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Prenatal drug exposure to illicit drugs alters working memory-related brain activity and underlying network properties in adolescence

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ABSTRACT

The persistence of effects of prenatal drug exposure (PDE) on brain functioning during adolescence is poorly understood. We explored neural activation to a visuospatial working memory (VSWM) versus a control task using functional magnetic resonance imaging (fMRI) in adolescents with PDE and a community comparison group (CC) of non-exposed adolescents. We applied graph theory metrics to resting state data using a network of nodes derived from the VSWM task activation map to further explore connectivity underlying WM functioning. Participants (ages 12–15 years) included 47 adolescents (27 PDE and 20 CC). All analyses controlled for potentially confounding differences in birth characteristics and postnatal environment. Significant group by task differences in brain activation emerged in the left middle frontal gyrus (BA 6) with the CC group, but not the PDE group, activating this region during VSWM. The PDE group deactivated the culmen, whereas the CC group activated it during the VSWM task. The CC group demonstrated a significant relation between reaction time and culmen activation, not present in the PDE group. The network analysis underlying VSWM performance showed that PDE group had lower global efficiency than the CC group and a trend level reduction in local efficiency. The network node corresponding to the BA 6 group by task interaction showed reduced nodal efficiency and fewer direct connections to other nodes in the network. These results suggest that adolescence reveals altered neural functioning related to response planning that may reflect less efficient network functioning in youth with PDE.

1. Introduction

The long-term impact of prenatal exposure to illicit drugs of abuse (PDE) on brain functioning remains poorly understood with relatively few published reports documenting significant effects (e.g., (Li et al., 2006; Hurt et al., 2008; Li et al., 2009b; Sheinkopf et al., 2009; Li et al., 2011; Roussotte et al., 2012; Li et al., 2013a; Li et al., 2013b)). Evidence for altered brain functioning in children and adolescents with a history of PDE may be difficult to detect because the effects of postnatal environmental factors are often confounded with the effects of the prenatal exposure (Frank et al., 2001; Ackerman et al., 2010; Buckingham-Howes et al., 2013). With many of the original cohorts entering adolescence, however, there is renewed interest in the population due to the recognition that cortical brain regions that may be affected by PDE undergo significant developmental changes during adolescence. Furthermore, evidence from nonhuman primate models of PDE suggests that disruption of performance on learning tasks may not emerge until adolescence (Lidow, 2003). Previous studies exploring cognitive functions, such as working memory (WM) demonstrate subtle differences in the PDE population (Schroder et al., 2004; Burden et al., 2005; Mayes et al., 2007; Li et al., 2009b; Ackerman et al., 2010; Buckingham-Howes et al., 2013), but not universally (e.g., Betancourt, Yan et al., 2011). These effects may persist after potentially confounding variables are controlled (e.g., birth head circumference, alcohol and tobacco prenatal exposure), (Li et al., 2009b) however studies vary in attempts to control for such factors. Most functional magnetic resonance imaging (fMRI) studies do not consider confounding environmental

Abbreviations: PDE, prenatal drug exposure; VSWM, visual spatial working memory; WM, working memory; fMRI, functional magnetic resonance imaging; DMN, default mode network; CC, community comparison group; IQ, intelligence quotient; IRB, institutional review board; NIDA, National Institutes of Drug Abuse, National Institutes of Health; BOLD, blood-oxygen-level-dependent; AFNI, Analysis of Functional Neuroimages; RT, response time; BA, Brodmann area; WASI, Wechsler Abbreviated Scale of Intelligence.

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variables (Ackerman et al., 2010; Buckingham-Howes et al., 2013). Thus, the controversy regarding the contribution of the postnatal environment versus PDE continues for adolescent-aged individuals with PDE.

Our group (Riggins et al., 2012) showed that children with PDE demonstrated worse memory performance in comparison to a community comparison (CC) group on standardized memory measures of list learning and story recall using the California Verbal Learning Test – Child Version (CVLT–C) (Delis et al., 1994) and Children's Memory Scale (CMS, (Cohen, 1997)). Our results suggested intact initial learning and recall of information on the simple recall task, but difficulty with increased task demands, such as under conditions involving interference in recall conditions. Furthermore, hippocampal volume, a structure known to support memory, was associated with memory performance. These group differences remained, even after controlling for early childhood environment. This current study further examines the relation between WM performance and neural functioning using functional magnetic resonance imaging (fMRI) and adjusting for early childhood environmental variables. WM, the ability to briefly maintain and manipulate information mentally (Baddeley, 2010), continues to develop during adolescence and into young adulthood with maturation and better performance associated with brain activity in frontal, parietal and cerebellar brain regions (Kwon et al., 2002; Crone et al., 2006; O'Hare et al., 2008). WM is a core cognitive function associated with academic performance, goal achievement and self-control (Hinson et al., 2003; Barkley, 2006; Shamosh et al., 2008; Gropper and Tannock, 2009; Alloway et al., 2010). Dopamine is related to WM functioning (Backman and Nyberg, 2013) and evidence from non-human primate models suggests that PDE can affect dopamine functioning in adult animals (Hamilton et al., 2010).

