48. ASSOCIATIONS BETWEEN ELECTROPHYSIOLOGICAL MEASURES OF SELECTIVE ATTENTION AND NEUROCOGNITIVE MEASURES OF WORKING MEMORY AND ATTENTION IN ANTIPSYCHOTIC-NAIVE, FIRST-EPISODE SCHIZOPHRENIA PATIENTS

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Background: Deficits in attention and working memory are already present in early stages of schizophrenia. The P3a and b event related brain potentials (ERPs) are believed to underlie processes of attention and working memory, but, only limited research has been performed on the associations between these psychophysiological and cognitive deficits, particularly in the early stages of schizophrenia. We aimed to investigate associations between P3a and P3b amplitudes and measures of attention and working memory in a large cohort of antipsychotic-naive, first-episode schizophrenia patients (AN-FES) and age and sex-matched healthy controls (HC).

Methods: Eighty-three AN-FES patients and 108 HC, matched for age and gender, were assessed for their P3a and b amplitude and latency with the selective attention paradigm from the Copenhagen Psychophysiological Test Battery (CPTB). In addition, the Spatial Working Memory (SWM) and Rapid Visual Information Processing test (RVP) from the Cambridge Neuropsychological Test Automated Battery (CANTAB) were used to assess working memory and attention. Outcome measure for the SWM was Strategie, wherein a low score represents a more effective strategy. For the RVP, we used the A’ measure as outcome. This measure represents how well the participant is able to detect target sequences.

Results: P3a and P3b amplitudes were significantly reduced in our AN-FES patients compared to HC. In addition, the P3a peak latency was earlier in the AN-FES patients than in HC, while P3b latency did not differ between the groups. Furthermore, AN-FES patients scored significantly lower on the SWM task and the RVP compared to HC. A positive association was found between RVP and P3b in our total group. However, this effect disappeared when split into the two subgroups. In contrast, SWM was positively associated with P3b in HC, while this effect was neither present in AN-FES nor in the total group.

Conclusion: Our results provide evidence for P3a and P3b amplitude reductions as well as neurocognitive deficits in AN-FES patients compared to age and gender matched HC. This supports previous data that electrophysiological and neurocognitive deficits already exist in early stages of schizophrenia, and are not due to use of antipsychotics. Our data support significant yet rather weak associations between P3b amplitude and both working memory and attention, although the association between working memory and P3b was only found in HC and not in AN-FES.

49. THE PREDICTIVE CODING ACCOUNT OF PSYCHOSIS: A META-ANALYSIS OF THE RELATIONSHIP BETWEEN MISMATCH NEGATIVITY AND SYMPTOM SEVERITY

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Background: The predictive coding (PC) theory of schizophrenia has gained traction in recent years as an explanatory model for the presence and severity of psychotic symptoms. PC posits that hallucinations and delusions emerge from a fundamental failure to accurately predict the environment and update prediction models when expectations are violated. Despite the conceptual link between the PC framework and symptom phenomena, however, a clear association between predictive coding abnormalities elicited by experimental paradigms and the severity of positive symptoms has not been consistently observed. Of the paradigms currently used to measure this phenomenon, the mismatch negativity (MMN) is arguably the most established. The MMN is an electrophysiological potential that is elicited when a sequence of tones is unexpectedly interrupted by a tone that deviates in one or more stimulus dimension, and is robustly impaired in people with schizophrenia (Erickson et al., 2015). The MMN is often held up as an exemplar index of the PC phenomenon (e.g., Wacongne et al., 2012), and some studies do suggest a relationship between impaired MMN and greater symptom severity (e.g., Fisher et al., 2011). However, one large study of MMN in people with schizophrenia (N = 877) revealed only a modest relationship between MMN amplitude and positive symptoms (r = .08; Light et al., 2014). Thus, there is a need to clearly establish the relationship between the MMN (a putative PC index) and symptom severity; failure to detect a consistent relationship between these measures may indicate that a need to reconceptualize the relationship between measures of PC and symptom expression.

Methods: The present study used a meta-analytic approach to examine the pattern of symptom severity and MMN impairment across studies. Of the 101 studies of MMN impairment in schizophrenia described in a previous meta-analysis (Erickson et al., 2015), 33 studies reported a PANSS positive symptom subscale score and 30 studies reported a PANSS negative symptom subscale score. Separate meta-regressions were used to quantify the relationship between the effect size of MMN impairment in people with schizophrenia and positive and negative symptom severity, respectively.

