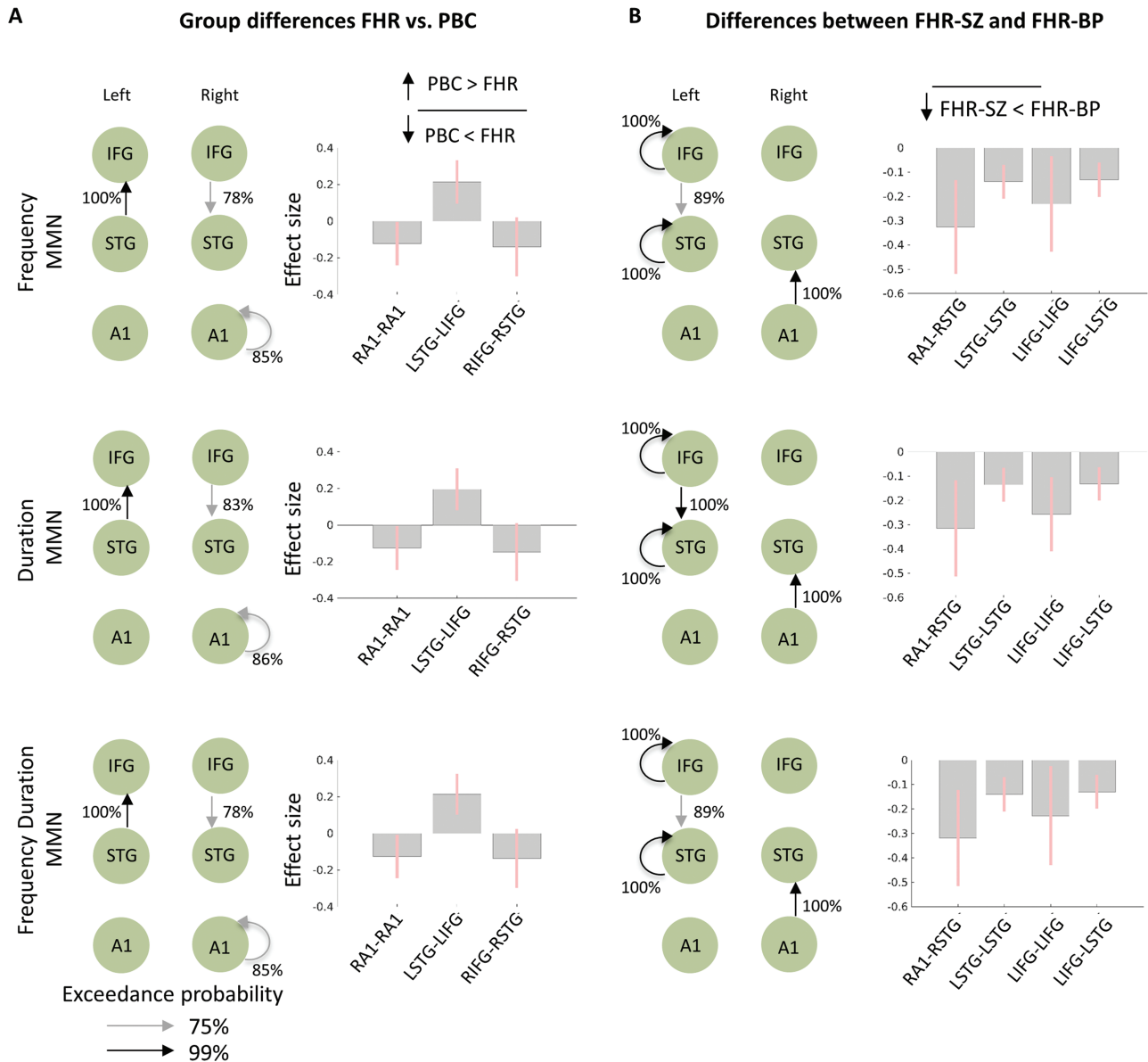
**Fig.3.** Groupwise connectivity results. (A) results from the main difference between familial high risk (FHR) and PBC. (B) results on the difference between the 2 high-risk groups, FHR-SZ and FHR-BP. First row results from the frequency MMN, second row is duration MMN and finally last row is the combined frequency and duration MMN. Gray arrows show results with threshold of 75% exceedance probability, black arrows with a threshold of 99% exceedance probability. Exceedance probabilities are shown next to each individual connection. Effect sizes are shown with bar plots for each of the highlighted connections. Positive effects for the PBC≠FHR show connections where PBC>FHR (population-based controls show higher connectivity compared to the 2 high-risk groups together), likewise negative effect sizes show PBC.

