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Direktor: Prof. Dr. med. Jürgen Gallinat

Decreased mismatch negativity and elevated frontal-lateral connectivity in first-episode psychosis

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Mahmut Martin Yüksel
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Decreased mismatch negativity and elevated frontal-lateral connectivity in first-episode psychosis

Mahmut Yüksel [a,1], Michael Murphy [b,c,1,*], Jaelin Rippe [c], Gregor Leicht [a], Dost Öngür [b,c]

[a] University Medical Center Hamburg-Eppendorf, Martinistraße 52, 20251, Hamburg, Germany
[b] Harvard Medical School, 25 Shattuck St, Boston, MA, 02115, USA
[c] McLean Hospital, 115 Mill St Belmont, MA, 02478, USA

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ABSTRACT

Decreased mismatch negativity (MMN) is a proposed biomarker for psychotic disorders. However, the magnitude of the effect appears to be attenuated in first-episode populations. Furthermore, how mismatch negativity amplitudes are related to brain connectivity in this population is unclear. In this study, we used high-density EEG to record duration-deviant MMN from 22 patients with first-episode psychosis (FEP) and 23 age-matched controls (HC). Consistent with past work, we found decreased MMN amplitude in FEP over a large area of the frontal scalp. We also found decreased latency over the occipital scalp. MMN amplitude was negatively correlated with antipsychotic dose. We used Granger causality to investigate directional connectivity between frontal, midline, left, and right scalp during MMN and found reduced connectivity in FEP compared to HC and following deviant stimuli compared to standard stimuli. FEP participants with smaller decreases in connectivity from standard to deviant stimuli had worse disorganization symptoms. On the other hand, connectivity from the front of the scalp following deviant stimuli was relatively preserved in FEP compared to controls. Our results suggest that a relative imbalance of bottom-up and top-down perceptual processing is present in the early stages of psychotic disorders.

1. Introduction

Schizophrenia and other psychotic disorders are common and severe psychiatric illnesses. Schizophrenia typically presents in young adulthood and can lead to major disruptions in academic, occupational and social achievement (Whiteford et al., 2015). The early course of schizophrenia may be a critical time for interventions to improve patient outcomes (McGorry, 1998). However, delivering effective treatments to this population is complicated by multiple factors. Current treatments for schizophrenia have limited efficacy and it is difficult to target these treatments to the population that will benefit. Both of these issues could be helped by a better understanding of the biological underpinnings of this disease. However, the pathology of schizophrenia is likely multifactorial and remains somewhat unclear. Several neurotransmitter systems have been implicated, including GABA, glutamate, dopamine, and acetylcholine (Lisman et al., 2008). A neuroimaging biomarker for psychotic disorders could be a non-invasive, easy to obtain way to identify patients and could also shed light on the pathophysiology of the disease.

One potential biomarker is mismatch negativity (MMN), an event-related potential that occurs when a sequence of repeated identical (standard) stimuli is interrupted by an odd (deviant) stimulus (Näätänen, 1995). MMN can occur in response to a variety of stimuli and deviations. MMN is an automatic, unconscious process that depends on bottom-up perceptual processing to detect deviant stimuli (Kenemans and Kähkönen, 2011). Auditory MMN paradigms are commonly employed in which either pitch or duration may be varied and are generally measured over frontocentral electroencephalographic (EEG) channels (Umbricht and Krljesb, 2005). Decreased auditory MMN has been widely reported in patients with schizophrenia and has been proposed to be a biomarker for psychotic disorders (Light and Näätänen, 2013; Umbricht and Krljesb, 2005). However, the magnitude of the decrease may be related to illness duration with first-episode patients showing no reduction in MMN to pitch deviants and small, but statistically significant reduction in MMN to duration deviants (Haigh et al., 2017). MMN impairment may reflect premorbid intellectual functioning

* Corresponding author. McLean Hospital, 115 Mill St, Belmont, MA, 02478, USA.
E-mail addresses: mahmut.yueksel@outlook.de (M. Yüksel), mmurphy@mgh.harvard.edu (M. Murphy), jrippe@mclean.harvard.edu (J. Rippe), g.leicht@uke.de (G. Leicht), dongur@partners.org (D. Öngür).
[1] MY and MM contributed equally to this work.

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in first-episode psychosis as well as a level of vulnerability to disease progression in high-risk psychosis population (Erickson et al., 2016; Salisbury et al., 2017). Furthermore, MMN deficits may not be specific to schizophrenia as they have also been reported in bipolar disorder, autism spectrum disorder, and with mixed evidence for major depressive disorder (Bissonnette et al., 2020; Hermens et al., 2018; Schwartz et al., 2018). This suggests that the neural circuits that produce MMN may be disrupted by a variety of psychiatric disorders.

Some have proposed that schizophrenia and other psychotic disorders are dysconnection syndromes (Friston and Frith, 1995). In this model, psychosis symptoms arise from aberrant functional integration across brain regions. There is a robust literature describing abnormalities in both task-related and resting state connectivity across multiple frequency bands in both high-risk, first episode and chronic populations (Perrottelli et al., 2021). Recently, altered directional functional connectivity during mismatch negativity has been reported in patients with chronic schizophrenia (Koshiyama et al., 2020). This suggests that MMN may function as a probe of dysconnectivity in this context though which features of the pathophysiology of schizophrenia contribute to decreased MMN has yet to be determined. Decreased MMN might be caused by impaired function of local cortical circuits within the auditory cortex and/or dysconnectivity across specific long-range cortico--thalamo-cortical connections implementing bottom-up processing. Furthermore, different patterns of dysconnectivity may underlie MMN impairments at different stages of illness.

In this study, we measured MMN to a duration deviant in patients with first-episode psychosis compared to healthy controls and investigated differences in brain connectivity following standard and deviant stimuli using high-density EEG. We hypothesized that, consistent with prior literature, the MMN would be present but attenuated in patients relative to controls. We also hypothesized that this difference would be related to differences in long-range cortical connectivity consistent with a relative weakening of bottom-up perceptual processing to deviant stimuli. We hypothesized that causal density, a measure of the complexity of the connectivity pattern in a network, would be abnormal in patients with first-episode psychosis consistent with the dysconnection hypothesis.

2. Methods

2.1. Participants and procedure

We recruited 30 patients with first-episode psychosis (FEP, within 3 years of initial diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder with psychotic features, or psychosis not otherwise specified) from inpatient units and outpatient clinics at McLean Hospital and 30 age-matched healthy controls (HC) with no history of mental illness who were recruited through advertisements in the community. Exclusion criteria were history of major medical or neurological illness, history of severe head injury, hearing loss, and history of electroconvulsive therapy. Control participants could not have any history of use of psychiatric medication or of psychiatric diagnoses. All participants from an inpatient unit had an independent evaluation of their ability to consent to the study procedures performed by a psychiatrist not involved in the study. All participants gave informed consent for all study procedures. All study procedures were approved by the Institutional Review Board of Partners Healthcare. All patient participants were receiving treatment at McLean Hospital and had clinical diagnoses were obtained from the medical record and confirmed with the Structured Clinical Interview for DSM-5 (First et al., 2015). All patients had a brief hearing screen. FEP patient participants underwent a video-recorded Structured Clinical Interview for the Positive and Negative Symptom Scale (SCI-PANSS) (Kay et al., 1987). Raw PANSS scores were converted to factors using a weighted sum approach (DiStefano et al., 2009; Wallwork et al., 2012). After the interview, participants EEG data was collected. Two control subjects and three patients did not tolerate the experiment and ended it early and their data was not included in this analysis. Following data collection, one control subject was found to not meet inclusion criteria (use of psychiatric medications) and three patients were subsequently found to not meet the first-episode criteria. Data from four control subjects and two patients was contaminated by persistent broadband EEG artifact. Therefore, the final data set consisted of 22 patients and 23 controls. Demographic information about the sample is presented in Table 1.

2.2. Electroencephalography

EEG data collection was performed using a Geodesic Sensor Net (Electrical Geodesics Incorporated; Philips Amsterdam, The Netherlands) with 129 Ag–AgCl electrodes. EEG data were collected at a 1 kHz sampling rate with a common vertex reference using the NetStation software package (EGI). The collection took place in an electrically and acoustically shielded room. Impedances were kept below 65 kΩ. Bad channels and artifactual segments of data were identified by visual inspection and a thresholding procedure. Bad channels were interpolated by spherical splines and artifactual segments of data were excluded from the analysis. The data were then bandpass filtered from 0.5 to 40 Hz, downsampled to 250 Hz, re-referenced to linked mastoids, and exported to MATLAB (MathWorks, Natick MA).

2.3. Auditory mismatch negativity

We elicited auditory MMN using a duration deviant. Participants were seated in a comfortable chair and watched a short, silent video of nature scenes. Auditory stimuli were delivered via in-ear headphones (Etymotics, ER3C). Standard stimuli were 1000 Hz, 50 ms and deviant stimuli were 1000 Hz, 100 ms. We presented 1000 stimuli with an average interstimulus interval of 500 ms. We presented 900 standard stimuli and 100 deviant stimuli. We first presented a run of 100 standard stimuli after which point deviant stimuli were randomly interspersed. For each participant, we calculated MMN then by subtracting the mean baseline-corrected response to the standard stimulus from the mean baseline-corrected response to the deviant stimulus. Latency was calculated as the time point of maximal difference in amplitude between the standard and deviant stimuli over this interval. We calculated the MMN amplitude by taking the mean difference over a 50 ms window centered on the latency time point.We used statistical nonparametric permutation tests (SnPM) at the single channel and cluster level to identify differences in MMN between the HC and FEP groups. In channel-level SNPM, t-statistics are calculated for each channel and the largest magnitude t-value is recorded. Then group labels are permuted, and this process is repeated for 10,000 permutations. The 95% percentile t-value is used as a threshold for the t-values from the non-permuted comparison and any t-values in excess of this percentile are considered statistically significant. For SnPM cluster tests, a similar permutation analysis is performed using the size of spatially contiguous cluster of channels that all exceed a chosen t value threshold. Given that little is known about the relationship between symptom severity and connectivity during MMN paradigms in people with early course psychosis, we

Table 1
Demographic and clinical information.

	Control	Patient
Sample Size	23	22
Age (Years, Mean ± SEM)	23.2 ± 0.5	22.6 ± 0.6
Sex (Male, Female)	12,11	16,6
Chlorpromazine Equivalents (mg, Mean ± SEM)	–	208.3 ± 32.8
PANSS Positive Factor (Mean ± SEM)	–	7.6 ± 0.7
PANSS Negative Factor (Mean ± SEM)	–	10.4 ± 0.8
PANSS Disorganized Factor (Mean ± SEM)	–	4.6 ± 0.4
PANSS Excited Factor (Mean ± SEM)	–	5.3 ± 0.4
PANSS Depressed Factor (Mean ± SEM)	–	4.2 ± 0.3

performed a hypothesis-generating, exploratory analysis by calculating the Pearson correlation coefficient between MMN connectivity parameters and medication dose and symptom scores. Because these comparisons are hypothesis-generating they are not corrected for multiple comparisons.

2.4. Connectivity analyses

We used Granger causality (GC) to measure the long-range connectivity between four channels in a 350 ms window following stimulus presentation. These channels were chosen because they were located at opposite ends of a cluster that showed decreased MMN amplitude in FEP compared to HC (see below). We chose to analyze a subset of the cluster because neighboring electrodes can be highly correlated. The Granger causality from signal *A* to signal *B* is a measure of how much information about past values of *A* improves the prediction of future values of *B* beyond what can be learned from past values of *B*. In multivariate Granger causality analysis, the connectivity value for each channel is conditioned on the contributions from other channels (Barnett and Seth, 2014), Therefore, having multiple correlated channels would obscure the connectivity results. By choosing four spatially distinct channels, we minimize correlations due to volume conduction and bridging while covering the spatial extent of the cluster. We calculated the causal density of the network formed by these four channels. Causal density of a network is the average pairwise GC conditioned by the other connections (Seth et al., 2011). Causal density is a measure of the complexity of a network because a network composed of tightly correlated channels will have a low value for causal density as will a network composed of independent channels. High values of causal density indicate a complex pattern of GC between elements of a network.

3. Results

3.1. Mismatch negativity amplitude is decreased frontally and latency is decreased occipitally

For each participant, we calculated the mismatch negativity (MMN) amplitude and latency for each channel and the average MMN amplitude and latency across all channels (Fig. 1a and b). We found no statistically significant difference between mean amplitude in HC (−2.04 μV, standard error of the mean (SEM) 0.20 μV) and FEP (−1.49 SEM 0.19 μV, p = .078, unpaired *t*-test, Fig. 1b). We also found no statistically significant difference in mean latency between HC (183.74 SEM 3.70 ms) and FEP (182.23 SEM 5.31 ms, p = .80, unpaired *t*-test). We found that increased mean latency was associated with increased magnitude of the MMN in FEP (Pearson's r = -.49, p = .021) but not in HC (Fig. 1c). Within FEP, we found that CPZ equivalents were associated with decreased amplitude of the MMN (Pearson's r = 0.51, p = .015) and with decreased latency (Pearson's r = -.50, p = .017).

There were no statistically significant correlations between MMN amplitude or latency and any symptom factor nor were any significant differences seen in MMN parameters between diagnostic subgroups (all p > .13).

We expanded upon these results by investigating the spatial topography MMN amplitude and latency in HC and FEP (Fig. 2). In both HC and FEP, MMN amplitude was greatest in a broad region over the front of the scalp. Latency was longest in the occipital scalp in HC but this was not the case in FEP. We found a cluster of 63 channels over the front half of the scalp that had decreased MMN amplitude in FEP compared to HC (SnPM suprathreshold cluster test, p = .039). We also found a small cluster of 6 occipital electrodes that had longer latencies in HC compared to FEP (SnPM suprathreshold cluster test, p = .047).