PDE research is beginning to consider how exposure is associated with the integrity of brain functioning in large-scale networks via connectivity measures (Li et al., 2006; Li et al., 2013a; Li et al., 2013b). Li et al., (2011) investigated the relation between PDE and functional connectivity in the default mode network (DMN). A seed-based approach demonstrated that PDE was associated with stronger functional connectivity during resting state and less deactivation in the DMN during WM performance than in a comparison group. This same group (Li et al., 2013a) identified a set of cortical landmarks associated with adolescents who experienced PDE, and used the landmarks to discover functional connectomic signatures that differentiate the PDE brain from control subjects. They identified 10 structural landmarks that were altered in the adolescents with PDE that were associated with the functional connectomic signatures. The authors noted that the structural landmarks they identified as discrepant in PDE studies are brain networks associated with processes thought to be affected in PDE including working memory, language, executive function, motor, attention and vision processing. Graph theory analyses have the potential to further characterize network functioning by quantifying the topological organization of connectivity within the brain (He and Evans, 2010); however, this method has yet to be applied to the PDE population. Networks based on functional and anatomical nodes involved in cognitive functioning are related to age (Dosenbach et al., 2010; Fair et al., 2012b), IQ (Li et al., 2009a; van den Heuvel et al., 2009) and clinical disorders (Fair et al., 2012b; Tye and Bolton, 2013). Individual task performance is positively associated with topological efficiency of brain networks during both resting (Giessing et al., 2013; Langer et al., 2013) and task performance (Bassett et al., 2009). Graph theory may enhance understanding of the neuronal integrity of brain regions associated with task performance as functional connectivity alterations may impact behavioral performance.

The present study explores whether adolescents with PDE versus a non-exposedCC group evidence differences in brain functioning associated with performance during a VSWM task. We derived a network of nodes supporting WM performance from the fMRI data and then applied a graph theory analysis to the resting data to test for group differences in coherence in regions associated with WM performance. We hypothesized group differences in task-related activation with reduced measures of topological efficiency in the underlying network supporting WM functioning, which would serve as evidence for the long-term consequences of PDE on neural functioning in an important cognitive domain.

2. Methods

2.1. Participants

We recruited 12 to 15-year-old participants with intrauterine exposure to cocaine and/or heroin from a larger longitudinal study of drug-using women and their infants at a university hospital serving a predominately inner-city, African American population (Nair et al., 2008). Women were eligible in the original study if they or their infants had a urine toxicology screen at birth positive for cocaine and/or heroin or a self-reported history of cocaine and/or heroin use during pregnancy ($\geq 2\times$/week), and their infants were ≥ 32 weeks gestational age and 1750 g birth weight. The initial enrollment included 265 women who met eligibility. Non-drug-exposed CC participants were recruited at 5 years of age ($n = 70$) or 14 years of age ($n = 24$). The CC participants were born in the same hospital as the PDE group, with negative toxicology screens, no history of drug use in the mother's medical records and denial of drug use by the mother. At the early adolescent follow up, 76 PDE and 62 CC were in the main study and approached for the imaging study if they met the additional criteria of no neurological or medical illness (e.g., diabetes, HIV, endocrinopathies, epilepsy, anemia or hypertension) that might confound data interpretation, no regular use of medications that might affect the imaging results (e.g., albuterol inhaler within 24 h of scan session) and no pregnancy or current illegal drug use (both verified by urine screens). At the time of the imaging study, none of the participants had been diagnosed with a psychiatric disorder or were receiving psychotropic medications. Left-handed participants were included, as subtle differences in PDE may affect handedness preference (Olsen, 1995). Of the original sample, 45% were ineligible and 68% of eligible participants were scanned.

The final cohort of 47 youths (27 PDE and 20 CC, after excluding one PDE for excessive movement) did not differ by exposure in age, gestational age, sex, IQ, birth head circumference and handedness, but differed on percent in continuous maternal care from birth to 6 years old, prenatal exposure to alcohol and cigarettes and birth weight and length (see Table 1). The resting network analysis included one fewer PDE and CC participant due to a participant request to stop the scan session early and a technical problem respectively. The groups remained similar in age, sex, IQ, birth head circumference and handedness without these two participants. WM behavioral data were missing for one CC subject due to a computer malfunction, however data from the behavioral practice suggested adequate performance, thus the imaging data were retained for all 47 participants. In this sample 12/27 were exposed to both heroin and cocaine, 13/27 were exposed to cocaine but not heroin and 2/27 were exposed to heroin but not cocaine. Our cohort is consistent with the majority of studies in PDE in that there was poly-substance abuse (e.g., (Rao et al., 2007; Li et al., 2011)),(see Buckingham-Howes et al.(2013) for a review) in mothers during pregnancy including exposure to non-illicit substances (e.g., nicotine). As Lester (1998) and Bauer et al.(2002) demonstrated polydrug experience is much more common than use of a single drug during pregnancy when the mother is using illicit drugs and therefore, illicit drug use is typically now considered polydrug exposure. The Bauer analysis of data from 11,811 mothers in the Maternal Lifestyle Study (Bauer et al., 2002) found that 93% of women using cocaine or opiates admitted to using other substances, such as alcohol or tobacco, that are known to produce negative outcomes on a fetus.

Participants and caregivers received gift certificates to compensate their time. Parents/guardians gave written informed consent;