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RESEARCH ARTICLE

Cortical miscommunication after prenatal exposure to alcohol

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Abstract We report on the effects of prenatal alcohol exposure on resting-state brain activity as measured by magnetoencephalography (MEG). We studied 37 subjects diagnosed with fetal alcohol spectrum disorder in one of three categories: fetal alcohol syndrome, partial fetal alcohol syndrome, and alcohol-related neurodevelopmental disorder. For each subject, the MEG signal was recorded for 60 s during rest while subjects lay supine. Using time series analysis, we calculated the synchronous neural interactions for all pair-wise combinations of 248 MEG sensors resulting in 30,628 partial correlations for each subject. We found significant differences from control subjects in 6.19 % of the partial zero-lag crosscorrelations (synchronous neural interactions; Georgopoulos et al. in J Neural Eng 4:349–355, 2007), with these differences localized in the right posterior frontal, right parietal, and left parietal/posterior frontal regions. These results show that MEG can detect functional brain differences in the individuals affected by prenatal exposure to alcohol. Furthermore, these differences may serve as a biomarker for future studies linking symptoms and signs to specific brain areas. This may lead to new insights into the neuropathology of fetal alcohol spectrum disorders.

Keywords Magnetoencephalography · Fetal alcohol syndrome · Synchronous neural interactions · Resting state

Introduction

Alcohol is a well-known teratogen causing adverse developmental outcomes in the offspring of mothers consuming alcohol during pregnancy. Prenatal exposure to alcohol can lead to physical, mental, behavioral, and social effects that often have lifelong implications and a profound impact on the quality of life of the affected individuals (Stade et al. 2006). The broad range of impairments and symptoms that are characteristic for the teratogenic effects of alcohol are associated with the dose and pattern of the gestational alcohol exposure, the stage of development when alcohol was present as well as genetic and epigenetic factors (Kobor and Weinberg 2011; Zhou et al. 2011a, b), reflected in maternal and fetal metabolism or functional sensitivity to alcohol, and other relating factors, such as nutrition, smoking, and other substance abuse (Jacobson et al. 1998). This variability led to establishing the umbrella term fetal alcohol spectrum disorder (FASD) comprising several diagnostic categories. Fetal alcohol syndrome (FAS) represents the severe end of the spectrum. It is characterized by a distinct pattern of facial dysmorphology, growth restriction, and brain function deficits. Partial fetal alcohol syndrome (pFAS) is diagnosed when facial features are present but growth or neurobehavioral deficits are not fully expressed (May et al. 2014). Animal research models showed that facial features pathognomonic for FAS/pFAS are induced by alcohol during the time-limited critical period of facial morphogenesis

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(Sulik 2005). Facial dysmorphology is therefore not always present in individuals with prenatal alcohol effects. Individuals with neurocognitive and behavioral deficits and absent facial dysmorphology comprise the alcohol-related neurodevelopmental disorder (ARND) diagnostic group (Stratton et al. 1996; Bertrand et al. 2005; Chudley et al. 2005; May et al. 2014).

The most important effect of alcohol on fetal development is on brain development, and alcohol has been classified as a behavioral teratogen (Jones 2011). At present, FASD is the leading preventable cause of developmental disability (Center for Disease Control 2004), with the prevalence in the USA reported as 9 in 1000 births (Sampson et al. 1997; May and Gossage 2001). In a recent epidemiology study, all levels of FASD rates were estimated as high as 3-5 % for the US and some Western European countries in a population of younger school children (May et al. 2009). FASD represents a significant concern for mental health and medical professionals.

