Event-related electroencephalographic responses in children at familial high risk for schizophrenia or bipolar disorder: a single-site EEG sub-study of the Danish High Risk and Resilience Study – VIA 11

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Abstract

Aim: Studying children of parents with schizophrenia or bipolar disorder, i.e. who are at familial high-risk of developing similar disorders, offers the possibility to identify abnormalities preceding the emergence of mental health disorders during adolescence. This paper reports the rationale and methodology of a single-site electroencephalography-study of the register-based Danish High Risk and Resilience Study–VIA 11. Focusing on event-related electroencephalographic read-outs that have previously been proposed as endophenotypes for schizophrenia, we set out to retrieve these endophenotypes in children at familial high-risk.

Method: Event-related cortical responses to repetitive auditory stimuli or visuospatial flanker stimuli will be recorded with 128-channel electroencephalography in eleven-year-old children with one or two parents diagnosed with schizophrenia spectrum psychosis ($n > 40$) or bipolar disorder ($n > 40$) and control children without familial high-risk ($n > 40$). We will test for between-group differences in auditory processing, focusing on the auditory steady-state response and mismatch negativity. We will also assess between-group differences in visually evoked cortical activity implicated in the resolution of a visuomotor response conflict such as P3b potential and lateralized readiness potential. We will further examine whether the individual expression of these electroencephalographic read-outs scale with clinical characteristics.

Conclusions: The study will clarify whether potential electroencephalographic-derived endophenotypes are expressed in children of parents with schizophrenia and possibly also in children of parents with bipolar disorder. The multiple electrophysiological-based read-outs of brain reactivity will enable additional exploratory analyses. Together, the study will contribute to current attempts to validate and identify electroencephalographic-based endophenotypes of vulnerability for mental health disorders.

Keywords: Bipolar disorder, electroencephalography, endophenotypes, familial high-risk, offspring, schizophrenia.

Introduction

Schizophrenia (SZ) and bipolar disorder (BP) are among the most severe mental disorders imposing a huge impact on patients and their families (Millier et al., 2014) and show considerable overlap in their genetic, symptomatic and neurobiological characteristics (Purcell et al., 2009). Behavioural, cognitive and emotional abnormalities are present before the prodromal phases of both illnesses, though deficits are more severe in those who will develop SZ (Bora, 2016), which argues for a stronger neurodevelopmental nature in SZ compared to BP (Owen, O'Donovan, Thapar, & Craddock, 2011). Studies that include children born to parents with SZ or BP, which are at a familial high risk (FHR) for developing these disorders, provide the opportunity to investigate vulnerability and protective factors, as well as factors of resilience in those who present with the typical endophenotypes, but do not develop the disorder (Rasic, Hajek, Alda, & Uher, 2014).

Prospective longitudinal FHR-studies suggested several cognitive endophenotypes for both disorders (Bora & Ozerdem, 2017; Hameed & Lewis, 2016). Few studies included electroencephalography (EEG), a non-invasive and cost-effective technique to investigate early information-processing abilities (Friedman & Squires-Wheeler, 1994; Schreiber, Stolz, Rothmeier, Kornhuber, & Born, 1989). EEG provides a direct measure of electrical activity with high temporal resolution, which is essential to study oscillatory activity and event-related potentials (ERPs). Furthermore, EEG has greatly contributed to the search for endophenotypes in psychiatry; in SZ (Earls, Curran, & Mittal, 2016), BP (Ethridge et al., 2015) and in other psychiatric disorders (Riva et al., 2018). The following section describes three aspects of neural mechanisms being tested as part of the current study 1) auditory steady-state responses, 2) automatic cortical processing of changes in regularity of auditory input and 3) event-related cortical responses of visuomotor control.

Auditory steady-state responses

Auditory steady-state responses (ASSRs) are evoked by brief tones or clicks and provide readily available, noninvasive means of probing impaired neural gamma synchrony in the auditory system (Larsen et al., 2017; Thune, Recasens, & Uhlhaas, 2016). The ability to generate 40 Hz ASSR relies on the GABAergic interneurons (Bartos, Vida, & Jonas, 2007; Sohal, Zhang, Yizhar, & Deisseroth, 2009; Traub et al., 2003) by exerting a finely timed inhibition onto the pyramidal cells. ASSR at 40 Hz is well-studied in patients with chronic SZ; 17 out of 20 studies reported reductions in power and phase-locking of 40 Hz ASSR compared to healthy subjects (Thune et al., 2016). Additionally,

unaffected first-degree relatives (UFDR) of patients with SZ showed reduced 40 Hz ASSR (Rass et al., 2012). The few studies that investigated ASSR in patients with BP reported similar results (O'Donnell, Hetrick, et al., 2004; Rass et al., 2010) suggesting circuit dysfunctions in both disorders. Furthermore, evidence shows that deficits in early gamma-band responses arise after the onset of psychosis while the late gamma-band response is already premorbid impaired (Tada et al., 2016). These findings indicate its potential role as endophenotype for SZ whereas their potential role as an endophenotype of BP is not well elucidated.