FHR-BP children (figure 3, right column). This expression was consistent across deviant types.

*Effect of Lifetime Axis 1 Diagnosis Modulates Brain Connectivity Within the MMN Network.* We wished to examine whether the presence of any lifetime axis 1 diagnosis has an impact on the groupwise connectivity findings, see figure 4. To this end, we repeated the groupwise analysis, now including the presence of a lifetime axis 1 diagnosis as a regressor in our model. The difference between the 2 FHR groups persisted after controlling for axis 1 diagnosis. Notably, the group difference between the FHR groups and PBC groups showed stronger results for the duration MMN when adding the axis 1 diagnosis to the model (figure 4). Here, the connection from right IFG to right STG showed 100% exceedance probability, together with the intrinsic connection within right A1. The extended analysis also enabled us to ask which connections within the network that are modulated by the presence of a lifetime axis 1 diagnosis, Figure 4C. Here, connections from right IFG to right STG were decreased with the presence of an axis 1 disorder vs. no presence.
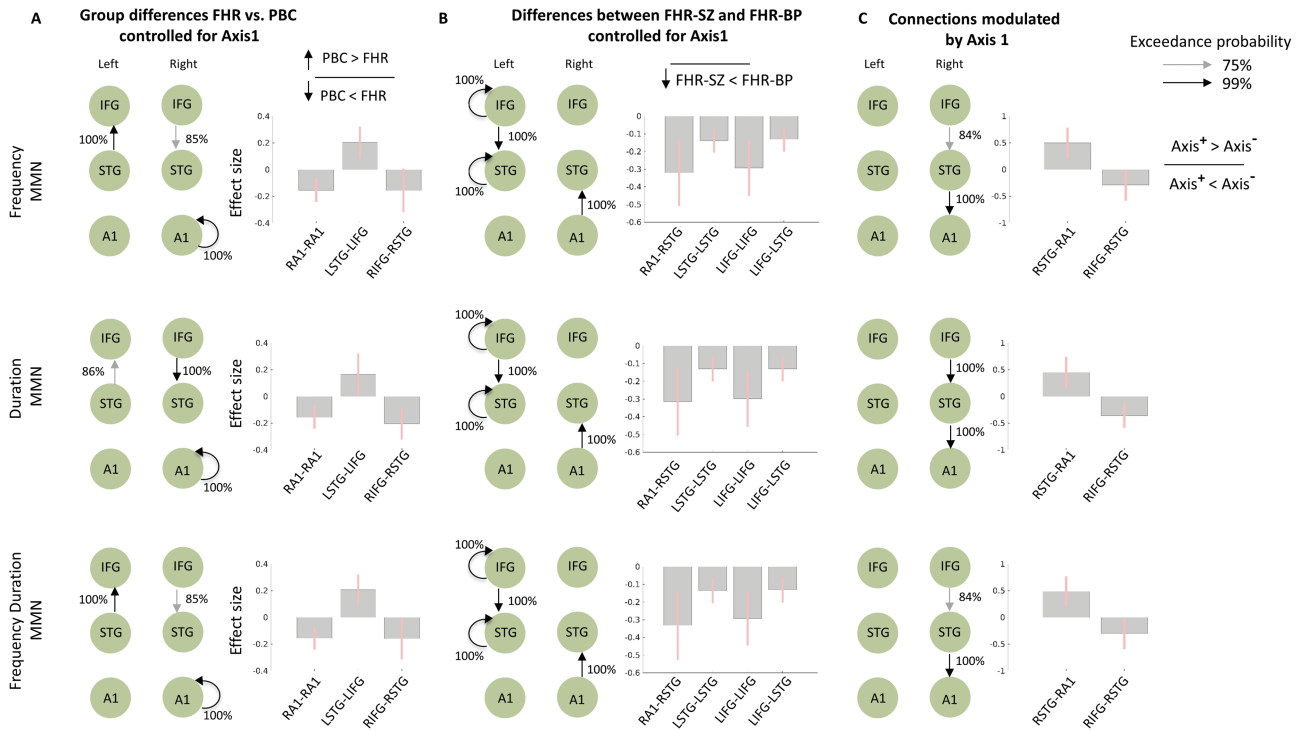
**Fig. 4.** Results for groupwise analysis with the presence of a lifetime axis 1 disorder included in the model. (A) group differences between PBC and both familial high-risk (FHR) groups now controlling for axis 1 diagnosis. Positive effects mean PBC shows increased connectivity when compared to the 2 high-risk groups. Negative effects mean PBC has decreased connectivity compared to both FHR groups. (B) difference between the 2 FHR groups, negative effects mean FHR-SZ express less connectivity when compared to FHR-BP. (C) modulatory effect of axis 1 diagnosis on the connectivity network underlying MMN. Exceedance probabilities are shown next to each individual connection. Positive effects are axis+ (having an axis 1 diagnosis) > axis− (not having an axis 1 diagnosis).