Neurocognitive and behavioral deficits related to FASD include cognitive and intellectual disability, learning, memory, attention, communication, executive, and motor functioning disabilities (for review, Kodituwakku 2007). Neuroimaging studies have identified structural brain abnormalities in individuals prenatally exposed to alcohol, including volume reduction in the total intracranial vault and of specific regions, alterations of cortical shape, symmetry and thickness, and white and gray matter disorganization (Lebel et al. 2011; Yang et al. 2012; Wozniak et al. 2013; Treit et al. 2014; De Guio et al. 2014; Meintjes et al. 2014; Leigland et al. 2013; Fan et al. 2016; Treit et al. 2016; Robertson et al. 2016). Functional neuroimaging studies have shown impairments of the task-related neuronal circuitry associated with the prenatal exposure to alcohol (Coles and Li 2011). MEG studies have demonstrated task-dependent differences in all cerebral cortical lobes comparing FASD and healthy control subjects (Stephen et al. 2012; Coffman et al. 2013; Stephen et al. 2013; Tesche et al. 2014). Altered EEG, i.e., decreased alpha activity and lower alpha frequencies, was reported over the left hemisphere in the children with FAS compared to the healthy children (Kaneko et al. 1996b). Altered left hemisphere perfusion (i.e., mild hypoperfusion) was found using single-photon emission computed tomography (SPECT) and MRI in a sample of 10 children with FAS (Riikonen et al. 1999). However, there is an ongoing debate whether specific brain structural (Treit et al. 2016) or functional impairments can be established/determined/pinpointed for the FASD cohort and used for diagnostic purposes, especially in non-syndromal individuals with prenatal alcohol teratogenic effects. Progress in the diagnosis of FASD is needed for improved intervention targeting and preventing maladjustment of affected/handicapped individuals.

In the present study, we aimed to investigate brain communication patterns in resting, task-free state cortical activity in individuals with FASD. Structural impairments of the brain cortical regions have been well documented, as well as their abnormal activity during task-related activity (Coles and Li 2011). Underlying abnormal neuronal structure associated with the prenatal alcohol effects might be expressed by alterations of neuronal activity/connectivity also during resting state. A recently published fMRI study reported alteration of resting-state brain activation in FASD (Santhanam et al. 2011; Donald et al. 2016). We aimed to investigate the resting functional connectivity using magnetoencephalography (MEG) that provides a direct measure of neuronal activity. Also, resting-state connectivity measures should not be confounded by factors such as activity changes restricted to cortical regions activated by the task or task performance related to group differences in cognitive ability that represent a common challenge in the FASD research (Coles and Li 2011).

Previous studies showed that neuronal interactions derived from magnetoencephalography (MEG) recordings are consistently found within a specific pattern in healthy individuals during resting state (Langheim et al. 2006). Tests of synchronous neuronal interactions (SNI) have been successfully used to identify alteration of neuronal cortical synchronization in different disease states and have been proposed as a functional biomarker (Leuthold et al. 2005; Georgopoulos et al. 2007, 2010).

We analyzed MEG recordings of the resting-state brain cortical activity in the individuals with FASD to assess if a specific pattern of abnormal resting-state neuronal synchronization can be identified in this patient cohort. These findings would help to elucidate specific regions affected by the adverse impact of the prenatal alcohol exposure and improve the diagnosis of affected individuals.

Materials and methods

Participants

All subjects participated in the study after providing informed consent, in adherence to the Declaration of Helsinki, and were financially compensated for their time. All study protocols were approved by the respective Institutional Review Boards.

FASD group

Subjects were recruited through the nonprofit, patient support organization Minnesota Organization on Fetal Alcohol Syndrome (MOFAS) with referrals from the Fetal Alcohol Diagnostic Program (Duluth, MN) and the Fetal Alcohol

Spectrum Disorders Clinic, University of Minnesota. The diagnosis was provided by these clinics/organizations and confirmed by reviewing diagnostic criteria at the time of the study using the Hoyme et al. (2005) modification of the Institute of Medicine criteria (Hoyme et al. 2005). Forty-one subjects were recruited. Four subjects were excluded due to the diagnosis of an additional developmental disorder or due to excessive motion during the MEG acquisition. A total of 37 subjects were evaluated in the final analysis, 5 subjects with the FAS diagnosis, and 32 subjects with the ARND. Fourteen subjects were on the stimulant medication of methylphenidate and its derivatives.