Results: We found that MMN effect size was not significantly associated with either positive (P = .24) or negative symptoms (P = .94).

Conclusion: The present results suggest that a simple account of PC as it relates to symptom expression may not be adequate, and that a more nuanced conceptualization of this relationship is needed. For example, it is possible that MMN represents a “low-level” prediction error—one that occurs at a low level of the cortical hierarchy. By contrast, prediction errors that occur at higher levels of the hierarchy may exhibit stronger relationships with symptom measures. Future studies will be needed to test this hypothesis.

50. NEGATIVE AFFECT, GABA, AND THE MEDIAL PREFRONTAL CORTEX IN PSYCHOSIS

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Background: GABAergic abnormalities are the most consistent findings in the post-mortem literature in schizophrenia, but the functional significance of these findings is unknown. We have reported that changes in GABA tone (revealed by lorazepam challenge in a pharmaco-MRI paradigm) in the medial prefrontal cortex (mPFC) occurred in the direction predicted by the post-mortem abnormalities and correlated with negative affects in patients and healthy control subjects. Negative affects (NA), including sensitivity to everyday stresses, are increasingly recognized as an important clinical dimension of psychosis, particularly in the early phases. To investigate links between NA and GABA, we examined GABA concentrations in patients with a first episode of psychosis (FEP) and attenuated psychosis syndrome (APS) using magnetic resonance spectroscopy (MRS).

Methods: Subjects underwent MRI scanning on a 3T Philips Achieva scanner. Voxels (18 cc) were placed on the mPFC and midline occipital cortex.
(Occ), and MRS was performed with the point-resolved spectroscopy sequence (PRESS). Voxel data were analyzed for MEGA-PRESS spectroscopy with Gaussian curve fitting to the GABA peaks and LCModel software to determine peak concentrations of GABA+ (including signal from macromolecules) and creatinine (Cr), yielding GABA+/Cr ratios for analysis. All subjects completed the 9-item Psychological Stress Index (PSI-9), a validated measure of stress sensitivity and NA in psychosis.

Results: We have completed a preliminary analysis of 28 subjects (FEP: n = 11, 21.8 ± 2.7 years; HC: n = 11, 20.5 ± 3.2 years; APS: n = 6, 20.2 ± 3.9 years). Of the patient subjects, 6 APS subjects and 1 FEP subject were off medications. Analysis with ANCOVA, with group as a factor and PSI-9 scores as a covariate, yielding a significant inverse relationship of PSI-9 scores with mPFC GABA concentration (F[1,24] = 6.61, P = .02), but no effect of group (F[2,24] = 1.74, P = .20). There were no effects of group or relationships with PSI-9 scores in the Occ voxel (Ps > .05). We compared all subjects based on whether they were taking antipsychotic medications and found no differences for either voxel (Ps > .05). There were no other significant relationships between GABA concentrations and clinical symptoms, cognitive variables (MCCB) or functional level.

Conclusion: The data provide support for a relationship between GABA levels and NA, measured by the PSI-9 such that lower GABA concentrations in the mPFC are associated with higher levels of NA. The small sample size and preliminary nature of the data warrant caution. Nevertheless, given that potentiation of GABA activity with benzodiazepines reduces NA, the findings are of potential clinical relevance in understanding the role of GABA systems in affect regulation in psychosis.

51. OCCIPITAL ALPHA POWER DURING RESTING-STATE EEG IN CLINICAL RISK FOR PSYCHOsis AND SCHIZOPHRENIA

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Background: Identification of valid schizophrenia risk biomarkers, prior to the onset of psychosis, is critical for early treatment intervention and for understanding the progression from prodromal symptoms into full psychosis. Occipital alpha power is known to be impaired in schizophrenia patients, during both the resting state and during cognitive task activation. However, the status of this measure during the pre-clinical risk period is unknown. We investigated occipital lobe alpha power during resting state EEG as a potential biomarker of clinical risk and schizophrenia, and explored correlations with cognitive functioning and clinical symptoms.