Likewise, increased connectivity from right STG to right A1 was present in individuals with an axis 1 diagnosis compared to those without an axis 1 diagnosis.

## Discussion

We provide first-time evidence that effective cortical connectivity is altered during pre-attentive processing of an auditory prediction error in same-aged preadolescent children at FHR of schizophrenia or bipolar disorder. We also found differences in the connectivity pattern between high-risk children with a parent with schizophrenia or a parent with bipolar disorder. These alterations persisted even when controlling for past or present psychiatric diagnoses.

The comparison of EEG-based causal dynamic models yielded strong evidence for increased effective connectivity in cortico-cortical connections between the inferior frontal and STG in high-risk children, along with increased intrinsic connectivity within right primary auditory cortex, when compared to PBC. The present findings echo the changes in fronto-temporal functional connectivity during the MMN response that have been previously reported in adult patients with schizophrenia.[46–49] Dynamic causal models have previously identified alterations in directed connectivity from right IFG to right STG as well as intrinsic connectivity within A1 in both

psychiatric populations,[26,31] as well as in a group at genetically high risk of psychiatric disorders.[50] In this DCM study, we observed altered functional connectivity in the same 2 connections, showing differences at the group level between the population-based controls and both high-risk groups (FHR-SZ and FHR-BP). Backward connections from inferior frontal to superior temporal cortex may convey internal predictions about auditory stimulus features and intrinsic connections in A1 may contribute to flexible adjustments of cortical auditory processing depending on the incoming auditory information stream.[51] Our DCM findings thus may indicate that both processes are affected within the 2 familial high-risk groups at the age of 11 or 12.

While the above-mentioned DCM results suggest connectivity alterations that are shared across the risk for psychiatric disorders, we also found connectivity differences between FHR-SZ and FHR-BP children. The FHR-SZ group showed decreased connectivity between right A1 to right STG, left IFG to left STG, and attenuated intrinsic connectivity in left IFG and left STG compared to the FHR-BP group. The results suggest that children at FHR for schizophrenia show a more impaired connectivity pattern than children at FHR for BP. To the best of our knowledge, this is the first DCM-based connectivity study that included more than one high-risk group.