There were 37 (22 male and 15 female) participants in the study between the ages of 9–34 years (average age of 15.7 years ± 5.2 SD) of diverse ethnicity (15 Caucasian, 15 African-Americans, 4 Native American, 2 of mixed African-American/Native American parentage, and 1 of mixed Asian/Pacific Islander parentage). The following diagnostic categories were used for fetal alcohol spectrum disorder: fetal alcohol syndrome (FAS), partial fetal alcohol syndrome (pFAS), and alcohol-related neurodevelopmental disorder (ARND). Some participants received the fetal alcohol effects (FAE) diagnosis that has been used previously in individuals who did not fully express signs of fetal alcohol syndrome and has since been replaced by the ARND diagnostic category (Stratton et al. 1996). For the purpose of this study, participants with FASD were classified into the group with facial dysmorphology, including individuals with the FAS or pFAS ("FAS" group, $N = 5$) and the non-dysmorphic group of individuals with the ARND or FAE ("ARND" group, $N = 32$). Due to the low number of FAS subjects, the analysis was performed on the FAS and ARND group combined.

Controls

Age- and sex-matched, healthy individuals with no history of prenatal alcohol exposure ($N = 101$) were recruited from the general public for this and other projects in the Brain Science Center. Health was assessed by clinical interview of the subject (upon initial contact and again in more detail at the time of consent). This included a general medical history, medication use, and a detailed review of neurologic and psychiatric history.

Task and data acquisition

MEG signal was recorded during rest without engaging in any specific task. Subjects lay supine in the MEG instrument, fixated their eyes on a spot ~65 cm in front of them, for 60 s fixation. MEG data were acquired using a 248-channel axial gradiometer system (Magnes 3600 WH, 4-D Neuroimaging, San Diego, CA, USA), band filtered between 0.1 and 400 Hz, and sampled at 1017.25 Hz. Data with artifacts (e.g., eye blinks and saturation) were eliminated from further analysis.

Data analysis

Single-trial MEG data from all sensors underwent "prewhitening" using a (50,1,1) autoregressive integrated moving average (ARIMA) model (Box and Jenkins 1976). The MATLAB package (version 2011b) was used to fit the model and obtain innovations (i.e., residuals). All possible pairwise zero-lag crosscorrelations ($N = 30{,}628$, given 248 sensors) were computed between the prewhitened MEG time series. Finally, the partial crosscorrelations were computed for all sensor pairs (synchronous neural interactions, SNI; Georgopoulos et al. 2007); thus, for any given pair of sensors (from a total of 248) the effects of the remaining 246 sensors were partialed out. The partial correlation r was z-transformed (Fisher 1958) to normalize its distribution: $\mathrm{SNI} = z = \mathrm{atanh}(r)$.

Standard statistical methods (Snedecor and Cochran 1989) were used to compare variables between groups and assess relations among variables. Statistical analyses were performed using the IBM SPSS (version 20; SPSS Inc.) and the Intel Visual Fortran Compiler Professional Edition (version 11.1; Intel Corporation). A 0.01 level of significance was adopted a priori consistent with our previous MEG studies.

Results

Analyses of SNI were performed using the age and gender as covariates. Multiple logistic regression analysis performed to identify variables associated with the partial crosscorrelation did not show significant effects of the stimulant medication (methylphenidate and its derivatives) or gender on the SNI in the FASD population.

When the age and gender variables were used as covariates in the analysis of the effect of the fixed group factor, i.e., the whole group of the fetal alcohol syndrome spectrum (FASD) patients versus control group ANCOVA, 1895/30,628 partial crosscorrelations (6.19 %) exceeded the threshold of $p < 0.01$. This difference is highly significant in comparison with other MEG studies (Georgopoulos et al. 2007, 2010; Engdahl et al. 2010).