Methods: Participants included 23 patients with schizophrenia (SZ), 31 clinical high-risk individuals (CR), and 30 healthy controls (HC). Participants underwent a structured clinical interview to assess symptoms using the Structured Interview for Prodromal Syndromes (SIPS) and completed a computerized battery to assess major domains of neurocognitive functioning. Resting state EEG was recorded for 2 minutes each in eyes-closed and eyes-open conditions. Data were segmented into 2-second artifact-free epochs and Fast Fourier Transform into the frequency domain. Mean occipital alpha power (8–12 Hz) was then computed from O1, O2 and O2 electrodes.

Results: Both CR (P = .03) and SZ (P = .02) exhibited reduced alpha power in the eyes-closed condition compared to HC. SZ and CR were not significantly different from each other. There were no differences across groups in the eyes-open condition. Clinical symptoms and cognitive functioning were not significantly correlated with mean eyes-closed alpha power in the SZ or CR groups. However, in the CR group, lower alpha power was associated with poorer overall cognitive performance (r = .37, P = .04) and poorer complex reasoning (r = .51, P = .004). It was also paradoxically associated with fewer disorganized symptoms (r = .55, P = .002).

Conclusion: This study extends previous findings of decreased eyes-closed occipital alpha power in SZ to CR. Our results suggest that neural abnormalities detectable by EEG are present prior to the onset of threshold psychotic symptoms and associated with early cognitive impairment. The augmentation of occipital alpha power with eye closing has been linked to the modulation of neuronal input from the pulvinar nucleus to the visual cortex. Our findings therefore implicate a specific thalamocortical disconnection associated with psychosis risk. The routine use of EEG in the clinical assessment of the psychosis prodrome may provide a physiological marker linking neural pathology to higher order functioning. The predictive utility of this measure for transition to overt psychosis remains to be determined.

52. ABNORMAL ANTERIOR INSULA ACTIVITY DURING FEAR GENERALIZATION IN SCHIZOPHRENIA

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Background: Generalization from previous experiences allows us to evaluate the affective value of novel events. A breakdown of this fundamental ability may lead to incorrect attributions of affective value that could give rise to psychotic symptoms. To examine this hypothesis, we tested whether the generalization of conditioned fear responses is abnormal in schizophrenia, using functional magnetic resonance imaging (fMRI).

Methods: 37 schizophrenia and 32 healthy subjects, matched for age, sex, underwent an fMRI scan while participating in a Pavlovian fear conditioning and generalization paradigm. During the conditioning phase, one face was used as a conditioned stimulus and paired with an electrical shock (the CS+), whereas a different face was used as a neutral stimulus that was never paired with a shock (the CS−). In the generalization phase, five stimuli that were different morphs between the CS+ to the CS− were selected based on each individual’s ability to discriminate the two faces. Afterwards, subjects were asked to rate the likelihood each stimulus was followed by a shock (explicit ratings). In the fMRI analyses, we identified the regions of the brain that showed significant CS+ vs. CS− responses during the conditioning phase in both groups. Those regions were then tested for generalization responses using an anatomical regions-of-interest approach and a mixed design ANOVA.

Results: There were no between-group differences in CS+ vs. CS− responses of the brain during the conditioning phase. In both groups, CS+ > CS− activation was observed in the anterior insula and dorsal anterior cingulate cortex, whereas the reversed pattern (CS− > CS+) was observed in the ventromedial prefrontal cortex and angular gyrus. During the generalization phase, patients with schizophrenia exhibited impaired generalization, both behaviorally (explicit ratings) and in the brain, most prominently in the right anterior insula, due to a lack of differentiation between the morphs and the CS−. This abnormality correlated with positive symptom severity.

Conclusion: Schizophrenia patients are able to successfully acquire conditioned fear responses, but show impaired generalization of those fear memories. This impairment in fear generalization is associated with abnormal functioning of the anterior insula. These findings suggest that psychosis may arise in part from a deficit in the immediate retrieval of associative memory traces—a basic process that can be quantified as impaired fear generalization.

53. HIGHLY PSYCHOSIS-PRONE ADOLESCENTS SHOW INCREASED CAPTURE BY DISTRACTER Stimuli AND MORE EFFORT TO INHIBIT EMOTIONAL Stimuli THAN TYPICALLY DEVELOPING CONTROLS

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International Congress on Schizophrenia Research