3.2. Directional connectivity is decreased following deviant stimuli compared to standard stimuli and in FEP compared to HC

We selected four channels, located at opposite ends of the large amplitude cluster, to investigate long-range connectivity following stimulus presentation (Fig. 3a). We calculated the Granger causality between each pair of channels and the causal density across the network formed by the channels (Fig. 3b). For causal density, multivariate ANOVA showed effects of group ($F_{1,89}$ = 4.98, p = .028) and stimulus type ($F_{1,89}$ = 30.68, p < .0001) and no statistically significant interaction between group and stimulus ($F_{1,89}$ = 0.01, p = .92). Post-hoc testing

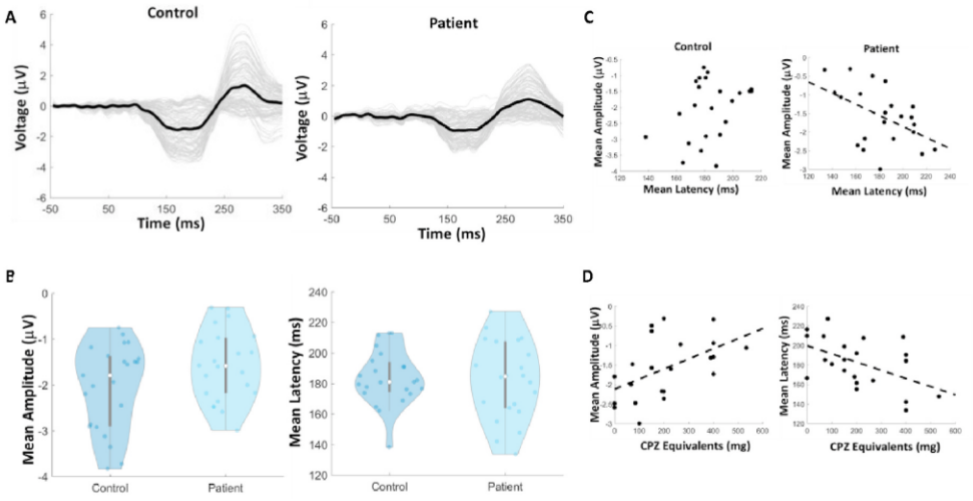

Fig. 1. Mismatch negativity amplitude and latency. A) Average difference waves for deviant – standard stimuli in all channels in controls and patients. The black traces are the average difference waves across all channels. B) Violin plots of the average MMN amplitude and latency across all channels in controls and patients. C) Scatterplots showing the relationship between mean amplitude and mean latency across all channels in controls and patients. Trendline indicates a statistically significant relationship in the patient group (Pearson's r = −.49, p = .020). D) Scatterplots showing the relationship between chlorpromazine equivalents and mean amplitude (Pearson's r = .51, p = .015) and latency (Pearson's r = -.50, p = .017) across all channels.

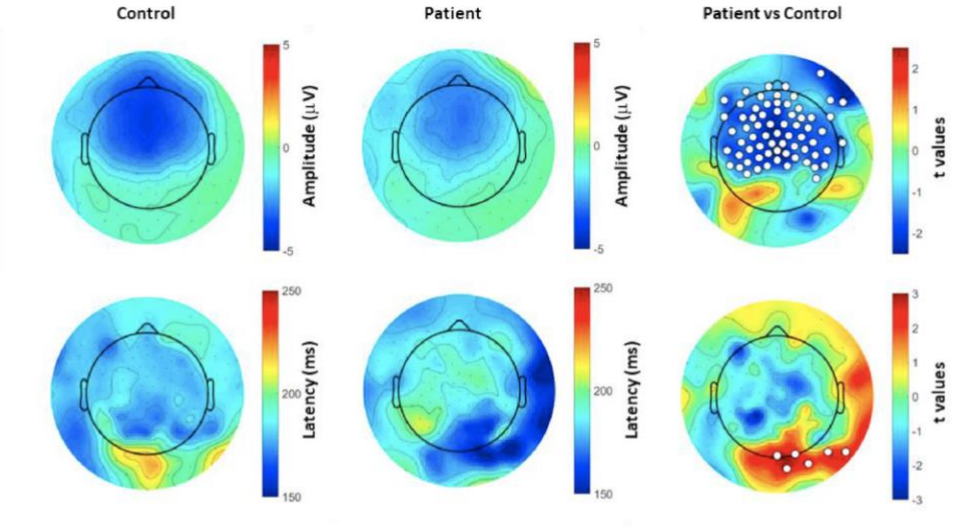

Fig. 2. Topography of aberrant mismatch negativity amplitude and latency in first-episode psychosis. The first column shows the topography of the mean MMN amplitude and latency in controls. The second column shows the topography of the mean MMN amplitude and latency in patients. The third column shows the comparison between patients and controls. The white dots indicate electrodes that statistically significantly different (SnPM suprathreshold cluster test, $p < .05$).

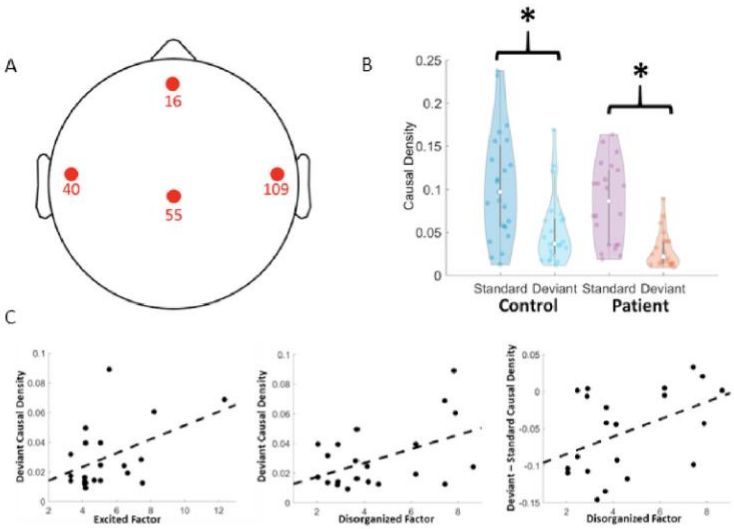

Fig. 3. Long-range causal density is higher during standard stimuli compared to deviant stimuli. A) Four spatially distinct electrodes from the cluster identified in Fig. 2 were chosen for the causal density analysis. B) Violin plots showing the mean causal density during standard and deviant stimuli in patients and controls. * $p < .000002$, Tukey's HSD test. C) Scatterplots showing the relationship between causal density during the deviant stimuli and Excited factor (Pearson's $r = .47$, $p = .028$) and Disorganized factor (Pearson's $r = 0.46$, $p = .030$ as well as between the difference between deviant and standard causal density and the Disorganized factor (Pearson's $r = 0.44$, $p = .038$).

(Tukey's HSD) showed that HC (0.08 SEM 0.007) had higher causal density than FEP (0.06 SEM 0.007, $p = .027$) and standard stimuli (0.09 SEM 0.007) had higher causal density than deviant stimuli (0.04 SEM 0.007, $p < .00001$). Furthermore, HC standard stimuli (0.10 SEM 0.01) had greater causal density than HC deviant stimuli (0.04 SEM 0.008, $p < .0001$) and FEP deviant stimuli (0.03 SEM 0.005, $p < .0001$). FEP standard stimuli (0.08 SEM 0.01) had greater causal density than FEP deviant stimuli ($p < .0001$). In an exploratory analysis, we tested whether there were associations between causal density and symptom scores (Fig. 3c). We found that causal density following deviant stimuli was associated with both the Disorganized (Pearson's $r = 0.47$, $p = .02$) and the Excited factor (Pearson's $r = 0.46$, $p = .03$). Patients who had greater Disorganization scores had smaller differences in causal density between deviant and standard stimuli (Pearson's $r = 0.44$, $p = .04$). Causal density was not associated with MMN amplitude or latency in either HC or FEP (all $p > .09$).

3.3. *Abnormal connectivity during deviant stimuli is associated with psychosis symptoms*

Next, we examined the topography of connectivity between the four electrodes (Fig. 4). Overall and consistent with the causal density findings, most connections had decreased magnitude in the deviant stimuli compared to standard stimuli. For each group and condition, we

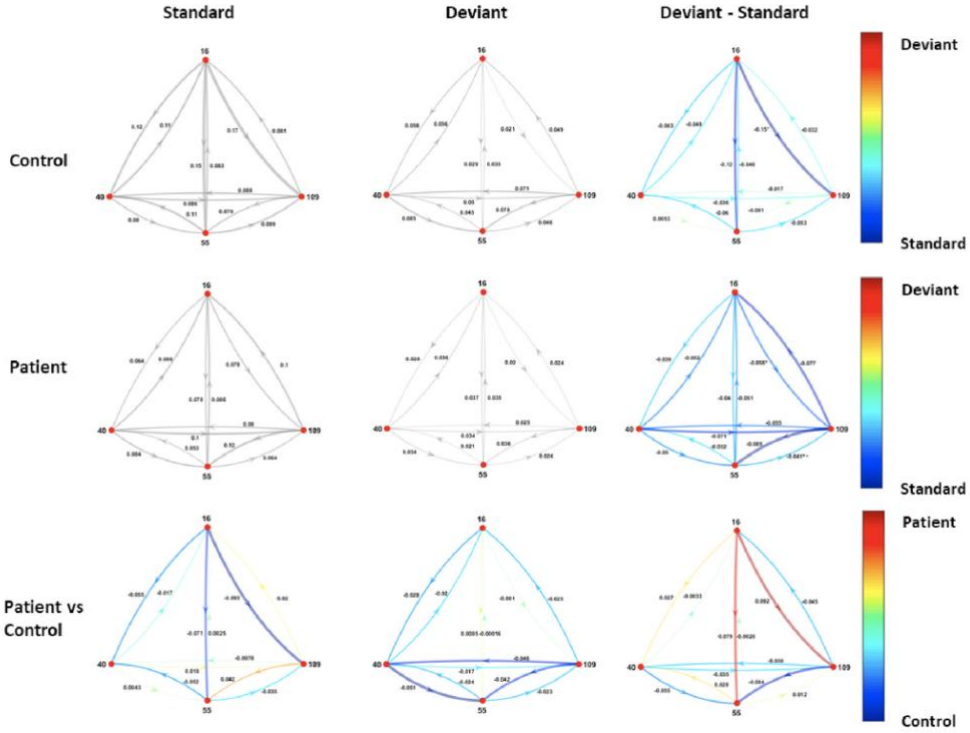

Fig. 4. Granger causality directed graphs. Top row shows the Granger causality (GC) values for the connections between the channels identified in Fig. 3a. The thickness of the line is proportional to the magnitude of the GC. The third column shows the difference between GC in the deviant vs the standard stimuli. Red connections are stronger in the deviant condition and blue connections are stronger in the standard condition. * p = .0002, SnPM test. Second row shows the GC values for the patient group. ** p = .01, SnPM test * p = .04, SnPM test. Third row shows the difference between patients and controls during standard stimuli, deviant stimuli, and the difference between deviant and standard stimuli. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

calculated an ANOVA to probe for topographic variation in connectivity strength. After correction for multiple comparisons, we found evidence of topographic variation in connection strength in the HC, deviant stimuli condition ($F_{11,242} = 3.6$, $p_{adjusted} = 0.0004$). Post-hoc testing showed that connectivity from channel 40 (left) to channel 55 (central) was greater than connectivity in both directions between channel 16 (frontal) and channel 55 (p = .0047,.022, respectively, Tukey's HSD) as well as greater than connectivity between frontal and channel 109 (right, p = .0004,Tukey's HSD). In the same condition, connectivity from right to central was greater than connectivity from frontal to central (p = .032) and from frontal to right (p = .004).

In order to assess patterns of directional connectivity following the different stimuli, we categorized each connection as front-to-back, back-to-front, left-to-right, and right-to-left. The front-to-back group consisted of the following connections: frontal-to-central, frontal-to-left, frontal-to-right, right-to-central, and left-to-central. The back-to-front group consisted of the opposite connections. The right-to-left group consisted of the following connections: right-to-frontal, right-to-left, right-to-central, central-to-left, and frontal-to-left. The left-to-right group consisted of the opposite connections. Some connections were assigned to more than one category. Bonferroni-corrected ANOVAs on group x direction showed evidence of a stimulus effect for all directions (all $p_{adjusted} < .0003$). In HC, we found that front-to-back connectivity was decreased following the deviant stimuli compared to the standard stimuli ($p_{adjusted} = .010$, paired *t*-test, Bonferroni corrected, Cohen's d = 0.95) as were back-to-front connectivity ($p_{adjusted} = .026$, paired *t*-test, Bonferroni corrected, Cohen's d = 0.68) and left-to-right connectivity ($p_{adjusted} = .011$, paired *t*-test, Bonferroni corrected, Cohen's d = 0.94). In contrast, in FEP, all directions of connectivity were decreased: front-to-back ($p_{adjusted} = .0005$, paired *t*-test, Bonferroni corrected, Cohen's d = 1.28), back-to-front ($p_{adjusted} = .002$, paired *t*-test, Bonferroni corrected, Cohen's d = 1.14), right-to-left ($p_{adjusted} = .0034$, paired *t*-test, Bonferroni corrected, Cohen's d = 0.95), and left-to-right ($p_{adjusted} = .009$, paired *t*-test, Bonferroni corrected, Cohen's d = 1.10). Comparing HC to FEP, we found that during deviant stimuli right-to-left connectivity was higher in HC compared to FEP ($p_{adjusted} = .04$, unpaired *t*-test, Bonferroni corrected, Cohen's d = 0.65). There were no other statistically different connectivities between HC and FEP. Right-to-left connectivity was not correlated with CPZ equivalents (Pearson's r = -.08, p = .72) but was associated with Excited (Pearson's r = 0.44, p = .04) and Disorganized (Pearson's r = 0.48, p = .023).

We then compared how connectivity between pairs of channels differed between the standard and deviant stimuli. We found that in both HC and FEP, connectivity from frontal to right was decreased following deviant stimuli compared to standard stimuli (SnPM, p = .0002 and p = .01, respectively). In FEP, connectivity from central to right was also statistically significantly decreased following deviant stimuli compared to standard stimuli (SnPM, p = .04). There were no statistically significant differences between HC and FEP. There were no statistically significant associations between frontal to right and center to right connectivity and symptom scores or CPZ.

For each channel, we calculated net information flow for each

channel by subtracting the inward Granger causality from the outward Granger causality (Fig. 5). There were no differences in flow in any channel between HC and FEP. We then calculated whether there were differences in flow between stimuli type. In HC, we found a statistically significant increase in flow in the right channel in deviant stimuli compared to standard stimuli ($p_{adjusted}$ = .016, paired *t*-test, Bonferroni adjusted).

4. Discussion

We used auditory duration mismatch negativity to probe long-range, directional cortical connectivity in HC and FEP using high-density EEG. Consistent with past work, we found that MMN amplitudes were largest over the fronto-central region of the scalp in both HC and FEP and that MMN amplitude was broadly decreased over this same region in FEP compared to HC. We also found that MMN latency was decreased in the occipital scalp. Within a four-channel network consisting of frontal, central, left, and right channels we found increased causal density in HC compared to FEP and increased causal density following standard stimuli compared to deviant stimuli. Relatively high causal density following deviant stimuli was associated with higher symptom scores for disorganization and excitement. Connectivity involving the right side of the scalp was modulated by the stimulus type. Aberrant modulation of connectivity to and from the right scalp in response to stimulis type was noted in FEP and was associated with greater symptom burden. In HC, the right side of the scalp becomes a relative information source following deviant stimuli compared to standard stimuli, however this effect was not observed in FEP. Taken together, our results suggest that bottom-up processing abnormalities in long-distance cortical circuits contribute to the well-known MMN abnormalities observed in psychotic disorders.