The locations of significant effects in sensor space are shown in Fig. 1 at a higher threshold ($p < 0.00075$) to keep plotted ellipses distinct. It can be seen that sensors with significant effects form clusters, in the (1) right posterior frontal region, (2) right parietal region, and (3) left parietal/posterior frontal region, respectively.

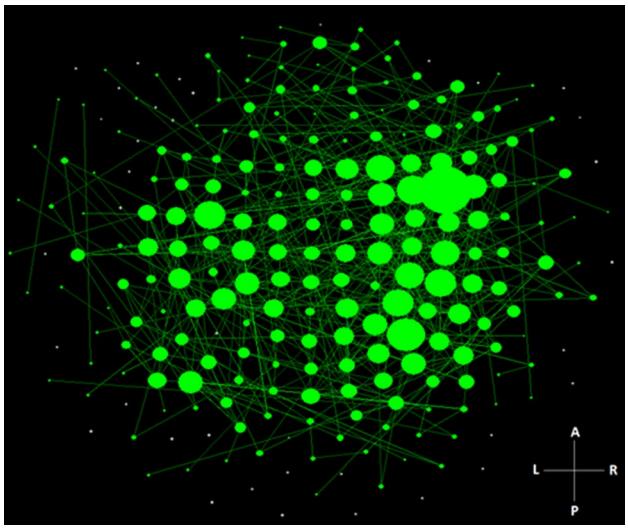

Fig. 1 Two-dimensional sensor-space plot depicting the SNI differences between FASD and control groups. White dots indicate MEG sensor location on a plane. *Lines* ($N = 525$) indicate the presence of a statistically significant effect ($p < 0.00075$, F test in ANCOVA; see text); the *color intensity* of a *line* is proportional to the value of the F statistic for Group in the ANCOVA. The radius of the ellipses is proportional to the maximum F value related to the specific sensor (out of 247 possible). *A* anterior, *P* posterior, *L* left, *R* right

Discussion

Altered resting-state cortical synchronicity in FASD

Results of our study show abnormal brain activation and synchronization in the individuals with FASD in the task-free baseline resting state. Our results expand the findings of previous studies, as magnetoencephalography (MEG) provides complementary information to those methodologies using delayed and indirect markers of brain activity, such as fMRI and PET/SPECT. MEG uses a more direct approach to assess neuronal processing, i.e., analysis of the spontaneous MEG signal to investigate the cortical communication of neuronal populations. Further, magnetic fields measured by MEG are not biased by low skull conductivity as are the electrical potentials in electroencephalography (EEG).

In a recent study, alterations of baseline resting-state network in adults with FASD were measured by the means of the default mode network using functional magnetic resonance imaging (fMRI). The brain regions identified as default mode areas have been localized most often to medial structures, including the medial prefrontal gyrus (MPFC), the posterior cingulate cortex (PCC), precuneus, inferior parietal lobules (IPL), and medial temporal regions. Santhanam et al. (2011) identified MPFC, PCC, and IPL regions by significant task-related deactivation compared to activity during resting state in the FASD individuals. In the FASD group compared to the controls, lower correlations between the medial prefrontal cortex and posterior cingulate cortex (MPFC-PCC) and between bilateral inferior parietal lobules and the posterior cingulate cortex (IPL-PCC) indicated altered resting-state networks (Santhanam et al. 2011). Our findings confirm the evidence of abnormal baseline neuronal functioning in the FASD population. We identified several cortical regions with abnormal functional connectivity during resting state in the individuals with the FASD compared to the control group that were localized in the left and right parietal/posterior frontal cortical regions.