Automatic cortical processing of changes in regularity of auditory input

The preconscious process of detecting change in regularity of auditory input is expressed by the mismatch negativity (MMN). MMN reflects an automatic predictive processing system that is evoked when an expectation regarding upcoming stimuli is violated. This results in a fronto-temporal negative deflection that peaks between 150-250 ms after the mismatching stimulus (Näätänen, 1990). MMN amplitude reductions are consistently found in patients with chronic SZ, with effect sizes (ES) between 0.95 and 0.99 and are greatest in response to duration-deviant tones (Earls et al., 2016; Umbricht & Krljes, 2005) and are also observed in UFDR of patients with SZ (Earls et al., 2016). MMN alterations are associated with poorer psychosocial functioning and ratings on global functioning in daily life (Light, Swerdlow, & Braff, 2007) and are also reported in children with autism (Vlaskamp et al., 2017) and adolescents with ADHD (Rydkjaer et al., 2017). Recent findings revealed that MMN amplitude reductions may be due to a decreased connectivity from higher to lower cortical areas, indicative of predictive processes going wrong (Larsen et al., 2018). Evidence of MMN changes in patients with BP is more controversial and meta-analyses reported moderate ESs between 0.37 and 0.45 (Chitty, Lagopoulos, Lee, Hickie, & Hermens, 2013; Erickson, Ruffle, & Gold, 2016). UFDR of patients with BP showed no MMN deficits compared to healthy subjects (Hall et al., 2009; Umbricht et al., 2003). These findings suggest MMN deficits as potential endophenotype for SZ, whereas this has not yet been documented for BP.

Event-related cortical responses of visuomotor control

In visuomotor tasks assessing interference control, e.g. the flanker task (Eriksen, 1995), cortical responses reflect higher cognitive processes. To investigate neural correlates of interference control, three ERP-components N200, P3b and the lateralized readiness potential (LRP) are of interest (Coles, 1989; Eichele et al., 2016; Xie, Ren, Cao, & Li, 2017). N200 is a frontocentral negative peak at

approximately 200 ms after stimulus onset and its amplitude is enhanced in tasks eliciting response conflict (Heil, 2000; Kopp, Rist, & Mattler, 1996). P3b is a parietal positive peak at approximately 300 ms after stimulus onset. P3b amplitude reflects the degree of cognitive demand during task processing and P3b latency reflects the time required to detect a target stimulus (Polich, 2007). Alterations in N200 and P3b amplitudes reflect impaired attention-dependent processing in higher cortical regions and are linked to other disorders with attention and inhibition disturbances, such as ADHD (Tsai, Hung, & Lu, 2012). Specifically, reductions in N200 amplitudes have been shown in patients with SZ, but not in patients with BP (O'Donnell, Vohs, Hetrick, Carroll, & Shekhar, 2004), whereas both patient groups show reduced P300 amplitudes and prolonged P300 latencies (Jahshan et al., 2012; O'Donnell, Vohs, et al., 2004), which also precede psychosis onset (Hamilton et al., 2019). UFDR of patients with SZ, compared to healthy subjects, display prolonged N200 latencies (Frangou et al., 1997; Schreiber et al., 1989), reduced P300 amplitudes (ES: 0.52-0.61) and prolonged P300 latencies (ES: 0.44-0.50) (Bramon et al., 2005; Earls et al., 2016). UFDR of patients with BP only show smaller P300 amplitudes (Hall et al., 2009; Schulze et al., 2008), though fewer studies have been conducted. Finally, the LRP reflects the difference in motor cortex activation between the two cerebral hemispheres and is related to response preparation and execution (Coles, 1989). Delayed onset of the LRP, i.e. lengthening of motor response selection and preparation processes, are present in both SZ and BP (Van Voorhis et al., 2019). When our cohort was aged 7, children with FHR-SZ showed motor impairments relative to control children (Burton et al., 2017), which gives reason to study the LRP. In addition to the stimulus-locked ERPs, response-locked ERPs such as the error-related negativity (ERN) and error positivity (Pe) allow us to study processes of error monitoring. Specifically, the ERN indexes automatic error detection and arises immediately after an erroneous response (Ford, Jorgensen, Roach, & Mathalon, 2009). Subsequently, Pe emerges approximately 300 ms after an erroneous response and reflects the evaluation and awareness of the incorrect response (Davies, Segalowitz, & Gavin, 2004).