5. Mismatch negativity and psychosis

Decreased amplitude of duration MMN has been repeatedly reported in patients with schizophrenia. However, some evidence suggests that the magnitude of the effect is larger in chronic populations compared to first-episode or ultra-high risk populations (Atkinson et al., 2012; Haigh et al., 2017; Salisbury et al., 2002). Furthermore, patients with bipolar disorder have diminished MMN compared to healthy controls, but not as diminished as patients with schizophrenia (Jahshan et al., 2012; Umbricht et al., 2003). Our transdiagnostic sample of patients with first-episode psychosis compliments this literature and provides further evidence for attenuated MMN in this population. The relationship between medication and MMN is not entirely clear. Small, longitudinal studies of risperidone and olanzapine found no effect of these medications on MMN (Iwanami et al., 2001; Korostenskaja et al., 2005). Another study showed that clozapine dose was negatively correlated with MMN amplitude (Horton et al., 2011). We found that MMN amplitude was negatively correlated with antipsychotic medication dose, suggesting either a direct medication effect on MMN or, more likely, confounding by severity where more severely affected patients have greater MMN abnormalities and are on higher doses of medication. When interpreting out results in the context of this literature, note that we measured average MMN amplitude across the entire scalp, rather than restricting our analysis to a single channel or small set of channels. We chose this analysis because our results suggest that mismatch negativity deficits can be detected broadly over the scalp rather than only in a small subset of channels. While decreased MMN latency has been previously reported in schizophrenia, previous studies have not shown consistent effects of antipsychotic medication on MMN latency (Kärgel et al., 2014; Korostenskaja et al., 2005; Umbricht et al, 1998, 1999). The spatial considerations mentioned above and the fact that our sample was transdiagnostic and early course may explain the difference between our results and this literature.

Our directed connectivity results are partially consistent with a recent report that patients with chronic schizophrenia have decreased inter-hemispheric effective connectivity during MMN, however, we found increased connectivity from front to back in patients while the chronic population had increased connectivity from back to front (Koshiyama et al., 2020). This suggests that different patterns of dysconnectivity may underlie MMN deficits in early vs chronic schizophrenia perhaps reflecting the progression of disease.

Predictive coding, has been hypothesized to contribute to MMN generation (Michie et al., 2016). In predictive coding models, the brain uses information from previous sensory inputs to generate models to predict future sensory inputs. Prediction errors occur when there is a discrepancy between the predicted and actual input. These errors are used to update and refine the predictive model while also allocating neural resources to the unexpected stimuli. In the predictive coding framework, bottom-up inputs from sensory cortices are inhibited by top-down inputs from frontal cortex (Kenemans and Kähkönen, 2011). Dynamic causal modelling studies of MMN indicate that such hierarchical models are best able to recapitulate the MMN response (Garrido et al., 2009; Kirihara et al., 2020). Furthermore, NDMA receptors, which are known to modulate MMN, provide a biologically plausible mechanism for generation and maintenance of predictive coding models (Michie et al., 2016). In addition, NMDA receptor antagonists decrease the MMN response (Heekeren et al., 2008) with smaller MMN amplitudes being associated with schizophrenia-like negative symptoms (Thiebes et al., 2017). Our findings are consistent with disrupted NMDA receptor function in our transdiagnostic sample.

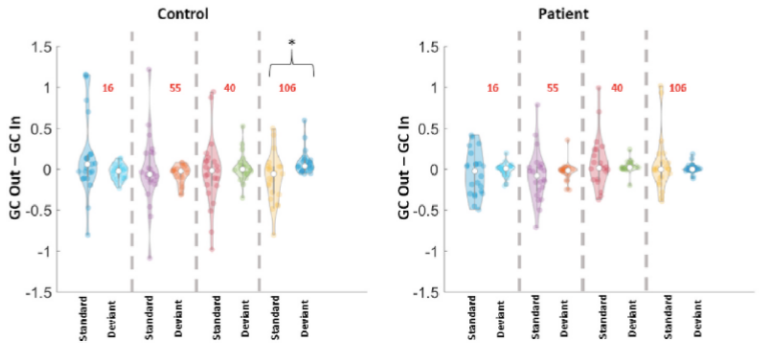

Fig. 5. Flow (Granger causality out – Granger causality in). Violin plots showing the difference between GC out and GC in in each of the four channels during deviant and standard stimuli in the control and patient groups. * $p_{adjusted}$ = .032, paired *t*-test, Bonferroni correction.

6. Dysconnectivity and top-down vs bottom-up processing

Auditory MMN is largely driven by neural activity in the auditory cortex but is modulated by the frontal cortex and the thalamus (Lakatos et al., 2020). This suggests that MMN relies on bottom-up processing but can be impacted by top-down inputs. Given this reliance on both local cortical microcircuits and longer-range cortico-thalamo-cortical networks, it is unsurprising that psychotic disorders, which are characterized by myriad forms of cortical dysconnectivity, are accompanied by decreased MMN. Dysconnectivity in schizophrenia is complex with research findings depending upon brain regions, behavioural state, illness duration, medication status, and connectivity measures (Anticevic et al, 2014a, 2014b; Di Lorenzo et al., 2015). Causal density analysis provides a way to quantify dysconnectivity in the brain. Our causal density results suggest that abnormally complex patterns of connectivity during deviant stimuli and failure to attenuate the complexity of the pattern of connectivity, were associated with psychotic symptoms. Furthermore, we report a general decrease in connectivity within the front half of the head in FEP compared to HC. This is consistent with tractography data showing broadly decreased anisotropy in schizophrenia (Kelly et al., 2018). We found that, following deviant stimuli, long-range Granger causality across the scalp is decreased compared to following standard stimuli. Therefore, in the deviant condition, EEG signals are more driven by local activity than by long range inputs. The relative freeing of local micro-circuits from global modulation is consistent with a greater role of bottom-up vs top-down processing following the deviant stimuli in both HC and FEP. Connectivity differences between HC and FEP were driven by smaller front-to-midline connectivity following standard stimuli and smaller horizontal connectivity following deviant stimuli. The aberrant persistent connectivity from frontal regions to midline and right temporal regions in FEP compared to HC is consistent with a model in which MMN deficits in FEP are the result of failure of inappropriately preserved top-down processing and/or diminished bottom-up processing following a novel stimulus in patients. Increased top-down processing in schizophrenia has been widely reported and may be related to hallucinations (Aleman et al., 2003). Impaired bottom-up processing has also been reported in some auditory paradigms as well (Adcock et al., 2009). Our work builds on these reports by providing evidence for specific failures to modulate the balance between these processes in FEP and relates this failure to thought disorder. Future work should incorporate visual paradigms to test whether these processing abnormalities exist in other sensory modalities and other regions of the brain such as the occipital cortex. Future work should also identify whether there is evidence for dysconnectivity, and therefore top-down vs bottom-up imbalance, in pitch variant MMN paradigms where amplitude deficits are not present in first episode psychosis but are present in patients with chronic psychosis. This would provide clarity as to whether inappropriate modulation of processing is non-specific global phenomenon or whether there are varied, more subtle, deficits in modulation which rely on distinct neural circuits and can be interrogated by specific stimulus parameters.

7. Limitations

Our study has several limitations that should be considered when interpreting our results. The cross-sectional design of this study limits our ability to investigate the relationship between abnormal MMN and disease progression or medication exposure. Further work could investigate whether the administration of antipsychotic medications to healthy controls produces reliable changes in MMN. In addition, our transdiagnostic sample makes direct comparison to previous studies restricted to schizophrenia non-trivial. Inferences from EEG recordings to cortical activity are limited by the complicated relationship between neural activity and detectable scalp voltages. Nonetheless, the data presented in this study are broadly consistent with past work showing diminished MMN in individuals with psychotic disorders. We expand on this past work by identifying specific patterns of dysconnectivity during the MMN paradigm in patients with early course psychosis and linking this dysconnectivity to symptom burden. We note EEG data is easy to collect compared to other imaging methods and that connectivity measures described in this study are relatively straightforward to calculate suggesting that GC may be a widely accessible clinical measure.

Author statement

Mahmut Yüksel: Writing- Original draft preparation, Visualization, Formal Analysis. **Michael Murphy:** Conceptualization, Methodology, Formal Analysis, Visualization, Investigation, Resources, Funding Acquisition, Writing – Review and Editing. **Jaelin Rippe**: Writing – Review and Editing. **Gregor Leicht:** Writing – Review and Editing, Supervision. **Dost Öngür:** Writing – Review and Editing, Resources, Supervision.

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Table of contents

1 Objectives

This thesis embraces the contents of the scientific study “Decreased mismatch negativity and elevated frontal-lateral connectivity in first-episode psychosis” from Yüksel et al. (Yuksel et al., 2021), which investigated the following four hypotheses:

Firstly, we were interested if mismatch negativity amplitude and latency is decreased in first-episode psychosis patients compared to the healthy control group. Secondly, we tested whether connectivity, more specifically directional connectivity, is decreased following deviant stimuli compared to standard stimuli and in FEP compared to HC. Thirdly, we were interested in finding correlations between symptomatic factors and abnormal connectivity because we assumed that the grade of abnormal connectivity is associated with severity of psychosis symptoms. Lastly, we hypothesized that causal density, a measure of the complexity of the connectivity pattern in a network, would be abnormal in patients with first-episode psychosis consistent with the disconnection hypothesis.

Summary:

I. Hypothesis:

Mismatch negativity amplitude and latency is decreased in FEP compared to HC.

II. Hypothesis:

Directional connectivity is decreased following deviant stimuli compared to standard stimuli and in FEP compared to HC.

III. Hypothesis:

Abnormal connectivity is associated with psychosis symptoms.

IV. Hypothesis:

Causal density is abnormal in patients with first-episode psychosis consistent with the disconnection hypothesis.

2 Introduction

Schizophrenia and other psychotic disorders are extremely severe psychiatric illnesses which are among the top 15 leading factors for disability worldwide (Vos et al., 2017). The intensive burden of psychotic disorders such as schizophrenia leads to an estimated lifetime risk of 5,6 % for suicide (Hor & Taylor, 2010). Schizophrenia typically presents in young adulthood and can lead to major disruptions in academic, occupational and social achievement (Whiteford et al., 2015). The early course of schizophrenia may be a critical time for interventions to improve patient outcomes (McGorry, 1998). However, delivering effective treatments to this population is complicated by multiple factors. Current treatments for schizophrenia have limited efficacy and it is difficult to target these treatments to the population that will benefit. Both issues could be helped by a better understanding of the biological underpinnings of this disease. However, the pathology of schizophrenia is likely multifactorial and remains somewhat unclear. Several neurotransmitter systems have been implicated, including GABA, glutamate, dopamine, and acetylcholine (Lisman et al., 2008). A neuroimaging biomarker for psychotic disorders could be a non-invasive, easy to obtain way to identify patients and could also shed light on the pathophysiology of the disease.

One potential biomarker is mismatch negativity (MMN). MMN marks the minimal peak of an event-related potential that occurs when a sequence of repeated identical-baseline, so called “standard”, stimuli is interrupted by odd, so called “deviant”, stimuli (Risto Näätänen, 1995; Yüksel et al., 2021). MMN occurs in response to a variety of stimuli and deviations. MMN is an automatic, unconscious process that depends on bottom-up perceptual processing to detect deviant stimuli (Kenemans and Kähkönen, 2011). Auditory MMN paradigms are commonly employed in which either pitch or duration may be varied and are generally measured over frontocentral electroencephalographic (EEG) channels (Umbricht and Krljesb, 2005). Decreased auditory MMN has been widely reported in patients with schizophrenia and has been proposed to be a biomarker for psychotic disorders (Light and Näätänen, 2013; Umbricht and Krljesb, 2005). However, the magnitude of the decrease may be related to illness duration with first-episode patients showing no reduction in MMN to pitch deviants and small, but statistically significant reduction in MMN to duration deviants (Haigh et al., 2017). MMN impairment may reflect premorbid intellectual functioning in first-episode psychosis as well as a level of vulnerability to disease progression in high-risk psychosis population (Erickson et al., 2016; Salisbury et al., 2017). Furthermore, it is known that MMN deficits are not highly specific to the model of schizophrenia, but they have also been found in patients with autism, with bipolar disorder and with mixed evidence for major depressive disorder (Bissonnette et al., 2020; Hermens et al., 2018; Schwartz et al., 2018). This suggests that the neural circuits that produce MMN may be disrupted by a variety of psychiatric disorders.

There is a robust literature describing abnormalities in both task-related and resting state connectivity across multiple frequency bands in both high-risk, first episode and chronic populations (Perrottelli et al., 2021). Recently, altered directional functional connectivity during mismatch negativity has been reported in patients with chronic schizophrenia (Koshiyama et al., 2020). This suggests that MMN may function as a probe of dysconnectivity in this context though which features of the pathophysiology of schizophrenia contribute to decreased MMN has yet to be determined. Decreased MMN might be caused by impaired function of local cortical circuits within the auditory cortex and/or dysconnectivity across specific long-range cortico-thalamo-cortical connections implementing bottom-up processing. Furthermore, different patterns of dysconnectivity may underlie MMN impairments at different stages of illness.

2.1 An introduction into psychotic disorders

Psychotic disorders as schizophrenia, schizoaffective disorder or bipolar disorders are diseases which are characterized by positive and negative symptoms like delusion, hallucinations, disorganization, excitement, depression, mania, emotional withdrawal or further negative/positive symptoms (Schrimpf et al., 2018). The overall lifetime prevalence is nearly 1% (Jablensky et al., 1992). The intensive burden of psychosis patients leads to an estimated lifetime risk of 5,6 % for suicide (Hor & Taylor, 2010). Data of several studies indicate that the risk of a suicide attempt is approximately 10% in early treatment phases, especially within the first twelve months (Nordentoft et al., 2015). Furthermore, early stages of psychosis have been shown to be crucial for setting trajectories for recovery (Hall et al., 2019). This illustrates the importance of early diagnosis and, therefore, early therapy of patients.

The term “psychosis” is derived from the ancient Greek word “psyche” which holds the meaning of “soul” in the English language (Dafermos, 2014) and meant to describe an abnormal condition of the mind (Lieberman & First, 2018). The onset of psychotic disorders is characterized by different stages/phases (Figure 1). From a premorbid phase with possible early-stages dysfunctions it can develop into a prodromal phase which is divided into three subphases: Firstly, early and then late at-risk of psychosis state and consecutively early psychosis (Fusar-Poli et al., 2013). Approximately 30 - 40% of patients in high-risk state are developing psychosis within 2 years (Fusar-Poli et al., 2013). Figure 1 illustrates the different stages until the manifestation of early psychosis and the correlation of symptom severity and the phases.