The abnormal pattern of activity observed in the individuals with FASD may indicate decreased efficiency of the relevant brain networks. Structurally, parietal regions are known to be especially sensitive to alcohol teratogenic effects, showing smaller volumes (Archibald et al. 2001; Sowell et al. 2002; Meintjes et al. 2014), shape abnormalities (Sowell et al. 2002), alterations of cortical thickness (Sowell et al. 2008; Yang et al. 2012; Wozniak et al. 2013; Treit et al. 2014; Robertson et al. 2016) or gray and white matter density (Sowell et al. 2001), abnormal diffusion parameters (Fryer et al. 2009; Lebel et al. 2011; Wozniak and Muetzel 2011), or metabolic abnormalities (Astley et al. 2009a; Fagerlund et al. 2006). Task-related abnormal fMRI activation within parietal cortices (Melisza et al. 2005; Astley et al. 2009b; Santhanam et al. 2009) and abnormal P2 and P3 components of the event-related potentials (Burden et al. 2009, 2011; Kaneko et al. 1996a) were demonstrated in the individuals prenatally exposed to alcohol.

Other studies found structural and functional alterations in the other brain lobes, particularly in the prefrontal cortex (Sowell et al. 2002; Melisza et al. 2005; Fryer et al. 2009; Astley et al. 2009a, b; Wozniak et al. 2013; Treit et al. 2014; Meintjes et al. 2014). Involvement of these regions was well supported by behavioral studies. Executive function deficits associated with prefrontal cortices are commonly detected in the FASD population, e.g., (Kodituwakku 2007; Rasmussen 2005).

In summary, the literature describes involvement of both frontal and parietal areas in FASD. Our findings support this localization and demonstrate that it can be detected in the resting state as measured by MEG. It is noted that fMRI studies have also noted abnormalities in deeper cortical structures, i.e., the medial prefrontal cortex and the cingulate cortex. This may reflect the task-dependent design of the studies or that MEG is less sensitive to deeper cortical structures.

FAS versus ARND

It is generally accepted that individuals with the fetal alcohol syndrome represent the most severe end of the prenatal teratogenic effects spectrum. However, behavioral studies

showed that individuals affected by prenatal exposure to alcohol without facial dysmorphology may suffer from significant cognitive and behavioral deficits (Mattson and Riley 1998; Sampson et al. 2000; Rasmussen 2005). Neuroimaging studies generally show findings falling into 2 groups. Some studies reported results revealing a trend, with the ARND group intermediate (but generally non-significantly different) to the FAS group and the controls. Other researchers reported no differences between results of dysmorphic versus controls and non-dysmorphic individuals versus controls comparisons, e.g., (Bookstein et al. 2001; Bjorkquist et al. 2010). Santhanam et al. (2011) found significantly lower task-related deactivation of the default mode network regions in the dysmorphic (FAS) group, while lower but not significantly different task-related deactivation in the non-dysmorphic group compared to controls. Average correlations over the MPFC and the bilateral IPL were significantly lower in both groups with the prenatal alcohol effects (PAE) as compared to the controls, and the two groups with the PAE showed comparable correlation. Our study cannot really address this issue due to the small sample size of our FAS group ($N = 5$).

Conclusions

Results of this study showed that tests of synchronous neural interactions on resting-state MEG data detect functional brain differences in the individuals suffering from the effects of the prenatal exposure to alcohol. This test is brief (1 min) and can be used in all subjects regardless of their ability to perform task-dependent studies. While the unifying history in this subject group is prenatal alcohol exposure, subjects also suffer from a number of comorbid disorders including poverty, abuse, depression, conduct problems, and attention deficit disorder (Popova et al. 2016). Future studies are warranted to separate the effects of these comorbidities and to show the ability of the test of synchronous neuronal interactions to serve as a specific correlate of prenatal alcohol effects.

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Compliance with ethical standards

Conflict of interests The authors declare that they have no conflicts of interest.

Ethical standard The study protocol was approved by the Institutional Review Boards of the Minneapolis VA Medical Center and the University of Minnesota. The study was performed in accordance with the ethical standards outlined in the Declaration of Helsinki.

Informed consent Informed consent was obtained prior to participating in the study.

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