We designed a study to identify potential electrophysiological endophenotypes for SZ and/or BP. Our primary aim is to clarify whether suggested electrophysiological-based endophenotypes can be retrieved in this FHR-cohort. Therefore, EEG will be recorded while children undergo a gamma entrainment paradigm to measure ASSR, an auditory oddball paradigm to measure MMN and a modified flanker task to measure the ERP-components N200, P3b and LRP. We hypothesize that children at FHR-SZ relative to control children show (1) reductions in power and inter-trial phase

coherence of the ASSR in response to regular auditory stimulation at 40 Hz, (2) reduced amplitudes of the MMN response, (3) altered N200, P3b and LRP in more attentional demanding conditions in the flanker task that require suppression of a prepotent response, and (4) altered ERN and Pe after the commission of an error. Given the overlap in SZ and BP, we expect that EEG outcome measures of children at FHR-BP will lie between those of FHR-SZ and control children. Further, we will perform exploratory analyses to identify novel endophenotypes related to GABAergic circuitry dysfunction through computational modelling (Shaw et al., 2019; Symmonds et al., 2018) within the network generating the ASSR as well as altered connectivity in the MMN network. Additionally, we expect associations between the individual EEG-outcomes and severity of behavioural problems, especially with symptomatology of autism and ADHD. Finally, we propose a combination of altered functional patterns constituting complementary network biotypes conferring risk for psychosis. This opens up for follow-up studies to investigate resilience factors.

Methods

Study design

This study was approved by The Danish Data Protection Agency as part of the Danish High Risk and Resilience Study - VIA 11 (Thorup et al., 2018). The Danish High Risk and Resilience Study - VIA 7 was initiated in 2013 when children were 7 years of age (Thorup et al., 2015) and a collaboration of two research sites in Denmark (Copenhagen and Aarhus). The EEG sub-study was added to the first follow-up (VIA 11) but only performed at the research site in Copenhagen, at the Danish Research Centre for Magnetic Resonance (DRCMR), Copenhagen University Hospital Hvidovre. Children of the cohort were evenly distributed over the two research sites based on place of residence, FHR status, and gender. EEG was performed by trained researchers who are blinded to the group status of the parent. Parents or legal guardians of participating children complete a written informed consent after written and oral explanation of the study procedures. Children receive a verbal, child-friendly explanation of the study. Although the current EEG study is cross-sectional, we plan to incorporate EEG in future waves of the Danish High Risk and Resilience Study that are intended to occur every four years.

Participants

This study will recruit at least 40 children at FHR-SZ, 40 children at FHR-BP and 40 control children. Eleven-year-old children with either zero, one, or two parent(s) diagnosed with schizophrenia

spectrum psychosis (defined as SZ, delusional disorder and schizoaffective disorder; ICD 10-codes: F20, F22 and F25 or ICD 8-codes: 295, 297, 298.29, 289.39, 298.89, 298.99) or BP (ICD 10-code F30 and F31 or ICD 8-codes: 296.19, 296.39) were recruited from VIA 7 (Thorup et al., 2015) and testing commenced in May 2017. The original cohort of VIA 7 was recruited through the Danish Civil Registration System and the Danish Psychiatric Central Research register (Mors, Perto, & Mortensen, 2011) and was required to have Danish as native language. Children not at FHR (population-based controls; PBC) were matched to children at FHR-SZ on municipality, sex and age. Children at FHR-BP were comparable to the other groups in terms of age and gender. Power calculations for the EEG read-outs were difficult to make due to a low number (or lack) of previous studies including children with FHR-SZ and FHR-BP. Our sample size of at least 40 children per group (total N=120) is high compared to the existing studies (Friedman, Cornblatt, Vaughan, & Erlenmeyer-Kimling, 1988; Schreiber, Stolz-Born, Kornhuber, & Born, 1992) and compared to studies including young and adult individuals with CHR for psychosis (Bruggemann, Stockill, Lenroot, & Laurens, 2013; Lepock et al., 2018), although effect sizes may be different due to different clinical characteristics.