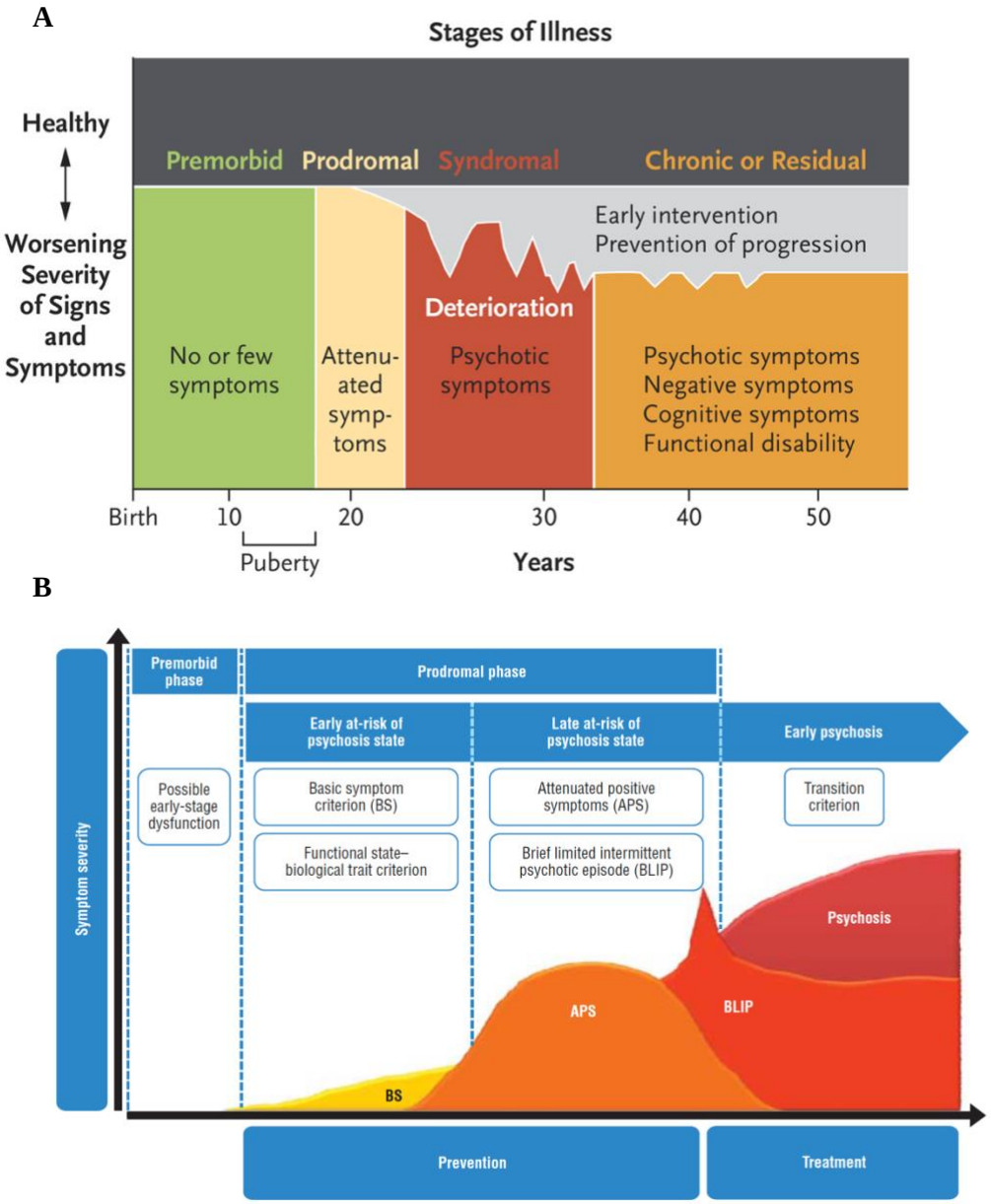


Figure 1 – Stages of psychosis: Both illustrations show the stages of psychosis onset with different emphasis. Figure 1A offers a rationale for preventing chronic stages. Figure 1B offers a more detailed insight into the prodromal phase.1A: Schematic illustration of natural history of schizophrenia and the rationale for preventing chronic stage (Lieberman & First, 2018). 1B: Model of psychosis onset from clinical high-risk state to early psychosis (Fusar-Poli et al., 2013). Abbreviations: BS=basic symptoms, APS = attenuated psychotic symptoms, BLIP = Brief limited intermittent psychotic episode subgroup

In this study, we concentrated on first-episode psychosis (FEP) or early psychosis patients. As psychotic disorders are highly variable in their severity, so are the several underlying variables causable for the symptomatic outbreak and manifestation of the disease. The following chapter describes most important factors for the pathogenesis of psychotic disorders.

2.2 Pathogenesis of psychotic disorders

The pathogenesis of psychotic disorders is not completely understood. However, several different influential factors could be identified, and they can explain the pathogenesis of psychotic disorders at least partially. These factors have been shown strong influence on the outbreak and on the progression of psychotic disorders.

2.2.1 Psychosocial stress

An often-underestimated factor remains the psychosocial stress of the individual patient. Many studies could show the relation between psychosocial stress and the increase of risk for psychosis (Van Os et al., 2003; Van Winkel et al., 2008). Different difficult life-situations are showing relevant influence on the outbreak of psychosis. For instance, migration seems to be one stress relevant factor (Cantor-Graae & Selten, 2005). This seems especially to be the case of second-generation individuals with emigrational background and ethnicities which are faced with high-frequency social discrimination (Veling et al., 2007). Also, a very relevant factors is the state of post-traumatic stress from child abuse (Read et al., 2005). Also, sexual, physical, emotional or neglected child abuse can be understand as relevant stressors in the psychosocial stress model for the outbreak of psychopathologies in children and adolescents (McMahon et al., 2003). Repetitive occurrence of these mentioned stressful events can lead to a "behavioral sensitization" and can aggravate the behavioral, neurochemical or psychotic-related symptom burden (Figure, 2, Van Winkel et al., 2008). This means equivalent stimuli can lead to more severe reaction of a subject over time and of a subject.

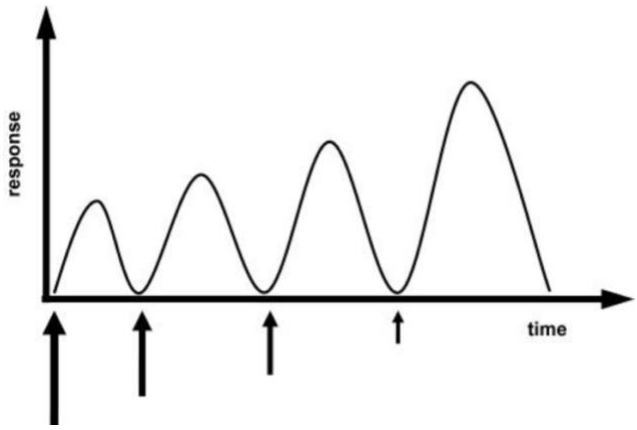


Figure 2: Schematic illustration of "Behavioral Sensitization" regarding psychosocial stressors from Van Winkel et al. (Van Winkel et al., 2008). Each vertical arrow shows an objective stressor with severity proportional to the arrow size. Each arrow induces a certain stress-adapted reaction. The repeated exposure of severe psychosocial stressors increases the behavioral, neurochemical or psychotic-related symptom burden even when the stressor is inferior or less severe as the previous one. The intervals can range from weeks to years and must not follow an even flow like in the schematic illustration.

2.2.2 Genetics

Several studies could prove the correlation between genetics and psychiatric diseases as schizophrenia and bipolar disorder (Geschwind & Flint, 2015). Especially family and twin studies could show that genetics contribute to the risk of psychiatric disorders (Lichtenstein et al., 2009), particularly in schizophrenia (Sullivan et al., 2003). For identical twins the risk for an outbreak of schizophrenia is approximately 50% when one twin has the disease (Tsuang, 2000). However, this concordance also shows that genetics are not fully responsible for the pathogenesis of schizophrenia otherwise the concordance would be nearly 100%. In the case of polygenic dispositions, several risk genes could be identified for the outbreak of psychosis, e.g. Neuregulin-1 (J. Hall et al., 2006), Dysbindin, G72 and other (Rees et al., 2015).

Also interesting, causal relationship between inactivation and activation of genetically defined cell types and in specific neuron groups and within neural circuits can have an influence on the behavior (Luo et al., 2008). Despite the fact that many compartments of the DNA architecture are not understood, we could understand the direct correlation between the structure-giving DNA and the resulting specific architecture of the neural system which is the fundament of mind and personality (Sousa et al., 2017). It can be assumed that certain structures and neural circuits are leading to the creation of a functioning human mind and, thereto, are influential if not crucial in the pathophysiology of psychiatric disorders (Giersch & Mishara, 2017; Parnas & Henriksen, 2016; Sass & Parnas, 2003).

However, according to the vulnerability-stress-model several factors are responsible for the outbreak and relapse of a psychotic disorder (Nuechterlein et al., 1994). Genetics is not the only major factor to consider for the outbreak of schizophrenia or other psychotic disorders.

2.2.3 Neurotransmission

The important role of neurotransmitters and neurotransmitter-systems for the pathophysiology in schizophrenia is not new (Nihart, 1996). Genetically-underlying aberrations and changes in neurotransmitter-systems are overlapping influences with strong importance for the development of schizophrenia (Howes et al., 2017). Especially, the Glutamate and Dopamine theories are popular pathoetiological models of schizophrenia (O. Howes et al., 2015) but it seems to be a complex mosaic of influences from a variety of neurotransmitters (Sarter et al., 2007). Indirect signs of correlation such as studies which have applied amphetamines and further substances to increase the extracellular dopamine level could induce psychotic symptoms like in schizophrenia (Lieberman et al., 1987).

A recent comparison between psychiatric disorders could show that schizophrenia patients show a significantly increased amount of tyrosine hydroxylase, a rare-limited enzyme for the synthesis of

dopamine in the substantia nigra when compared to patients with depression (O. D. Howes et al., 2013). Also, studies regarding the genetics of schizophrenia could show that there is an association between the DRD2 gene, which is responsible for the dopamine receptor D2, and schizophrenia (Ripke et al., 2014). Generally spoken, the findings in the last decades also indicate that locally different foci of changes are present in schizophrenia as the increased synaptic dopamine in associative networks compared to in limbic regions of the striatum (Kegeles et al., 2006). Patel et al. could depicture an informative illustration regarding the dopaminergic systems involved in the pathophysiology of schizophrenia (Figure 3). In other models, N-Methyl-D-Aspartate (NMDA) or its receptors play key roles for the pathogenesis of psychosis (Farber, 2003). Even theories about autoimmune influences regarding NMDA receptors are becoming more prominent for the model of psychosis (Jézéquel et al., 2017; Kayser & Dalmau, 2016). It is yet to be determined which neurotransmitters are the essential ones in the model of psychosis.

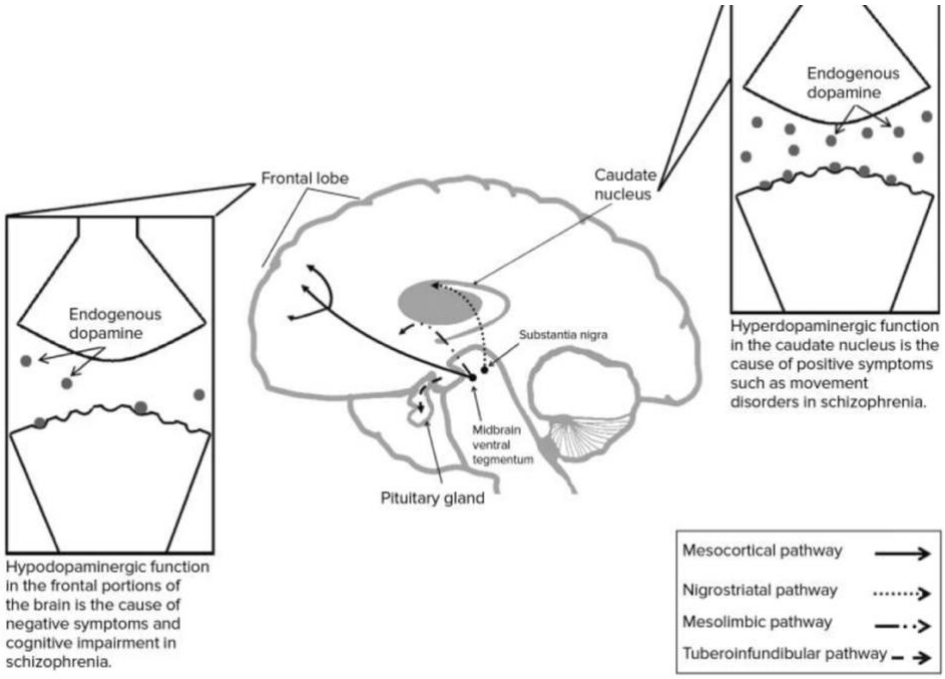


Figure 3: Pathophysiological model of schizophrenia in which the hypodopaminergic function in the frontal of the brain is causing negative symptoms and cognitive impairment in schizophrenia patients (Patel et al., 2014). The mesocortical pathway connects from the ventral tegmental area (VTA) to the cortex, the mesolimbic pathway connects from the ventral tegmental area (VTA) to the limbic areas, the nigrostriatal pathway links from the substancia nigra (SN) to the caudate nucleus (CN), and the tuberoinfundibular pathway extends from the hypothalamus to the pituitary gland (Patel et al., 2014).

2.2.4 Alterations in structural and functional connectivity

The connectivity alterations in psychotic disorders, as complex as they are, can be summarized as both, structural and functional (Ioakeimidis et al., 2020; Karlsgodt et al., 2010; Zhao et al., 2018). Structural alterations can be found in different stages of schizophrenia as decline of gray matter in different regions in schizophrenia, schizoaffective disorder and bipolar disorder (Dietsche et al., 2017) or hippocampus and amygdala changes in first-episode psychosis (Watson et al., 2012). These

and more findings indicate that these pathologies are correlating with altered structures of the complex neural architecture (Reinen et al., 2018). Also, several studies could show the reduction of white matter in schizophrenia (Dietsche et al., 2017; Douaud et al., 2007; Gur et al., 1999) and even in first-episode psychosis patients gray and white matter abnormalities were present (Bagary et al., 2003). Furthermore, it could be shown that schizophrenia patients seem to have less strongly integrated functional neural networks and significantly decreased functional connectivity than in healthy individuals (Lynall et al., 2010). For instance, in schizophrenia patients the default mode network showed altered temporal frequency and spatial location when comparing to healthy surjects (Garrity et al., 2007; Öngür et al., 2010). These results challenge our understanding of how psychotic disorders are influenced by structural and functional alterations within the human brain. All major factors in the model of psychosis considered, our study was inspired by the potential to understand the dysfunctional neural circuits and dysconnectivity within psychosis. The next chapter give a more detailed background.

