

## EEG Source Localization and Attention Differences Between Children Exposed to Drugs in Utero and Those with Attention-Deficit/Hyperactivity Disorder: A Pilot Study

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### Abstract

**Introduction:** Intrauterine drug exposure (IUDE) including neonatal abstinence syndrome (NAS) is a group of problems that occur in a newborn exposed to drugs in the womb. Currently, there is no consensus on diagnostic criteria for addressing the cluster of problems present in children suffering from IUDE. The current data sought to examine differences between IUDE and attention-deficit/hyperactivity disorder (ADHD) clients to elucidate specific differences between these groups in the Conners Continuous Performance Test (CPT-3/K-CPT) and EEG source localization data using standardized low-resolution electromagnetic brain tomography (sLORETA).

**Methods:** This study utilizes archived data from two groups 14 IUDE and 9 clients with standing diagnosis of ADHD between the ages of 4 and 13 without the presence of fetal alcohol syndrome (FAS). All clients completed a standard protocol to assess functional domains, including diagnostic interview, review of records, and tests of attention, executive functions, and psychological status. IUDE clients at time of initial assessment were taking one or more medications. ADHD clients consisted of medicated and unmedicated individuals. **Results:** Significant differences were found between resting-state baseline sLORETA parameters in temporal, limbic, and precuneus regions. **Conclusions:** IUDE presents a growing problem in the United States due to current opioid problems, and it is imperative to accurately classify these children according to this specific set of problems. sLORETA assessment may be useful as one marker of IUDE. Directions for future treatment paradigms are discussed as well as potential applications of neurofeedback and learning.

**Keywords:** intrauterine drug exposure; EEG; LORETA; sLORETA; attention deficits; neurophysiology

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### Introduction

Prenatal exposure to drugs of abuse (illicit, legal, or prescribed) has been a major public health concern for decades and is subsumed by the term *intrauterine drug exposure* (IUDE). In recent years the opioid epidemic and its effects have increased attention to this crisis. It is estimated that 5.9% of pregnant women engage in illicit drug use; thus, it is difficult to convey the very high need for specific diagnostic and

treatment paradigms to aid these children across the developmental continuum until one has encountered them in the clinical setting. The smallest victims of the opioid and polydrug exposure epidemic are underserved and present great challenges to socioeconomic, healthcare, and education systems. An extensive review of prenatal drug exposure and descriptive patterns of effects of substances on the developing brain provides a well-done knowledge base (Ross, Graham, Money, & Stanwood, 2015),

with projected rates of exposure and substance specific characteristics. Numerous studies have described behavior and attentional problems in children exposed to drugs in utero as well as associated patterns in overall cognitive functioning (Butz, Pulsifer, Leppert, Rimrodt, & Belcher, 2003; Franck, 1996; Freeman, 2000; Kelley, 1992; Kne, Shaw, Garfield, & Hicks, 1994; Mayes, Cicchetti, Acharyya, & Zhang, 2003; McNichol, 1999). The sequelae of IUDE include deficits of sustained attention, language, social and emotional comprehension and affect regulation, social executive, and adaptive functions. IUDE includes neonatal abstinence syndrome (NAS) and fetal alcohol spectrum disorder (FASD). Notably, FASD has surpassed genetic anomalies as the leading contributor to mental retardation in North America (Nash, Sheard, Rovet, & Koren, 2008; Ross et al., 2015). Disruptions to numerous systems of the body may accompany IUDE including motor slowing, gastrointestinal difficulties, cardiovascular issues, and other disrupted homeostatic and regulatory functions (Eiden et al., 2009; Kleiber et al., 2014; Li et al., 2009; Wu, Yan, Qu, Feng, & Jiang, 2012; Zhao et al., 2015).

IUDE may produce negative effects on neural proliferation, migration, dendrite growth, and axonal elongation (Geng, Salmeron, Ross, Black, & Riggins, 2018; Riley, Kopotiyenko, & Zhdanova, 2015; Roitbak, Thomas, Martin, Allan, & Cunningham, 2011; Yip et al., 2014), as well as the disruption of the functional integrity of neural networks (Chater-Diehl, Laufer, Castellani, Alberry, & Singh, 2016; Posner & Rothbart, 2007; Schweitzer et al., 2015; Willford, Singhabahu, Herat, & Richardson, 2018). Studies of neonatal electroencephalogram (EEG) have shown delayed maturation and reduced hemispheric functional connectivity in IUDE children at 1 month of age (Akyuz et al., 2014; Conradt et al., 2014; Fisher et al., 2011; LaGasse et al., 2011; Lester, 2000; Lester et al., 2012). IUDE children also show characteristics of attention-deficit/hyperactivity disorder (ADHD), tend to have poorer performance in an attention test battery and show EEG alterations in P300 and N200 event-related potential (ERP) measures. These findings suggest that there may be deleterious long-term effects of prenatal drug exposure on executive function domains of attention, classification, and decision-making (Jaeger, Suchan, Schölerich, Schneider, & Gawehn, 2015). Studies of prenatal development have shown important interdependencies between the insula and amygdala in affective and social adaptivity (Bellucci, Feng, Camilleri, Eickhoff, & Krueger, 2018; Di