Therefore, our results warrant replication to confirm specificity of these connections. One important point to note here, is that children at FHR-SZ and FHR-BP were grouped based on the psychiatric diagnosis of the parent(s). Having a parent with either SZ or BP does not only result in increased risk for that specific disorder, but more likely increases the risk for a broad range of psychiatric disorders.[2,3] Therefore, we cannot conclude from the results of the current article that the connections distinguishing children at FHR-SZ from FHR-BP is specific to the risk for SZ vs. BP itself or not. Longitudinal studies are needed to clarify whether the observed connectivity differences represent an increased risk for developing psychiatric disorders in general or a specific risk of developing severe mental illness.

Two findings speak against the possibility that manifest or previous psychopathology accounts for the reported group differences in effective connectivity revealed by EEG recordings during the MNN paradigm. Firstly, the frequency of past or present axis-1 diagnoses did not differ significantly among the 3 groups. Secondly and more importantly, the differences in effective connectivity persisted when controlling for past or present axis-1 diagnosis. This is not to say that the present or previous manifestation of an axis-1 disorder does not have any effect on the effective connectivity pattern related to the pre-attentive processing of an auditory prediction error. On the contrary, causal modeling indicated that the connection from right IFG to right STG showed a decrease in the presence of axis-1 disorder when compared to individuals with no axis-1 disorder across groups. This finding mirrors a previous study, in which decreased connectivity within the same connection (right IFG to right STG) was observed in patients with schizophrenia as well as patients with a psychiatric diagnosis but without psychosis.[31] Together, these findings suggest that an alteration of effective connectivity from right IFG to right STG is shared across psychiatric disorders and in the present study can be extended to children at risk for psychiatric disorders. Since the rate of presence of an axis-1 disorder was comparable between the 3 groups, we attribute the differences in connectivity between the 2 familial high-risk groups and controls to the presence or absence of a familial high-risk status. It should be noted here that axis 1 diagnoses were added in the analysis as a binary variable. We know that those children with a diagnosis exhibit lower global functioning[39] and we can therefore use this post-hoc analysis to conclude that the observed connectivity results are not statistically driven by those children having a diagnosis.

In contrast to the DCM findings, conventional MMN analyses yielded moderate evidence against differences in MMN amplitude among groups. However, the assumption-free spatiotemporal analysis, revealed group differences in the cortical responses for the duration MMN, although not centered around the traditional MMN component. It is well documented that MMN evoked by deviants in the duration of the sound is altered along all clinical stages of psychosis, while the MMN elicited by a frequency deviant develops more gradually along illness progression.[21–25] Our results align with this, given that results at the cortical level were found for the duration deviant. However, the connectivity results were observed for all deviant types, although still stronger for the duration deviant. We, therefore, argue that considering combinations of markers is needed in the quest to find a best predictor of illness stage. Together, our findings suggest that FHR of schizophrenia or bipolar disorder alters directed functional and local intrinsic connectivity during the processing of a deviant auditory stimulus together with altered cortical responses, although without affecting the event-related cortical response, constituting the MMN per se. The altered connectivity pattern in the 2 FHR groups indicates an impaired ability to adapt to process a change in the environment which may contribute to the increased risk for developing a major psychiatric disorder. Since families of FHR children usually have socio-economic and health problems,[52] the altered connectivity may be caused by the genetic risk that these children have or the environmental risk, or both. Although only a minority of the children with a predisposition will show a conversion during later life,[53] studies of high-risk children offer an unique possibility to longitudinally measure MMN responses through the vulnerable period of adolescence and into adulthood.

In conclusion, we have provided novel evidence that connectivity underlying MMN responses in children at FHR for schizophrenia and bipolar disorder at a narrow age range is altered, echoing findings that have been found in individuals with manifest schizophrenia. These risk-related changes in effective connectivity persisted when controlling for past or present psychiatric diagnoses, suggesting that these connectivity changes may be an endophenotype for risk for psychiatric disorders. Future follow-up investigations are planned to follow up on this cohort. This will enable us to examine at the single-person and group level whether the altered connectivity patterns during pre-attentive processing of an auditory prediction error are robustly expressed during adolescence and early adulthood or whether they are subject to dynamic changes.