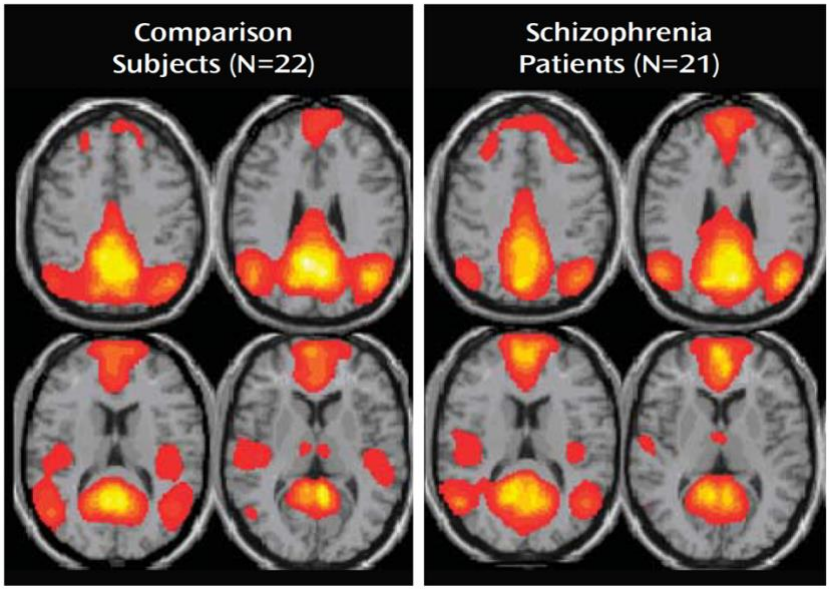


Figure 4: Default Mode Activation Map for patients with schizophrenia patients and healthy subjects via individual independent component analysis (Garrity et al., 2007)

2.3 Psychotic disorders as dysconnectivity syndromes

Schizophrenia, bipolar disorder and further psychosis associated disorders are severe psychiatric diseases characterized by disruptive positive and negative symptoms which are a growing and significant source of disability worldwide (Świtaj et al., 2012). Neuroimaging data suggests that schizophrenia and other psychotic disorders are disconnection syndromes (Friston & Frith, 1995). In this model, psychosis symptoms arise from the failure or change of appropriate functional integration across interacting brain regions (Patel et al., 2014). Recent studies have shown that these changes in connectivity can already be measured in early psychosis patients (Comparelli A, et al., 2019).

Applying dynamical analysis to measure functional connectivity could reveal those transient states of dysconnectivity and, thereto, could show that transient states of dysconnectivity are present in schizophrenia patients (Damaraju et al., 2014). At this point it is important to understand bottom-up and top-down processes and the implications for them. Bottom-up processing describes the hierarchical processing of primary sensory input to a higher, more integrated level of cognition (Javitt, 2009). On the other hand, top-down processing is driven by memory-based expectations and attention to put an incoming input in context with processed inputs for the past (Cook et al., 2012). The impairment of both processes is acknowledged in the model of psychosis (Berkovitch et al., 2018; Gold et al., 2007; Rominger et al., 2016). Impairment of top-down processes, especially of perceptual nature as the hollow mask illusion, could be shown in schizophrenia using causal dynamic modelling (CDM) (Dima et al., 2010).

In fact, the underlying states of dysconnectivity and losing of synaptic plasticity are discussed as key-mechanism for negative and positive symptoms in schizophrenia (Stephan et al., 2009). In this context, bottom-up and top-down processing are logically interconnected, bidirectional processes to be considered when analyzing functional connectivity in psychosis, especially, for the predictive coding model which is one possible causal explanation for MMN impairment in psychosis (Rauss & Pourtois, 2013; Wacongne et al., 2012). For instance, top-down connectivity has been observed as a underlying mechanism for psychotic experiences in healthy subjects (Dzafic et al., 2018). Thereto, dysconnectivity between key brain systems and the imbalance of top-down and bottom-up processing have been hypothesized to underlie the pathophysiology of schizophrenia (Li et al., 2015).

Nevertheless, connectivity and the neural failure or change of appropriate functional integration needs further scientific investigation for a better understanding of the complex interactions between brain regions and, therefore, of consequences resulting from altered interactions and structures. Therefore, our study builds on the existing literature and aims to contribute more evidence for the dysconnectivity-based imbalance of top-down and bottom-up processing in first-episode psychosis. We think that modern neuroimaging techniques and cutting-edge computational methods will be an irreplaceable part in understanding the underlying neural circuits in pathological brains. Historically, it was a long road to achieve this goal and to expand the possibilities in the modern psychiatry by cutting-edge neuroimaging methods. The next two chapters dive deeper into the history modern psychiatry and into the technical possibilities to understand further underlying neural circuits trough cutting-edge technologies and methods.

2.4 Historical development in psychiatry

The mind-body dualism was one example in the past of how societies have seen the human mind in correlation with the human body. In this context, the history of psychiatry has shown different turning points. Certainly, these turning points were influenced by the society and culture of the time

of being (Mehta, 2011). Medicine and society have experienced different changes in perspective before innovations and rationalized approaches could be valued in psychiatry. The philosopher and scientist Descartes described the mind-body dualism in which he described the human body and the human mind as separable compartments (Mehta, 2011).

Clinical psychiatry showed in the last 250 years several revolutions which changed the treatment of mental patients. Underlying these changes, we may look at four revolutions in psychiatry. The first revolution consisted of integrating moral support but also unchaining psychiatric treatment for patients with mental disorders. This was established by Pinel in the year 1793 (Micheal, 2007). As the electroconvulsive therapy for mental patients was introduced in the year 1935 in italy by Cereletti and Bini, the second markable revolution in psychiatry was historically marked (Faedda et al., 2010; Gautam, 2010; Sadock & Sadock, 2009). The ECT as one of the very first physically induced therapies in psychiatry changed the perspectives of physicians and society on psychiatric disorders and, therefore, lead eventually to the third revolution. The third revolution was born with introduction of psychotropic medications, as chlorpromazine in 1952 and further one, for the treatment of the psychiatric patient (Cambridge Textb. Eff. Treat. Psychiatry,2008). This changed the face of psychiatry considerably. It is becoming clearer that causal mechanisms are underlying the state of psychiatry patients. The fourth revolution will be consisting of different treatment approaches of mental and neurological disorders e.g. through neuromodulator technologies (Gautam, 2010). As we can observe today, several clinical treatments are using technologies to treat psychiatric and neurological patients. For instance TMS for depression or DBS for Parkinson patients became valued therapies (Malek, 2019; Pridmore & Belmaker, 1999). These developments are concentrated on the western society and do not highlight overall worldwide developments in other major countries or continents as in China or India.

Today, the fourth revolution in psychiatry has already proceeded as we see an astonishing rise in scientific observations which speak out for a bidirectional relationship between physical status and mental illness. The scientific fundamentals have been described and several observations via computer-aided technologies as EEG, fMRI or combined, could show significant differences between psychiatric patients and healthy subjects (Leicht & Mulert, 2014). This detection of patterns in mental patients are the fundament of the future treatment for these disorders (Wolfers et al., 2015). With the future technological developments, the detection of patterns will increase and, therefore, the treatment options will also increase. Modern software tools using artificial intelligence, data mining or time-series analysis will certainly lead to further physical pattern discoveries which can then be translated into further treatments for mental patients (Graham et al., 2019). The next chapter emphases these changes in modern medicine with a more technical perspective.

2.5 Technologies and computational neuroscience

Through neuroanatomical fundaments in the last hundred years, we learned that the human brain, especially the neocortex, adapted evolutionally a multi-layer-structure for the processing of high numbers of impulses through complex convolutions of convergences and divergences (Mumford, 1991). The complexity of these daily calculations becomes understandable when considering that the human brain roughly consists of 100 billion neurons and of 100 trillion connections (Herculano-Houzel, 2009). To put this in a relation: The human brain contains more connections than the Milky Way has stars (Castelvecchi, 2018; Hofman, 2014).

Fortunately, the human mind was able to develop mechanical computers which are highly valuable assistants on our mission to understand the computation within the human brain (Collkn, 1994). These computers have become faster, smaller and able to process more complex problems. Therefore, in Computational Neuroscience and Clinical Neuroimaging well-designed tools, as electroencephalograms (EEGs) and more complex machines as functional Magnet resonance imaging (fMRI) or brain positron emission tomography (PET) enabled researchers to measure, calculate and analyze the activity of neuronal populations via physical changes on atomic levels and computer-based analysis software. The several possible techniques and the combinations of techniques cause a complexity and diversity of computational tools so that certain applications of novel techniques are yet to be discovered.

More recently, novel methods e.g., predictive time-series analysis, high-performance data mining, artificial-intelligence-based pattern recognition, causality-connectivity analysis and further methods are developed and are showing strong potential for further understanding physiology and pathophysiology of the human brain (Savage, 2019). Clinical fields regarding the human brain like psychiatry, neurology, neurosurgery or neuroradiology do strongly benefit from these technical advances (Haller et al., 2014). Especially, psychiatry and computational neuroscience show a strong potential for these innovative techniques (Gautam, 2010). Prominent examples include the implementation of machine learning, artificial intelligence or virtual reality-based software for the purpose of automated clinical diagnosis, decision support or augmented therapy in the field of mental health (Hirschtritt & Insel, 2018). These developments are important for modern psychiatry and for the neuroscience community. Especially, computational neuroscience have shown a vast potential for further understanding of mental disorders (Mäki-Marttunen et al., 2019).

Conclusively, the aim of this study was also to address computational and mathematical approaches via duration mismatch negativity, clustering, and Granger causality time-series analysis to describe dysconnectivity within frontal-temporal-central networks and to outline the correlations between impaired mismatch negativity, dysconnectivity and clinical psychiatric symptoms in first-episode psychosis.

2.6 Evoked potentials and mismatch negativity

It has been discussed if mismatch negativity (MMN) could be used as a potential biomarker for psychotic disorders (Näätänen, 1995). As previously described, MMN is the minimal peak of an event-related potential that can be measured as a result of neural processing of a frequent sequence of repeated identical (also called "standard") stimuli that is interrupted by odd (also called "deviant") stimuli (Bishop & Hardiman, 2010). Due to a diversity of stimuli and deviations the MMN can occur. MMN is an automatic, unconscious process that depends on bottom-up perceptual processing to detect deviant stimuli (Kenemans and Kähkönen, 2011). Auditory MMN paradigms are commonly employed in which either pitch or duration may be varied and are generally measured over frontocentral electroencephalographic (EEG) channels (Umbricht and Krljesb, 2005). Decreased auditory MMN has been widely reported in patients with schizophrenia and has been proposed to be a biomarker for psychotic disorders (Light and Näätänen, 2013; Umbricht and Krljesb, 2005). However, the magnitude of the decrease may be related to illness duration with first-episode patients showing no reduction in MMN to pitch deviants and small, but statistically significant reduction in MMN to duration deviants (Haigh et al., 2017).

In MMN, the deviant stimuli induce strong currents, primarily in temporal auditory cortex, that manifests as a negative deflection in frontal-central electrodes. The MMN is generated unconsciously, automatically and, thereto, has been widely used in psychiatric research since it was discovered by Risto Näätänen in 1978 (R. Näätänen et al., 1978). MMN is calculated by subtracting the averaged standard stimuli response wave from the averaged deviant stimuli response wave and then the minimum amplitude of the resulting wave is determined in a specific time window, as it was in our case between 120ms and 320ms (Bishop & Hardiman, 2010).

Several theories are attempting to explain the phenomenon of MMN. The most common theory of the underlying mechanism is the memory-based hypothesis which claims that auditory MMN is produced by irregularities within a structured auditory sequence received by a subject which is then analyzed by temporo-prefrontal networks that compares current sensory inputs with a memory trace of previously registered stimuli (Garrido, Kilner, Stephan, et al., 2009). As a result, the mismatch is generated by interaction of temporal and frontal regional networks.

One further theory is the adaption hypothesis, which claims that SSA (specific somatic afferent fibers) of the auditory cortex (A1) neurons "adapt" or respond with much smaller activity to the repeated standard sound than to the "fresh afferents" of the less probable deviant stimuli (Fishman & Steinschneider, 2012). This adaption would lead to a delayed and an attenuated N1 wave for standard stimuli which will regularly occur for deviant stimuli (Garrido, Kilner, Stephan, et al., 2009). The N1 component of an auditory evoked potential is described to be a robust and frequently recorded metric of sensory-perceptional processing measured via EEG with typical latency at 100ms which is known to present with diminution in amplitude in schizophrenia patients (Foxe et al., 2011).

However, several other observations could not confirm the adaption hypothesis. For instance, the MMN duration and latency do not always match for duration and latency of the N1 (Winkler, 2007).

One of the most recent theories is the predictive coding framework hypothesis (Huang & Rao, 2011). This hypothesis is on account of the memory based MMN generation theory. From this perspective, MMN is considered as a kind of "prediction-error" of the neural predictive calculation hence to the less probable deviant stimulus. This predicative coding model is in agreement with several studies which could show that sensory cortex is optimized for prediction of future inputs in healthy individuals (Singer et al., 2018). Also, in theoretical neuroscience a "fresh afferent"-theory explains MMN as a result of neural populations vigorously reacting to the deviant stimulus and, thereto, are affecting linked difference neural populations which were processing standard stimuli which might produce the mismatch negativity (Mäkinen et al., 2004; May & Tiitinen, 2010).

Also, several studies indicate that both, duration and frequency MMN, are decreased in patients with chronic schizophrenia (P. T. Michie et al., 2000; Xiong et al., 2019). Nevertheless, it remains controversial if MMN is strictly impaired in first-episode psychosis and, thereto, if MMN is capable of being an appropriate clinical biomarker candidate for early schizophrenia and for early psychotic disorder predication (Haigh et al., 2017). It may also be asked at which stage of impairment an irreversible status of progression begins where remission is not probable (Kim et al., 2018).

One further important component in the understanding of the mechanism of MMN is the fact that MMN requires an intact NMDA receptor signaling. Studies have shown that pharmacological blockage of NMDA receptors led to reduced MMN in monkeys (Lee & Zhou, 2019). This is important considering NMDA receptors are responsible for the neural plasticity of glutamatergic synapses as they, most likely, play a central role in the pathogenesis of schizophrenia (Friston & Frith, 1995). Also, acetylcholine seems to have modulatory effects on MMN in humans (Baldeweg et al., 2006).

More controversial is the discussion if there are further neurotransmitters systems implicated in the mechanism behind MMN. As mentioned previously, dopamine systems seems to have a central role since MMN amplitude is decreased in patients with Parkinson's disease (Pekkonen et al., 1995). We think that EEG-based MMN data is suitable for combining with time-series analysis methods as Granger causality. In the next chapter, we will elaborate further on the role of Granger causal time-series analysis for calculation of functional connectivity.

2.7 Granger causality time-series analysis

The origin of the Granger causality was born in 1969 by the investigation of causal relations of econometric models (Granger, 1969). Therefore, most of the initial applications were in the field of economics. Today, Granger causality is also considered as a powerful method for neuroscience as

well (Anil K. Seth et al., 2015). Granger causality is a statistical model of causality to predict certain time-points within time-series. In short, this model describes that if an initial signal X is causing ("Granger-causing") a second or following signal Y, then we could find information about future values of signal Y in the past values of signal X. Furthermore, this information might contain more information than past values of signal Y (Kamiński et al., 2001; Liu & Bahadori, 2012) ([190.], Figure 4). The mathematical formulation is based on linear regression modeling of stochastic variables (Granger, 1969; Anil K. Seth & Edelman, 2007).