Procedure

After generally explaining EEG, participants are seated in a comfortable chair in a quiet room. Participants are carefully instructed about the experimental procedures. Three experimental tasks are presented in the following fixed-order; gamma entrainment paradigm, (2×6 minutes); modified flanker task (Eichele et al., 2016; Eriksen, 1995), (2×6 minutes); and an auditory oddball paradigm (MMN) (Düring, Glenthøj, & Oranje, 2016), (16 minutes). Training of the modified flanker task takes place prior to EEG testing, at an earlier MRI session in which the same task is also assessed (Thorup et al., 2018). In case children do not want to be scanned, the flanker-training is performed before the EEG session. The experimental part of the EEG takes approximately 45 minutes (including breaks).

Electroencephalography

EEG data is recorded with a Biosemi ActiveTwo (BioSemi, Amsterdam, Netherlands) 128-channel system at a sampling frequency of 4096 Hz. External electrodes record electro-oculography. Auditory stimuli are delivered binaurally via insert-earphones (E-ARTONE 3A). EEG signals will be pre-processed and analyzed using the FieldTrip toolbox (Oostenveld, Fries, Maris, & Schoffelen, 2011),

SPM, Brain Electrical Source Analysis (MEGIS Software GmbH, Gräfelfing, Germany) and customized scripts.

Paradigms/tasks

1) ASSR: participants are presented with auditory stimuli containing sequences of 40 Hz click trains. One sequence' stimulation lasts one second, followed by a two-second pause. We use a regular and irregular condition, see Larsen et al. (2017). In the regular condition, clicks with the duration of one second are distributed regularly at a rate of 40 clicks per second, while clicks are distributed irregularly over the one-second stimulation period in the irregular (control) condition. Each condition is recorded in separate blocks of six minutes. Participants are asked to relax while fixating on a fixation cross (see Figure 1).

2) MMN: participants are presented with an auditory oddball paradigm (Düring et al., 2016). This paradigm consists of 1800 stimuli in total with standard tones (76% occurrence) and deviant tones (8% occurrence) of three kinds. The standard tone is a pure tone with a frequency of 1000 Hz, an intensity of 75 dB and a duration of 50 ms. Deviant tones differ either in frequency (1200 Hz, 75 dB, 50 ms), duration (1000 Hz, 75 dB, 100 ms) or its combination (1200 Hz, 75 dB, 100 ms). Participants are asked to relax while watching a muted movie.

3) Modified flanker task: participants perform a modified flanker task (Eichele et al., 2016; Eriksen, 1995) running in E-Prime 2 (Psychology Software Tools, 2012). Trials start with a 700 ms fixation dot at the center of the screen. Six flanking arrows appear for 100 ms followed by the target arrow, which is present for 1000 ms in the middle of the six flankers. Flanking and target arrows point in the same (congruent condition, 50%) or in the opposite direction (incongruent condition, 50%). Participants are instructed to press the left button with their left thumb when the target arrow points to the left and vice versa. Four-hundred trials are presented in two blocks in fixed-order between subjects each lasting six minutes. An exclamation mark appears when participants respond too slow, either because of exceeding the response window (1000 ms) or their personal threshold calculated during the training, i.e. mean reaction time (RT) + 1.5 x SD of the mean RT on 10 incongruent trials.

Functional and clinical measures

Children will be assessed with the Reynolds Intellectual Screening Test (RIST) (Reynolds, Kamphaus, & Lutz, 2003), for estimating IQ. The Schedule for Affective Disorders and

Schizophrenia for School-Age Children - Present and Lifetime Version (K-SADS) (Kaufman et al., 1997) will be used to ascertain presence of psychiatric disorders and subsyndromal symptomatology. We included the following measures to assess daily functioning, global problem behaviour, positive symptomatology and specific severity of autism and ADHD. The Children's Global Assessment Scale (CGAS) (Shaffer et al., 1983) rates a child's psychological, social and daily functioning. The Childhood Behavior Checklist (CBCL) (Bilenberg, 1999) reports on various behaviours and emotions in children. Psychotic-Like Experiences (PLE) (Miller et al., 2003) assesses sub-threshold psychotic-like experiences. The Social Responsiveness Scale (SRS) (Constantino & Gruber, 2005) provides an index of the severity of autistic traits. The Attention-Deficit/Hyperactivity Disorder – Rating Scale (ADHD-RS) (Makransky & Bilenberg, 2014) assesses the severity of ADHD-symptomatology.