## Supplementary Material

Supplementary material is available at https://academic.oup.com/schizophreniabulletin/.

## Conflict of Interest

HRS has received honoraria as speaker from Sanofi Genzyme, Denmark and Novartis, Denmark, as consultant from Sanofi Genzyme, Denmark and as senior editor (NeuroImage) and editorin-chief (Neuroimage Clinical) from Elsevier Publishers, Amsterdam, The Netherlands. HRS has also received royalties as book editor from Springer Publishers, Stuttgart, Germany and Gyldendahl Publishers, Copenhagen, Denmark. All disclosures are independent of the work published here. All other authors report no financial disclosures.

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## References

1. Dean K, Stevens H, Mortensen PB, Murray RM, Walsh E, Pedersen CB. Full spectrum of psychiatric outcomes among offspring with parental history of mental disorder. *Arch Gen Psychiatry.* 2010;67(8):822–829. doi: 10.1001/ARCHGENPSYCHIATRY.2010.86

2. Rasic D, Hajek T, Alda M, Uher R. Risk of mental illness in offspring of parents with schizophrenia, bipolar disorder, and major depressive disorder: A meta-analysis of family high-risk studies. *Schizophr Bull.* 2014;40(1):28–38. doi: 10.1093/schbul/sbt114

3. Gottesman II, Laursen TM, Bertelsen A, Mortensen PB. Severe mental disorders in offspring with 2 psychiatrically Ill parents. *Arch Gen Psychiatry.* 2010;67(3):252–257. doi: 10.1001/ARCHGENPSYCHIATRY.2010.1

4. Umbricht D, Krljes S. Mismatch negativity in schizophrenia: A meta-analysis. *Schizophr Res.* 2005;76(1):1–23. doi: 10.1016/j.schres.2004.12.002

5. Raggi A, Lanza G, Ferri R. Auditory mismatch negativity in bipolar disorder: A focused review. *Rev Neurosci.* 2021;33(1):17–30. doi: 10.1515/REVNEURO-2021-0010

6. Hermens DF, Chitty KM, Kaur M. Mismatch negativity in bipolar disorder: A neurophysiological biomarker of intermediate effect? *Schizophr Res.* 2018;191:132–139. doi: 10.1016/J.SCHRES.2017.04.026

7. Friston K. A theory of cortical responses. *Philos Trans R Soc Lond B Biol Sci.* 2005;360(1456):815–836. doi: 10.1098/rstb.2005.1622

8. Erickson M, Ruffle A, Gold J. A meta-analysis of mismatch negativity in schizophrenia: From clinical risk to disease specificity and progression. *Biol Psychiatry.* 2016;79(12):980–987.

9. Haigh SM, Coffman BA, Salisbury DF. Mismatch negativity in first-episode schizophrenia: a meta-analysis. *Clin EEG Neurosci.* 2016;48:3–10. doi:10.1177/1550059416645980

10. Jessen F, Fries T, Kucharski C, *et al*. *Amplitude Reduction of the Mismatch Negativity in First-Degree Relatives of Patients with Schizophrenia*. Neuroscience Letters. Vol 309.; 2001. doi: 10.1016/S0304-3940(01)02072-9

11. Michie PT, Innes-Brown H, Todd J, Jablensky AV. Duration mismatch negativity in biological relatives of patients with schizophrenia spectrum disorders. *Biol Psychiatry.* 2002;52(7):749–758. doi: 10.1016/S0006-3223(02)01379-3

12. Atkinson RJ, Michie PT, Schall U. Duration mismatch negativity and P3a in first-episode psychosis and individuals at ultra-high risk of psychosis. *Biol Psychiatry.* 2012;71(2):98–104. doi: 10.1016/j.biopsych.2011.08.023