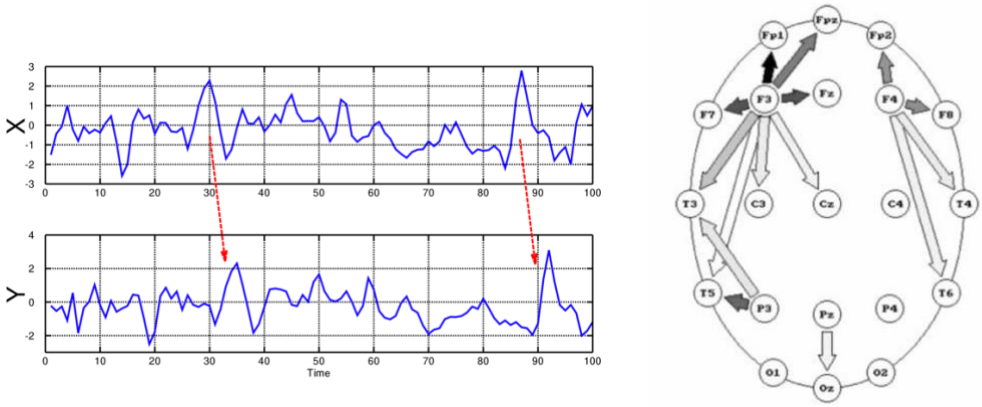


Figure 5: A. Two timeseries X and Y which can predict events of each other by application of Grangers causality (Liu & Bahadori, 2012). B. Causal interactions among EEG sensors (Kamiński et al., 2001).

As the number of neuroscientific methods has grown in the last decades due to computational developments, the research of brain activity has led to the understanding that we have high-density information flows within networks and circuits within brain regions (Lyoo et al., 2018). These flows of information by time can be understand as time-series, especially when measured via EEG. These time-series flows can be compared to each other when considering two separate time-series as functions X1(t) and X2(t) in a bivariate linear autoregressive model (Figure 5). Vector autoregression (VAR) in this context means a statistical model which explains the relationship of different variables as they change over time (G. Chen et al., 2011).

$$X_1(t) = \sum_{j=1}^{p} A_{11,j} X_1(t-j) + \sum_{j=1}^{p} A_{12,j} X_2(t-j) + E_1(t)$$

$$X_2(t) = \sum_{j=1}^{p} A_{21,j} X_1(t-j) + \sum_{j=1}^{p} A_{22,j} X_2(t-j) + E_2(t)$$

Figure 6: Bivariate linear autoregressive model of two variables X1 and X2 in dependence to the timepoint t. The A matrices contain the coefficients of the prediction model. E matrices contain prediction errors for each time series. [188]

Electroencephalography (EEG) neuroimaging is a commonly used and appreciated technique to receive dynamically changing time-series data of neuronal populations with a millisecond temporal resolution (Abreu et al., 2018). These received EEG time-series data contain information which can be decoded by different statistical and pattern recognition analysis approaches (Grootswagers et al., 2017; Hubbard et al., 2019).

2.8 Hypotheses

In this study, we investigated if impaired MMN is present in early psychosis and if in these cases we could use the topography of significant clusters to predict networks of abnormal connectivity via Granger causality time-series analysis in first-episode psychosis patients (FEP) compared to healthy subjects (HC). For connectivity calculations we will use multivariate Granger causality analysis. Granger causality as a statistical hypothesis test is designed to determine whether one time-series A in the past is predicting another time series B in the future. This analysis of time-series data is a suitable tool for analyzing EEG time-series data. Many studies could show the impairment of MMN amplitude and latency in schizophrenia compared to HC (Erickson et al., 2016; Garrido, Kilner, Stephan, et al., 2009). Furthermore, several studies could show that connectivity changes in schizophrenia are present and even asymmetrical (Ribolsi et al., 2009). As we know today, such reduced brain asymmetry is structural (Ribolsi et al., 2009) but also functional (Baker et al., 2014). In schizophrenia is was shown that abnormal asymmetry of functional connections are more present compared to healthy subjects (Jalili et al., 2010). Additionally, it could be shown that resting-state functional networks correlate with psychotic symptoms in schizophrenia (Rotarska-Jagiela et al., 2010).

Therefore, we hypothesize not only that (I.) mismatch negativity (MMN) amplitude and latency is decreased in first-episode psychosis patients (FEP) compared to healthy controls (HC) but also that (II.) directional connectivity is decreased following deviant stimuli compared to standard stimuli and in FEP compared to HC based on the understanding of the predictive coding model of the MMN and on the nature of the less probable deviant stimuli. Thirdly, we state that (III.) abnormal connectivity is associated with certain psychosis symptoms, disorganization and excitement. Lastly, we hypothesized that (IV.) causal density, a measure of the complexity of the connectivity pattern in a network, would be abnormal in patients with first-episode psychosis consistent with the disconnection hypothesis.

3 Methods

3.1 Participants and Procedure

We recruited 30 patients with first-episode psychosis (FEP, within 3 years of initial diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder with psychotic features, or psychosis not otherwise specified) from inpatient units and outpatient clinics at the HMS-affiliated McLean Hospital and 30 age-matched healthy controls (HC) with no history of mental illness who were recruited through advertisements in the community. Exclusion criteria were history of major medical or neurological illness, history of severe head injury, hearing loss, and history of electroconvulsive therapy. Control participants could not have any history of use of psychiatric medication or of psychiatric diagnoses (Yüksel et al., 2021).

All participants from an inpatient unit had an independent evaluation of their ability to consent to the study procedures performed by a psychiatrist not involved in the study. All participants gave informed consent for all study procedures. All study procedures were approved by the Institutional Review Board of Partners Healthcare. All patient participants were receiving treatment at McLean Hospital and had clinical diagnoses were obtained from the medical record and confirmed with the Structured Clinical Interview for DSM-5 (First et al., 2015). All patients had a brief hearing screen. FEP patient participants underwent a video-recorded Structured Clinical Interview for the Positive and Negative Symptom Scale (SCI-PANSS) (Kay et al., 1987; Yüksel et al., 2021).

After the interview, participants' EEG data was collected. Two control subjects and three patients did not tolerate the experiment and ended it early and their data was not included in this analysis. Following data collection, one control subject was found to not meet inclusion criteria (use of psychiatric medications) and three patients were subsequently found to not meet the first-episode criteria. Data from four control subjects and two patients was contaminated by persistent broadband EEG artifacts. Therefore, the final data set consisted of 22 patients and 23 controls. Demographic information about the sample is presented in Table 1 (Yüksel et al., 2021).

	Control	Patient
Sample Size	23	22
Age (Years, Mean ± SEM)	23.2 ± 0.5	22.6 ± 0.6
Sex (Male, Female)	12,11	16,6
Chlorpromazine Equivalents (mg, Mean ± SEM)	-	208.3 ± 32.8
PANSS Positive Factor (Mean ± SEM)	-	7.6 ± 0.7
PANSS Negative Factor (Mean ± SEM)	-	10.4 ± 0.8
PANSS Disorganized Factor (Mean ± SEM)	-	4.6 ± 0.4
PANSS Excited Factor (Mean ± SEM)	-	5.3 ± 0.4
PANSS Depressed Factor (Mean ± SEM)	-	4.2 ± 0.3

Table 1. Demographic and clinical information (Yüksel et al., 2021).

3.2 Electroencephalography

EEG data collection was performed using a Geodesic Sensor Net (Electrical Geodesics Incorporated; Philips Amsterdam, The Netherlands) with 129 Ag-AgCl electrodes (Figure 6). The EEG data were collected at a sampling rate of 1kHz with a standard reference to the vertex accordingly to NetStation software package (EGI). The collection took place in an electrically and acoustically shielded room. Impedances were kept below 65 kΩ. Bad channels and artifactual segments of data were identified by visual inspection and a thresholding procedure. Bad channels were interpolated by spherical splines and artifactual segments of data were excluded from the analysis. The data were then bandpass filtered from 0.5-40 Hz, down sampled to 250 Hz, re-referenced to linked mastoids, and then transferred into MATLAB (MathWorks, Natick MA), (Yüksel et al., 2021).

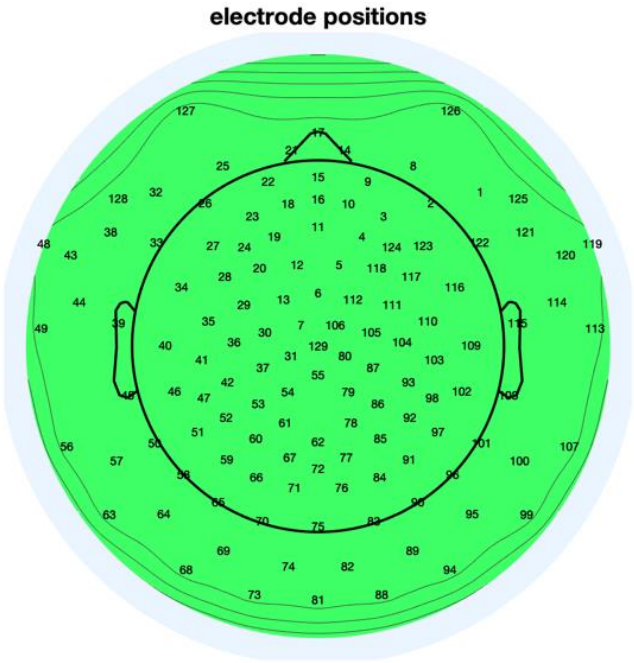


Figure 6: Electrode positions for Geodesic Sensor Net with 129 Ag-AgCl electrodes, self generated via implemented eeglab MATLAB toolbox.

3.3 MATLAB (MathWorks, Natick MA)

MATLAB, which stands as an abbreviation for “matrix laboratory”, is a multi-paradigm programming language and a computing environment. It was built by the American software corporation MathWorks. Especially for scientifical purposes MATLAB could enjoy a high popularity with its prebuilt toolboxes and function for scientific computing (Sobie, 2011).

For beginners to functional programming or programming at all, the MATLAB programming environment offers an excellent overview with several important compartments which are introduced very simplified in Figure 7. However, a certain training is enquired to understand and to implement code for analyzing neuroimaging data sets.

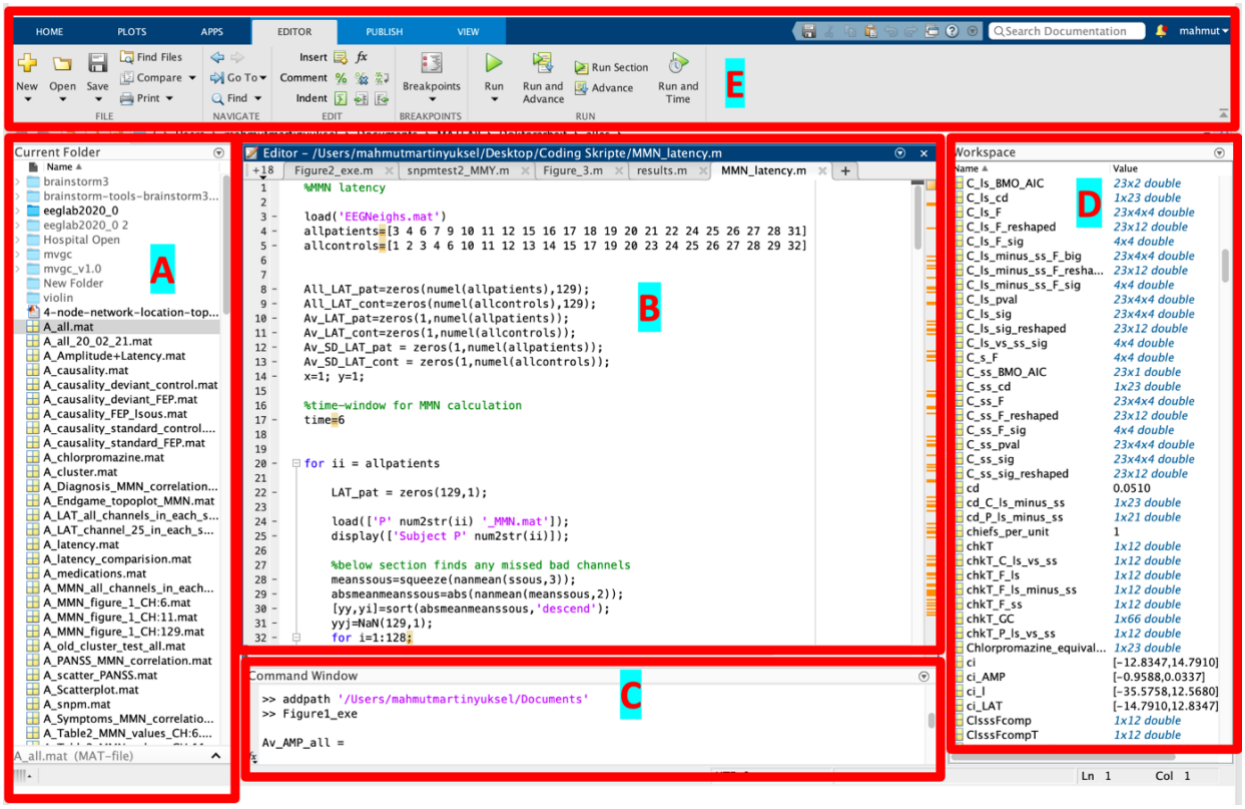


Figure 7: MATLAB R2020b (MathWorks, Natick MA) programming environment with simplified overview of important compartments (self-generated). [A] shows the folder overview via manually adjusted pathway. [B] shows a generated script of code which can be edited and saved. [C] shows the command window in which users can give commands e.g., running of code or giving command to save the current workspace in the current folder. [D] gives an overview of the workspace with containing variables, matrices and further structures which contain information. [E] shows the toolstrip of MATLAB and offers several implemented and automated modalities and functionalities to manipulate instances within MATLAB which could also be manipulated manually via the command window (C). For instance, you can also run coding scripts via the "Run" button or save scripts via the save button in the editor section.