Figure 1. The paradigms presented during EEG recordings. From left to right, are the gamma entrainment paradigm (Larsen et al., 2017) to study the auditory steady-state response (ASSR), the modified flanker task (Eichele et al., 2016; Eriksen, 1995) to elicit the N200, P3b and LRP, and an auditory oddball paradigm (Düring et al., 2016) to elicit mismatch negativity (MMN). The ASSR image is adapted with permission from (Larsen et al., 2017).

Statistical analyses

Demographic and clinical characteristics will be analyzed by using parametric (one-way analysis of variance (ANOVA)) or non-parametric methods where appropriate. Behavioural performance on the flanker task will be evaluated following the statistical analyses in Ridderinkhof (2002). To assess group differences in the EEG outcome variables we will employ two different approaches; one

hypothesis-driven approach assessing differences in prespecified channels known to produce highest responses for the given task (Handy, 2005) as well as a more unbiased assumption-free approach.

For the primary aim, we will test for group differences on the EEG outcome variables from the ASSR, MMN and flanker task by using a repeated-measures analysis of (co)variance (RM-AN(C)OVA) with the EEG outcome variable as the dependent variable, group-membership as between-subject factor (children at FHR-SZ, children at FHR-BP and PBC children) and condition as within-subject factor (i.e. congruent versus incongruent condition or correct versus incorrect for the flanker task). MMN is considered to show the highest amplitude at the frontal/midline EEG-channels (Hall et al., 2007; Light et al., 2007), whereas highest N200 and P3b amplitudes are typically found at frontal/midline and centro/parietal electrodes (Xie et al., 2017). Electrodes C3 and C4 will be used for the calculation of the LRP (Coles, 1989). ERN and Pe are considered maximal at frontal and central electrodes (Davies et al., 2004). Bonferroni correction for multiple comparisons will be applied to post hoc tests.

For the secondary aim, we will search for differences over the entire electrode-time (or frequency) volume and use random field theory to correct for multiple comparisons (Kilner & Friston, 2010). Using this approach, we can capture if differences are present outside of the expected component while still controlling for multiple comparisons. For the ASSR data we will use Dynamic Causal modelling (DCM) with the canonical microcircuit model to tap into potential GABAergic circuitry dysfunction (Shaw et al., 2019; Symmonds et al., 2018). For the MMN task we will employ DCM for ERPs (David et al., 2006) to infer on group differences in the connectivity of the underlying network generating the MMN responses. For each of the EEG outcome variables, we will explore how these are related to the clinical variables using either parametric or non-parametric correlation methods. Finally, we will use a multivariate machine learning approach to merge all parameters to learn from the data by doing a cluster analysis to look at potential overlaps.

Age and sex will be included in all analyses if they covary significantly. We will conduct a post hoc test for the effect of IQ. P-values will be reported significant if below 0.05.

Discussion

This paper describes the rationale and methodology of an EEG-investigation of 11-year-old children at FHR-SZ and FHR-BP and PBC children. Evidence suggests a considerable overlap in genetic, neuropsychological and neurobiological characteristics between SZ and BP (Purcell et al., 2009). However, the search for endophenotypes that could identify those individuals at highest risk to develop these disorders remains ongoing. This study is the first EEG-investigation in a young, large

FHR-sample of the same age assessing several electrophysiological measures within the context of a longitudinal cohort-study, namely ASSR, MMN, N200, P3b, LRP, ERN and Pe. By doing so, we aim to 1) identify potential electrophysiological endophenotypes for SZ and/or BP, 2) explore to what extent clinical characteristics correlate with these electrophysiological measures and 3) identify electrophysiological profiles that may distinguish children at FHR-SZ from children at FHR-BP, which can be validated in future follow-up studies.

We expect that our findings will contribute to gaining a deeper insight into potential electrophysiological endophenotypes for SZ and BP. Our findings may pave the way to follow-up studies on resilience factors because not all vulnerable children will develop the disorders. Finally, a better understanding of the underlying risk markers of SZ and BP may not only contribute to early diagnostic precision but also to the development of interventions designed to prevent or mitigate the individual expression of these severely disabling disorders.

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Conflict of interest statement

HRS has received honoraria as speaker from Sanofi Genzyme, Denmark and Novartis, Denmark, as consultant from Sanofi Genzyme, Denmark and as senior editor (NeuroImage) from Elsevier Publishers, Amsterdam, The Netherlands. He has received royalties as book editor from Springer Publishers, Stuttgart, Germany. The other authors declare they have no competing interests.

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