13. Perez VB, Woods SW, Roach BJ, *et al*. Automatic auditory processing deficits in schizophrenia and clinical high-risk patients: Forecasting psychosis risk with mismatch negativity. *Biol Psychiatry.* 2014;75(6):459–469. doi: 10.1016/j.biopsych.2013.07.038

14. Lavoie S, Jack BN, Griffiths O, *et al*. Impaired mismatch negativity to frequency deviants in individuals at ultra-high risk for psychosis, and preliminary evidence for further impairment with transition to psychosis. *Schizophr Res.* 2018;191:95–100. doi: 10.1016/j.schres.2017.11.005

15. Bodatsch M, Ruhrmann S, Wagner M, *et al*. Prediction of psychosis by mismatch negativity. *Biol Psychiatry.* 2011;69(10):959–966. doi: 10.1016/j.biopsych.2010.09.057

16. Bodatsch M, Brockhaus-Dumke A, Klosterkötter J, Ruhrmann S. Forecasting psychosis by event-related potentials-systematic review and specific meta-analysis. *Biol Psychiatry.* 2015;77(11):951–958. doi: 10.1016/j.biopsych.2014.09.025

17. Hamilton HK, Roach BJ, Bachman PM, *et al*. Mismatch negativity in response to auditory deviance and risk for future psychosis in youth at clinical high risk for psychosis. *JAMA Psychiatry.* 2022;79(8):780–789. doi: 10.1001/JAMAPSYCHIATRY.2022.1417

18. Chitty KM, Lagopoulos J, Lee RSC, Hickie IB, Hermens DF. A systematic review and meta-analysis of proton magnetic resonance spectroscopy and mismatch negativity in bipolar disorder. *Eur Neuropsychopharmacol.* 2013;23(11):1348–1363. doi: 10.1016/J.EURONEURO.2013.07.007

19. Randeniya R, Oestreich LKL, Garrido MI. Sensory prediction errors in the continuum of psychosis. *Schizophr Res.* 2017;191::109–122. doi:10.1016/j.schres.2017.04.019

20. Reichenberg A, Caspi A, Harrington H, *et al*. Static and dynamic cognitive deficits in childhood preceding adult schizophrenia: A 30-year study. *Am J Psychiatry.* 2010;167(2):160–169. doi: 10.1176/APPI.AJP.2009.09040574

21. Todd J, Michie PT, Schall U, Karayanidis F, Yabe H, Näätänen R. Deviant matters: duration, frequency, and intensity deviants reveal different patterns of mismatch negativity reduction in early and late schizophrenia. *Biol Psychiatry.* 2008;63(1):58–64. doi: 10.1016/j.biopsych.2007.02.016

22. Hirt V, Schubring D, Schalinski I, Rockstroh B. Mismatch negativity and cognitive performance in the course of schizophrenia. *Int J Psychophysiol.* 2019;145:30–39. doi: 10.1016/J.IJPSYCHO.2019.01.006

23. Lavoie S, Polari AR, Goldstone S, Nelson B, McGorry PD. Staging model in psychiatry: Review of the evolution of electroencephalography abnormalities in major psychiatric disorders. *Early Interv Psychiatry.* 2019;13(6):1319–1328. doi: 10.1111/EIP.12792

24. Nagai T, Tada M, Kirihara K, Araki T, Jinde S, Kasai K. Mismatch negativity as a "translatable" brain marker toward early intervention for psychosis: A review. *Front Psychiatry.* 2013;4:115. doi: 10.3389/fpsyt.2013.00115

25. Näätänen R, Todd J, Schall U. Mismatch negativity (MMN) as biomarker predicting psychosis in clinically at-risk individuals. *Biol Psychol.* 2016;116:36–40. doi: 10.1016/J.BIOPSYCHO.2015.10.010

26. Dima D, Frangou S, Burge L, Braeutigam S, James AC. Abnormal intrinsic and extrinsic connectivity within the magnetic mismatch negativity brain network in schizophrenia: A preliminary study. *Schizophr Res.* 2012;135(1-3):23–27. doi: 10.1016/j.schres.2011.12.024