3.4 Auditory Mismatch Negativity

We elicited auditory MMN using a duration deviant. Participants were seated in a comfortable chair and watched a short, silent video of nature scenes. Auditory stimuli were delivered via in-ear headphones (Etymotics, ER3C). Standard stimuli were 1000Hz, 50ms and deviant stimuli were 1000Hz, 100ms. We presented 1000 stimuli with an average interstimulus interval of 500ms. We presented 900 standard stimuli and 100 deviant stimuli. We first presented a run of 100 standard stimuli after which point deviant stimuli were randomly interspersed. For each participant, we calculated MMN then by subtracting the mean baseline-corrected response to the standard stimulus from the mean baseline-corrected response to the deviant stimulus (Figure 8). Latency was calculated as the time point of maximal difference in amplitude between the standard and deviant stimuli over 120ms to 320ms interval (Figure 8). We calculated the MMN amplitude by taking the mean

difference over a 50 ms window centered on the latency time point. We used statistical nonparametric permutation tests (SnPM) at the single channel and cluster level to identify differences in MMN between the HC and FEP groups. In channel-level SNPM, t-statistics are calculated for each channel and the largest magnitude t-value is recorded. Then group labels are permuted, and this process is repeated for 10,000 permutations. The 95% percentile t-value is used as a threshold for the t-values from the non-permuted comparison and any t-values in excess of this percentile are considered statistically significant. For SnPM cluster tests, a similar permutation analysis is performed using the size of spatially contiguous cluster of channels that all exceed a chosen t value threshold. Given that little is known about the relationship between symptom severity and connectivity during MMN paradigms in people with early course psychosis, we performed a hypothesis-generating, exploratory analysis by calculating the Pearson correlation coefficient between MMN connectivity parameters and medication dose and symptom scores. Because these comparisons are hypothesis-generating they are not corrected for multiple comparisons (Yüksel et al., 2021).

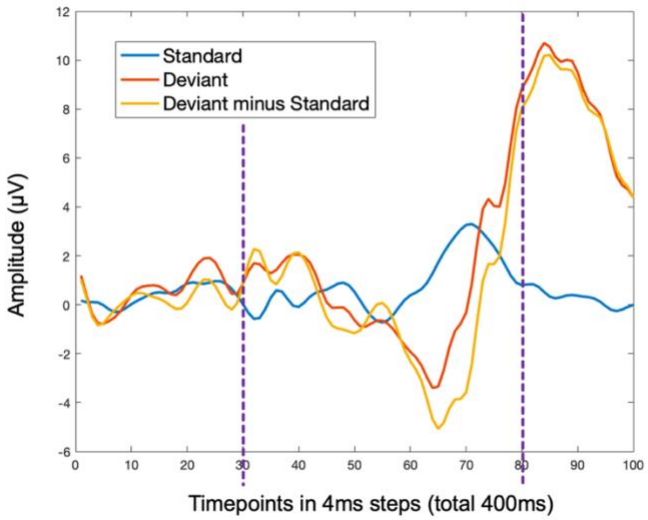


Figure 8: Example plot of mismatch negativity (MMN) calculation from one subject of the patient group. MMN can be calculated by subtraction of the averaged response wave resulting from a frequent occurrence standard stimulus (blue line) from the averaged response wave resulting from infrequent occurrence of rarer deviant stimuli (red line). The negative peak of this difference wave in the defined time window marks the MMN. In our study chose a time window between 30th (120ms) and 80th (320ms) timepoints which is translated a timeframe between 120ms and 320ms (purple dashed lines) which is in agreement with published literature (Garrido, Kilner, Stephan, et al., 2009). This figure is self-generated.

3.5 Connectivity Analysis

We quantified directional functional connectivity with Granger causality as implemented in the Multivariate Granger Causality Toolbox (mvgc) for MATLAB (Barnett & Seth, 2014). In brief, given two signals A and B, the Granger causality from A to B is a measure of how much information about past values of A helps predict future values of B beyond any information obtained from past

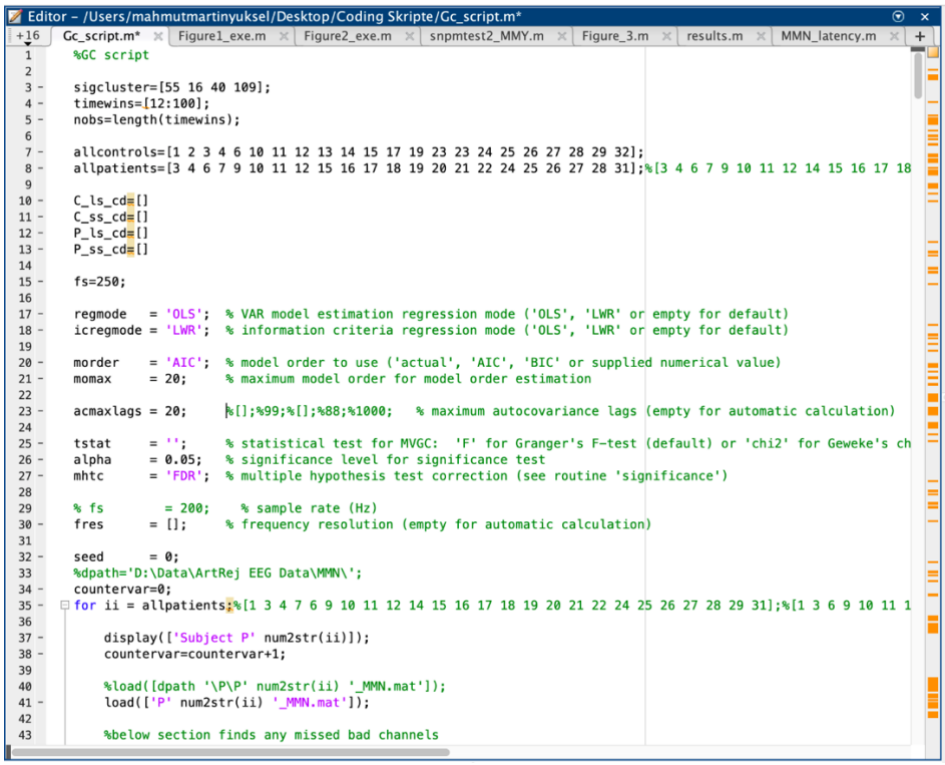
values of B (A. K. Seth et al., 2015). The mathematical corner stone of the Granger's causality analysis is built on linear regression models of stochastic variables (Figure 9; Granger, 1969).

$$X_1(t) = \sum_{j=1}^{p} A_{11,j} X_1(t-j) + \sum_{j=1}^{p} A_{12,j} X_2(t-j) + E_1(t)$$

$$X_2(t) = \sum_{j=1}^{p} A_{21,j} X_1(t-j) + \sum_{j=1}^{p} A_{22,j} X_2(t-j) + E_2(t)$$

Figure 9: Bivariate linear autoregressive model of two variables X1 and X2 [190].
p represents the maximal number of lagged observations which are included in the model,
A contains the coefficient matrix fitting to the model,
E1 and E2 are representing calculated prediction errors for each time series (A. Seth, 2007)

We used Granger causality (GC) to measure the long-range connectivity between four channels in a 350 ms window following stimulus presentation. These channels were chosen because they were located at opposite ends of a cluster that showed decreased MMN amplitude in FEP compared to HC (see below). We chose to analyze a subset of the cluster because neighboring electrodes can be highly correlated. The Granger causality from signal A to signal B is a measure of how much information about past values of A improves the prediction of future values of B beyond what can be learned from past values of B. In multivariate Granger causality analysis, the connectivity value for each channel is conditioned on the contributions from other channels (Barnett and Seth, 2014), Therefore, having multiple correlated channels would obscure the connectivity results. By choosing four spatially distinct channels, we minimize correlations due to volume conduction and bridging while covering the spatial extent of the cluster. We calculated the causal density of the network formed by these four channels. Causal density of a network is the average pairwise GC conditioned by the other connections (Seth et al., 2011). Causal density is a measure of the complexity of a network because a network composed of tightly correlated channels will have a low value for causal density as will a network composed of independent channels. High values of causal density indicate a complex pattern of GC between elements of a network. Following linear detrending in a 350ms window, model order was selected using the Akaike Information Criterion, AIC (Akaike, 1974), as seen in Figure 10. Maximum autocovariance lags were set at 20 and sample rate ("fs") was set at 200 (Figure 10). The core code of the calculation scripts which were used as guiding code for the self-written scripts of this study can be found online at [2] (Yüksel et al., 2021).



```
%GC script

sigcluster=[55 16 40 109];
timewins=[12:100];
nobs=length(timewins);

allcontrols=[1 2 3 4 6 10 11 12 13 14 15 17 19 23 23 24 25 26 27 28 29 32];
allpatients=[3 4 6 7 9 10 11 12 15 16 17 18 19 20 21 22 24 25 26 27 28 31];%[3 4 6 7 9 10 11 12 14 15 16 17 18

C_ls_cd=[]
C_ss_cd=[]
P_ls_cd=[]
P_ss_cd=[]

fs=250;

regmode   = 'OLS';  % VAR model estimation regression mode ('OLS', 'LWR' or empty for default)
icregmode = 'LWR';  % information criteria regression mode ('OLS', 'LWR' or empty for default)

morder    = 'AIC';  % model order to use ('actual', 'AIC', 'BIC' or supplied numerical value)
momax     = 20;     % maximum model order for model order estimation

acmaxlags = 20;     %[];%99;%[];%88;%1000;   % maximum autocovariance lags (empty for automatic calculation)

tstat     = '';     % statistical test for MVGC:  'F' for Granger's F-test (default) or 'chi2' for Geweke's ch
alpha     = 0.05;   % significance level for significance test
mhtc      = 'FDR';  % multiple hypothesis test correction (see routine 'significance')

% fs        = 200;    % sample rate (Hz)
fres      = [];     % frequency resolution (empty for automatic calculation)

seed      = 0;
%dpath='D:\Data\ArtRej EEG Data\MMN\';
countervar=0;
for ii = allpatients;%[1 3 4 7 6 9 10 11 12 14 15 16 17 18 19 20 21 22 24 25 26 27 28 29 31];%[1 3 6 9 10 11 1

    display(['Subject P' num2str(ii)]);
    countervar=countervar+1;

    %load([dpath '\P\P' num2str(ii) '_MMN.mat']);
    load(['P' num2str(ii) '_MMN.mat']);

    %below section finds any missed bad channels
```

Figure 10: Modified Granger Causality (GC) script for time-series analysis of EEG data from FEP and HC.

3.6 Statistics

For the statistical comparison of groups as for comparison of the MMN amplitude or latency between FEP and HC we applied an unpaired (independent) t-test. Unpaired t-test is eligible for comparison of averages/means of two independent groups. It is a statistical test which can be used to determine if between two groups a significant difference is present (Figure 11). For deviations we used the standard error of the mean (SEM, Figure 12).

$$t = \frac{(x_1 - x_2)}{\sqrt{\frac{(s_1)^2}{n_1} - \frac{(s_2)^2}{n_2}}}$$

$x_1 = Mean\ value\ of\ the\ first\ group$

$x_2 = Mean\ value\ of\ the\ second\ group$

$n_1 = Size\ of\ the\ first\ group$

$n_2 = Size\ of\ the\ second\ group$

$s_1 = Standard\ deviation\ of\ the\ first\ group$

$s_2 = Standard\ deviation\ of\ the\ second\ group$

Figure 11: Unpaired t-test formula.

$$SE = \frac{\sigma}{\sqrt{n}}$$

$$SE = standard\ error\ of\ the\ sample$$
$$\sigma = sample\ standard\ deviation$$
$$n = number\ of\ samples$$

Figure 12: Standard error of the mean (SEM) or standard error (SE)

Furthermore, we used statistical nonparametric permutation tests (SnPM) at the single channel and cluster level to identify differences in MMN between the HC and FEP groups. Regarding correlations we used the Pearson correlation method as comparisons were taken on interval scale.

In channel-level SnPM, t-statistics are calculated for each channel and the largest magnitude t-value is recorded. Then group labels are permuted, and this process is repeated for 10,000 permutations. For comprehension, Figure 13 gives an illustration of an example permutation. The 95% percentile t-value is used as a threshold for the t-values from the non-permuted comparison and any t-values in excess of this percentile are considered statistically significant.

1. AAABBB	8. ABBAAB	15. BABABA
2. AABABB	9. ABBABA	15. BABABA
3. AABBAB	10. ABBBAA	17. BBAAAB
4. AABBBA	11. BAAABB	18. BBAABA
5. ABAABB	12. BAABAB	19. BBABAA
6. ABABAB	13. BAABBA	20. BBBAAA
7. ABABBA	14. BABAAB	

Figure 13: Example of permutations with 20 possible formations (Nichols & Holmes, 2002). Mathematically speaking, permutations enable calculations to be more representative due to considering several possible arrangements with regard to the order of the arrangements.

For statistical non-parametric mapping (SnPM) at cluster level, a similar permutation analysis is performed using the size of spatially contiguous cluster of channels that all exceed a chosen t-value-threshold, also called suprathreshold cluster testing (Nichols & Holmes, 2002). The modified MATLAB script was inspired by the work of Nichols & Holmes's work (Figure 14).

```
%Suprathreshold cluster testing
function [sigcluster,permNumber,apval,p95]=PTC2_MMY(data,firstgroupsize,neighs,threshold,permpercent)
datarv=[];
if threshold<0;
    warning('swapping group order for negative threshold');
    threshold=-threshold;
    totsubs=size(data,1);
    secondgroupsize=totsubs-firstgroupsize;
    datarv(1:secondgroupsize,:)=data((firstgroupsize+1):totsubs,:);
    datarv((secondgroupsize+1):totsubs,:)=data(1:firstgroupsize,:);
    data=datarv;
    firstgroupsize=secondgroupsize;
end;
%properms is what proportion of permutations to actually do (max=1)
totSubs=size(data,1);
firstgroupsize;
%C = combnk(1:totSubs,nSubsinFirstSubgroup);
if permpercent<1.001;
    permNumber = factorial(totSubs)/(factorial(firstgroupsize)*factorial(totSubs-firstgroupsize));%length(C);
    permNumber=floor(permNumber*permpercent);
else
    permNumber=permpercent;
end;
%Construct list of permutations with no duplicates
permnum=0;
allperms=[];
  h = waitbar(0,'Please wait...');
while permnum < permNumber
    permnum=permnum+1;
       waitbar(permnum/permNumber,h);
  rpi=randperm(totSubs,firstgroupsize);
  rpi=sort(rpi,'ascend');
  if permnum>1;
      LIA=ismember(rpi,allperms,'rows');    % checks for duplicates
      if LIA==0;
            allperms(permnum,:)=rpi;
      else;
          permnum=permnum-1;
      end;
  else
      allperms(permnum,:)=rpi;
  end;
end;
```

Figure 14: Self-generated suprathreshold cluster testing script inspired by (Thomas E.Nichols & Andrew P.Holmes, 2001). Production permutation list with no duplicates considering the threshold. The (X+Y)x129-matrix "data" containing information from both groups (FEP and HC) with X subjects (FEP) and Y subject across all 129 channels (Figure 6). Threshold must be chosen carefully with regard of previously calculated t-value from SnPM at channel-level (Nichols & Holmes, 2002).

For comparison of multivariate means of the F-values and causal densities from the Granger causality analysis, we used multivariate analysis of variance (MANOVA, Figure 19). It is well-known that analysis of variance (ANOVA) is suitable for the comparison of means of one dependent variable among several groups (Han & Park, 2015). Therefore, MANOVA is the generalization of the ANOVA (Han & Park, 2015). MANOVA as a statistical procedure for comparison and testing of mean differences among groups has proven to show valid and sufficient results (Allefeld & Haynes, 2014; Bathke et al., 2018).

4 Results

The publication "Decreased mismatch negativity and elevated frontal-lateral connectivity in first-episode psychosis" from Yüksel et. al. in the year 2021 (Yüksel et al., 2021) *shows a full disclosure of the results from this work.*

5 Discussion

We used auditory duration mismatch negativity to probe long-range, directional cortical connectivity in HC and FEP. Consistent with past work, we found that MMN amplitudes were largest over the fronto-central region of the scalp in both HC and FEP. We found that MMN amplitude was broadly decreased over this same region in FEP compared to HC (Yüksel et al., 2021).

We also found that MMN latency was decreased in the occipital scalp. In addition, we found that higher doses of medication were associated with lower MMN. Within a four-channel network consisting of a frontal, central, left, and right channels we found increased causal density in HC compared to FEP and increased causal density following standard stimuli compared to deviant stimuli. Relatively high causal density following deviant stimuli was associated with higher symptom scores for disorganization and excitement. Also, there was topographic variability in connection strength across stimulus conditions and groups. Connectivity involving the right side of the scalp was associated with higher symptom burden (Yüksel et al., 2021).

These results leave space for further discussion on specific aspects which are structured as constructive discussion in the following subchapters.

5.1 Mismatch negativity

At least three distinct neural processes, including sensory memory, stimulus-specific adaptation (SSA), and predictive coding, have been hypothesized to contribute to MMN generation (Patricia T. Michie et al., 2016). Many investigators have proposed that MMN is the result of a comparison between a memory trace of previously-presented stimuli and the current stimulus (Ritter et al., 1995). However, MMN cannot be entirely explained by this notion because MMN can also be elicited when patterns of stimuli are violated, including when an expected stimuli is omitted (Fitzgerald & Todd, 2020; Yabe et al., 1997).

In SSA, repeated stimuli are specifically attenuated while novel or deviant stimuli can elicit a more robust response (Farley et al., 2010). Molecular studies indicate that cholinergic tone shapes neural responses to repeated auditory stimuli (Ayala et al., 2016). Many previous studies of SSA discounted its potential contributions to MMN because of its fast time scale (< 20 ms) and insensitivity to the activity of NMDA receptors (Patricia T. Michie et al., 2016). However, in cortical

excitatory neurons, there is a SSA-like phenomenon that is sensitive to NMDA activity and occurs on a time frame that is consistent with MMN which raises the possibility that this form of SSA may contribute to MMN (I. W. Chen et al., 2015).

In predictive coding models, the brain uses information from previous sensory inputs to generate models to predict future sensory inputs. Prediction errors occur when there is a discrepancy between the predicted and actual input. These errors are used to update and refine the predictive model while also allocating neural resources to the unexpected stimuli. In the predictive coding framework, bottom-up inputs from sensory cortices are inhibited by top-down inputs from frontal cortex (Kenemans & Kähkönen, 2011). Dynamic causal modelling studies of MMN indicate that such hierarchical models are best able to recapitulate the MMN response (Garrido, Kilner, Kiebel, et al., 2009; Kirihara et al., 2020). Furthermore, NDMA receptors, which are known to modulate MMN, provide a biologically plausible mechanism for generation and maintenance of predictive coding models (Patricia T. Michie et al., 2016).

5.2 Dysconnectivity and top-down vs bottom-up processing

Auditory MMN is largely driven by neural activity in the auditory cortex but is modulated by the frontal cortex and the thalamus (Lakatos et al., 2020). This suggests that MMN relies on bottom-up processing but can be impacted by top-down inputs. Given this reliance on both local cortical microcircuits and longer-range cortico-thalamo-cortical networks, it is unsurprising that psychotic disorders, which are characterized by myriad forms of cortical dysconnectivity, are accompanied by decreased MMN. Dysconnectivity in multivariable is multivariable with research findings depending upon brain regions, behavioral state, illness duration, medication status, and connectivity measures (Anticevic, Cole, et al., 2014; Anticevic, Yang, et al., 2014; Di Lorenzo et al., 2015). Causal density analysis provides a way to quantify dysconnectivity in the brain. Our causal density results suggest that abnormally complex patterns of connectivity during deviant stimuli and failure to attenuate the complexity of the pattern of connectivity, were associated with psychotic symptoms.

In this study, we report a general decrease in connectivity within the front half of the head in FEP compared to HC. This is consistent with tractography data showing broadly decreased anisotropy in schizophrenia (Kelly et al., 2018). We found that, following deviant stimuli, long-range Granger causality across the scalp is decreased compared to following standard stimuli. Therefore, in the deviant condition, EEG signals are more driven by local activity than by long range inputs. The relative freeing of local micro-circuits from global modulation is consistent with a greater role of bottom-up vs top-down processing following the deviant stimuli. Connectivity differences between HC and FEP were driven by smaller front-to-midline connectivity following standard stimuli and smaller horizontal connectivity following deviant stimuli.

The aberrant persistent connectivity from frontal regions to midline and right temporal regions in FEP compared to HC is consistent with a model in which MMN deficits in FEP are the result of failure of inappropriately preserved top-down processing and/or diminished bottom-up processing following a novel stimulus in patients. Increased top-down processing in schizophrenia has been widely reported and may be related to hallucinations (Aleman et al., 2003). Impaired bottom-up processing has also been reported in some auditory paradigms as well (Adcock et al., 2009). Our work builds on these reports by providing evidence for specific failures to modulate the balance between these processes in FEP and relates this failure to thought disorder. Future work should incorporate visual paradigms to test whether these processing abnormalities exist in other sensory modalities and other regions of the brain such as the occipital cortex.

Also, future work should identify whether there is evidence for dysconnectivity, and therefore top-down vs bottom-up imbalance, in pitch variant MMN paradigms where amplitude deficits are not present in first episode psychosis but are present in patients with chronic psychosis

5.3 Future potentials: Machine intelligence and neurotechnology

Our study is showing the complexity of multimodal networks and their interactions. These calculations over 129 channels, over different timeframes and over several subjects give room for countless permutations. Different computational techniques based on machine intelligence can be beneficial to work further upon our results:

High-density EEG data contain more information and pattern than it is visible for the human eye and which can be accessed with computational techniques from the field of computational data mining (Anguera et al., 2016). Due to the variety of interacting components within the human brain, artificial intelligence-based (AI-based) analysis can be a very beneficial expansion of this analysis when it comes to complex bidirectional connectivity pattern analysis with multi-time-series of several channels (Cirstea et al., 2018; Wan et al., 2019). Furthermore, more predictive connectivity analysis via neural activity in early psychosis can help to gain further understanding of the pathogenesis of psychosis or even predict future progress (Collin et al., 2020). Also, this prediction process can be enhanced by machine learning approaches (Rezaii et al., 2019). Further computational approaches, such as deep learning algorithms, can be applied for prediction of pathological progress in schizophrenia (Oh et al., 2020). Especially, long short memory networks could prove to predict certain patterns for psychiatric pathologies (Kumar & Subha, 2019; Nikhil Chandran et al., 2021). Also, non-invasive and invasive neurotechnological developments as closed-loop-stimulation are showing tremendous potential for next-generation treatment strategies in psychiatry (Lo & Widge, 2017). The authors of this study see the possibility of expansion of this study via machine-intelligence-based methods.

6 Summary

English version:

Considering the initial hypotheses, we can use these as the guiding line, and we could confirm our four hypotheses. These were initially presented in the publication "Decreased mismatch negativity and elevated frontal-lateral connectivity in first-episode psychosis" from Yuksel et. al. in the year 2021 (Yüksel et al., 2021). The four initial hypotheses were:

I. Mismatch negativity amplitude and latency is decreased in FEP compared to HC
II. Directional connectivity is decreased following deviant stimuli compared to standard stimuli and in FEP compared to HC
III. Causal density is abnormal in patients with first-episode psychosis consistent with the disconnection hypothesis.
IV. Abnormal connectivity is associated with psychosis symptoms

Firstly, we tested if MMN amplitude and latency is significantly different in FEP when compared to HC. Our analysis via unpaired t-test showed that difference in MMN amplitudes were not significantly different with p=.078. Also, MMN latency showed not significant difference. However, we could upon these results expand our analysis via cluster analysis. We found that a cluster of 63 channels had significantly decreased MMN amplitudes in FEP compared to HC. Also, we found a cluster of 6 occipital channels which showed significantly longer MMN latencies in FEP compared to HC.

Secondly, we could show that directional connectivity is decreased for deviant stimuli compared to standard stimuli and in FEP compared to HC. These results were won upon the Granger causality analysis within the four-node-network which was built by extracting the four channels which are located at opposite ends of the large significant amplitude cluster.

Thirdly, we calculated causal densities in each network for deviant and standard stimuli and found that long-range causal density is higher for standard stimuli compared to deviant stimuli and significantly decreased in FEP compared to HC.

Lastly, we compared connectivity in the created networks via causal density calculation and via comparison of the Granger causality flow-values. Afterwards, we correlated these results with several symptom factors. It could be shown that abnormal connectivity to the right scalp during deviant stimuli is associated with psychosis symptoms as excited and disorganized factors.

German version:

Wir können die initialen Hypothesen als einen Leitfaden für diese Studie betrachten. Diese wurden initial in der Publikation „Decreased mismatch negativity and elevated frontal-lateral connectivity in first-episode psychosis" von Yuksel et. al. im Jahr 2021 veröffentlicht. Die Hypothesen waren wie beschrieben:

I. Mismatch Negativität Amplitude und Latenz sind erniedrigt in Erst-Episoden-Psychose Patienten verglichen zur gesunden Kontrollgruppe.
II. Gerichtete Konnektivität ist erniedrigt für abweichende Stimuli verglichen zu Standard-Stimuli, sowie in der Gruppe der Erst-Episoden-Patienten verglichen zur gesunden Kontrollgruppe.
III. Kausale Dichte ist abnormal in Erst-Episoden Psychose Patienten, vereinbar mit der Diskonnektivitäts-Hypothese.
IV. Abnormale Konnektivität ist assoziiert mit psychotischen Symptomen.

Zu Beginn haben wir die kalkulierten Wertematrizen für Mismatch Negativität (MMN) Amplituden und Latenzen zwischen Erst-Episoden Psychose-Patientengruppe und gesunder Kontrollgruppe verglichen. Wir konnten mittels ungepaarten T-Test keinen signifikanten Unterschied für die Amplituden zeigen mit einem p-Wert von 0.078. Ebenfalls konnten wir keinen signifikanten Unterschied für die Latenzen zwischen den beiden Gruppen zeigen. Allerdings konnten wir mittels Cluster-Analyse mehrere zusammenhängende Kanäle finden, welche Signifikanzen für Amplituden und Latenzen zwischen Erst-Episoden Psychose-Patientengruppe und gesunder Kontrollgruppe aufwiesen. Das Cluster für Amplituden beinhaltet 63 Kanäle und das für Latenzen beinhaltet 6 okzipitale Kanäle. Darauffolgend haben wir innerhalb des großen Clusters für Amplituden ein 4-Knoten-Netzwerk gebildet, welches aus den vier gegenüberliegenden Kanälen innerhalb des Clusters besteht. Innerhalb des Netzwerkes konnten wir die gerichtete Konnektivität mittels Grangers Kausalität bestimmen und vergleichen. Gerichtete Konnektivität war signifikant erniedrigt für devianten Stimuli sowie in der Erst-Episoden Psychose-Patientengruppe im Vergleich zur gesunden Kontrollgruppe. Drittens haben wir die kausalen Dichten innerhalb der Netzwerke für beide Stimuli in beiden Subjektgruppe kalkuliert. Wir fanden signifikante höhere kausale Dichten für Standardstimuli verglichen mit devianten Stimuli und signifikant erniedrige kausale Dichte in der Patientengruppe verglichen mit der Kontrollgruppe. Schlussendlich haben wir Konnektivitätsflusswerte mit Psychose-spezifischen Symptomen korreliert. Wir konnten zeigen, dass abnormale Konnektivität zur rechten Hemisphäre, während devianten Stimuli, ist signifikant mit den PANSS-verzeichneten Aufgeregtheitsfaktoren und Desorganizationsfaktoren assoziiert.

7 Declaration of personal contribution to the thesis and the publication

7.1 Declaration of personal contribution to the main project of the thesis

Title: Decreased mismatch negativity and elevated frontal-lateral connectivity in first-episode psychosis

Description of personal contribution: Patient examination, scoring and interviewing, marketing for study, EEG-data acquisition, data pre-processing, EEG-cap hardware setting adjustments, data post-processing, patient service, figures preparation, statistical analysis, writing the first manuscript and subsequently the thesis.

7.2 Declaration of personal contribution in the publication

Title: Decreased mismatch negativity and elevated frontal-lateral connectivity in first-episode psychosis

Authors: Mahmut Yüksel, Michael Murphy, Jaeline Rippe, Gregor Leicht, Dost Ongur

Journal: Journal of Psychiatric Research

Publication status: published (2021)

Description of personal contribution:
Writing of original draft, Conceptualization, Methodology Visualization, Formal Analysis, Funding Acquisition, Resources, Investigation, Review and Editing

8 Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

9 Abbreviations

This table gives an overview of all abbreviations used in this thesis.

Abbreviation used	Meaning
A1	Auditory cortex
ACh	Acetylcholine
AI	Artificial intelligence
AIC	Akaike Information Criterion
Ag-AgCl	Silver-silver chloride
ANOVA	Analysis of variance
AP	Antipsychotic
APS	Attenuated psychotic symptoms
BLIP	Brief limited intermittent psychotic episode subgroup
BS	Basic symptoms
CDM	Causal dynamic modelling
CN	Caudate nucleus
CPZ	Chlorpromazine
DBS	Deep-brain stimulation
DNA	Desoxyribonucleic acid
DRD2	Dopamine receptor D2
ECT	Electroconvulsive therapy
EEG	Electroencephalogram
ERP	Event-related potential
FEP	First-episode psychosis patients
fMRI	Functional magnetic resonance imaging
GC	Granger causality
HC	Healthy controls
HMS	Harvard Medical School
Hz	Hertz
MANOVA	Multivariate analysis of variance
ms	Milliseconds
mvgc	Multivariate Granger causality toolbox
NMDA	N-methyl-D-aspartate

PANSS	Positive and Negative Syndrome Scale
PET	Positron emission tomography
PD	Privat Dozent (German for „ private lecturer “)
SEM	Standard error of the mean
SN	Substancia nigra
SnPM	Stochastical non-parametric mapping
SSA	specific somatic afferent fibers
TMS	Transcranial magnetic stimulation
Tukey’s HSD	Tukey’s Honest significance difference
UKE	University Medical Center Hamburg-Eppendorf, Germany
VAR	Vector autoregression
VTA	Ventral tegmental area

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13 Curriculum Vitae

Lebenslauf wurde aus datenschutzrechtlichen Gründen entfernt.

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