27. Dzafic I, Larsen KM, Darke H, *et al*. Stronger top-down and weaker bottom-up frontotemporal connections during sensory learning are associated with severity of psychotic phenomena. *Schizophr Bull.* 2021;47(4):1039–1047. doi: 10.1093/SCHBUL/SBAA188

28. Ranlund S, Adams RA, Díez A, *et al*. Impaired prefrontal synaptic gain in people with psychosis and their relatives during the mismatch negativity. *Hum Brain Mapp.* 2016;37(1):351–365. doi: 10.1002/hbm.23035

29. Larsen KM, Mørup M, Birknow MR, *et al*. Altered auditory processing and effective connectivity in 22q11.2 deletion syndrome. *Schizophr Res.* 2018;197:328–336. doi: 10.1016/j.schres.2018.01.026

30. Larsen KM, Mørup M, Birknow MR, *et al*. Individuals with 22q11.2 deletion syndrome show intact prediction but reduced adaptation in responses to repeated sounds: Evidence from Bayesian mapping. *NeuroImage Clin.* 2019;22:101721. doi: 10.1016/J.NICL.2019.101721

31. Larsen KM, Dzafic I, Darke H, *et al*. Aberrant connectivity in auditory precision encoding in schizophrenia spectrum disorder and across the continuum of psychotic-like experiences. *Schizophr Res.* 2020;222:185–194. doi: 10.1016/J.SCHRES.2020.05.061

32. Adams RA, Pinotsis D, Tsirlis K, *et al*. Computational modeling of electroencephalography and functional magnetic resonance imaging paradigms indicates a consistent loss of pyramidal cell synaptic gain in schizophrenia. *Biol Psychiatry.* 2022;91(2):202–215. doi: 10.1016/J.BIOPSYCH.2021.07.024

33. Ver Loren van Themaat AH, Oranje B, Larsen KM, *et al*. Mismatch negativity and P3a amplitude in children with familial high risk of schizophrenia or bipolar disorder – A Danish register-based EEG study. *Schizophr Res.* 2022;246:187–194. doi: 10.1016/J.SCHRES.2022.06.035

34. Thorup AAE, Jepsen JR, Ellersgaard DV, *et al*. The danish high risk and resilience study – VIA 7 - a cohort study of 520 7-year-old children born of parents diagnosed with either schizophrenia, bipolar disorder or neither of these two mental disorders. *BMC Psychiatry.* 2015;15(1):233. doi: 10.1186/s12888-015-0616-5

35. Thorup AAE, Hemager N, Søndergaard A, *et al*. The danish high risk and resilience study—VIA 11: study protocol for the first follow-up of the VIA 7 cohort −522 children born to parents with schizophrenia spectrum disorders or bipolar disorder and controls being re-examined for the first time at age 1. *Front Psychiatry.* 2018;9: article 661. doi: 10.3389/fpsyt.2018.00661

36. Achenbach, T. M., Edelbrock C. *Manual for the Child Behavior Checklist and Revised Child Behavior Profile.* University of Vermont, Burlington; 1983.

37. Shaffer D, Gould MS, Brasic J, Fisher P, Aluwahlia S, Bird H. A children's global assessment scale (CGAS). *Arch Gen Psychiatry.* 1983;40(11):1228–1231. doi: 10.1001/ARCHPSYC.1983.01790100074010

38. Kaufman J, Birmaher B, Brent D, *et al*. Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): Initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry.* 1997;36(7):980–988. doi: 10.1097/00004583-199707000-00021

39. Gregersen M, Søndergaard A, Brandt JM, *et al*. Mental disorders in preadolescent children at familial high-risk of schizophrenia or bipolar disorder - a four-year follow-up study: The danish high risk and resilience study, VIA 11. *J Child Psychol Psychiatry.* 2021;63:1046–1056. doi:10.1111/JCPP.13548

40. Gogtay N, Giedd JN, Lusk L, *et al*. Dynamic mapping of human cortical development during childhood through early adulthood. *Proc Natl Acad Sci U S A.* 2004;101(21):8174–8179. doi: 10.1073/PNAS.0402680101

41. Corcoran CM, Stoops A, Lee M, *et al*. Developmental trajectory of mismatch negativity and visual event-related potentials in healthy controls: Implications for neurodevelopmental vs. neurodegenerative models of schizophrenia. *Schizophr Res.* 2018;191:101–108. doi: 10.1016/J.SCHRES.2017.09.047

42. Kaczkurkin AN, Raznahan A, Satterthwaite TD. Sex differences in the developing brain: Insights from multimodal neuroimaging. *Neuropsychopharmacol.* 2018 441. 2018;44(1):71–85. doi: 10.1038/s41386-018-0111-z

43. Garrido MI, Kilner J, Kiebel S, Friston K. Dynamic causal modeling of the response to frequency deviants. *J Neurophysiol.* 2009;101(5):2620–2631. doi: 10.1152/jn.90291.2008

44. Zeidman P, Jafarian A, Seghier ML, *et al*. A guide to group effective connectivity analysis, part 2: Second level analysis with PEB. *Neuroimage.* 2019;200:12–25. doi: 10.1016/J.NEUROIMAGE.2019.06.032

45. Laurens KR, Murphy J, Dickson H, Roberts RE, Gutteridge TP. Trajectories of mismatch negativity and p3a amplitude development from ages 9 to 16 years in children with risk factors for schizophrenia. *Biol Psychiatry Cogn Neurosci Neuroimaging.* 2020;5(12):1085–1094. doi: 10.1016/J.BPSC.2020.07.012

46. Stripeikyte G, Potheegadoo J, Progin P, *et al*. Fronto-temporal disconnection within the presence hallucination network in psychotic patients with passivity experiences. *Schizophr Bull.* 2021;47(6):1718–1728. doi: 10.1093/SCHBUL/SBAB031

47. Molent C, Olivo D, Wolf RC, Balestrieri M, Sambataro F. Functional neuroimaging in treatment resistant schizophrenia: A systematic review. *Neurosci Biobehav Rev.* 2019;104:178–190. doi: 10.1016/J.NEUBIOREV.2019.07.001

48. O'Donoghue S, Holleran L, Cannon DM, McDonald C. Anatomical dysconnectivity in bipolar disorder compared with schizophrenia: A selective review of structural network analyses using diffusion MRI. *J Affect Disord.* 2017;209:217–228. doi: 10.1016/J.JAD.2016.11.015

49. Yüksel M, Murphy M, Rippe J, Leicht G, Öngür D. Decreased mismatch negativity and elevated frontal-lateral connectivity in first-episode psychosis. *J Psychiatr Res.* 2021;144:37–44. doi: 10.1016/J.JPSYCHIRES.2021.09.034

50. Larsen KM, Mørup M, Birknow MR, *et al.* Altered auditory processing and effective connectivity in 22q11.2 deletion syndrome. *Schizophr Res.* 2018;197:328–336. doi:10.1016/j.schres.2018.01.026

51. Kiebel SJ, Garrido MI, Moran RJ, Friston KJ. Dynamic causal modelling for EEG and MEG. *Cogn Neurodyn.* 2008;2(2):121–136. doi: 10.1007/s11571-008-9038-0

52. Falkenberg Krantz M, Hjorthøj C, Ellersgaard D, *et al.* Examining selection bias in a population-based cohort study of 522 children with familial high risk of schizophrenia or bipolar disorder, and controls: The danish high risk and resilience study VIA 7. *Soc Psychiatry Psychiatr Epidemiol.* 2022;1:1–28. doi: 10.1007/S00127-022-02338-3

53. Seidman LJ, Nordentoft M. New targets for prevention of schizophrenia: Is it time for interventions in the premorbid phase? *Schizophr Bull.* 2015;41(4):795–800. doi: 10.1093/SCHBUL/SBV050