Cesare, Marchi, Errante, Fasano, & Rizzolatti, 2018; Grecucci, Giorgetta, Bonini, & Sanfey, 2013; Klumpp, Post, Angstadt, Fitzgerald, & Phan, 2013). The interactions between these regions and the noted deficits suggest important to potential treatment paradigms for IUDE given the rate of growth in the prenatal period and disruptions in connectivity amongst these regions in adolescents and adults with IUDE or cocaine dependence (K. Li et al., 2013; Li et al., 2009; Z. Li et al., 2013; McHugh et al., 2013; McHugh et al., 2014; McHugh, Gu, Yang, Adinoff, & Stein, 2017). Differences in functional connectivity between insula, amygdala, orbitofrontal, anterior cingulate, and sensorimotor cortices have been implicated in behavioral issues including attention and arousal deficits found in IUDE children (Grewen, Salzwedel, & Gao, 2015; Salzwedel et al., 2015). Connectivity issues associated with the consequences of IUDE involve numerous regions and functions. Of these, the orbitofrontal, amygdala, insula, sensorimotor, anterior cingulate, cuneus, precuneus, inferior parietal, subcortical, and limbic regions are also found disrupted in adolescent and adult populations with substance use disorders (SUD). IUDE children have shown reduced global brain volume as well as regional differences in the cortex, amygdala, nucleus accumbens, cerebellum, brainstem, and basal ganglia. White matter volume and disruptions in functional connectivity at rest have been noted in IUDE, as well as associations with cognitive deficits related to processing speed, mathematics ability, executive functions, and eye-blink conditioning (Adinoff et al., 2015; Grewen et al., 2015; Lotfipour et al., 2010; McHugh et al., 2017; Rando, Chaplin, Potenza, Mayes, & Sinha, 2013; Riggins et al., 2012; Roussotte et al., 2012; Salzwedel, Grewen, Goldman, & Gao, 2016; Salzwedel et al., 2015; Tamnes et al., 2010).

The effects of IUDE opioid and polydrug exposure on the brain continue into childhood, and data have shown reduced cortical volume and thinner layer surface than normative controls (Nygaard et al., 2018). It has also been proposed that many of the regulatory difficulties found in these children may not be fully actualized until they begin the education process. These problems are proposed to increase after the age of 4 and progress over the course of further development. The reasons for this increase are suggested to include the increasing complexity of social, educational, and adaptive demands and the lack of functional integration of multiple concepts by these children. It has been reported that 36% of individuals exposed to substances prenatally are likely to receive a diagnosis of ADHD as contrasted to

2% of nonexposed controls (Nygaard, Slinning, Moe, & Walhovd, 2016). In the current data set, 99% of the IUDE population had received a diagnosis of ADHD—primarily combined type prior to admission—and 96% of these children were being treated with traditional and nontraditional pharmacological agents.

Low-resolution electromagnetic brain tomography (LORETA) is a method of probabilistic source estimation of EEG signals in a standardized brain atlas space utilizing a restricted inverse solution (Pascual-Marqui, Esslen, Kochi, & Lehmann, 2002; Pascual-Marqui et al., 1999). LORETA and standardized LORETA (sLORETA) have been used to examine EEG sources in depression (Pizzagalli, Oakes, & Davidson, 2003), in epilepsy (Zumsteg, Wennberg, Treyer, Buck, & Wieser, 2005) and to evaluate temporal changes associated with differential task-specific default network activity (Cannon & Baldwin, 2012). LORETA has been adapted to provide real-time feedback to participants in order to facilitate operant conditioning. For example, LORETA investigation has documented learning of improved regulation of the current source density in a specific frequency range at a specific region of training within Talairach space. The effects of LORETA neurofeedback have also been replicated (Cannon, Congedo, Lubar, & Hutchens, 2009; Cannon et al., 2007; Cannon, Lubar, Sokhadze, & Baldwin, 2008), and seen increasing use clinically (Cannon, 2014; Cannon, Strunk, Carroll, & Carroll, 2018). In recent years LORETA and the standardized version have been shown to localize medial default network regions with complementary accuracy, as well as detecting anomalies in network connectivity (Cannon, Kerson, Hampshire & Coleman, 2012).

It is important to consider the greatest common factors (e.g., sustained attention, mood regulation, social and emotional delays, and specific cognitive issues) found in IUDE populations across specific substances and then progress on a course to influence the brain in such a way as to facilitate learning and self-regulation of one or more of the identified regional connective hubs to adjust the brain's performance (e.g., neural efficiency) and facilitate data acquisition, encoding, and learning. The most salient symptoms found in IUDE across the developmental continuum include emotional dysregulation and reactivity, developmental delays, motor slowing, impulsivity and hyperactivity, difficulties with sustained attention, impaired executive functions and self-regulation, deficient social comprehension and interactions, social

development delays, learning impairment, and processing speed difficulties.

This study sought to examine differences between groups of children with IUDE and a contrast group of children with ADHD. We hypothesized that there would be significant differences on the functional measure of attention and notable group differences between EEG sources in an eyes-opened baseline sample using sLORETA.

## Participants

This study examined archived data from 23 (10 female) children and early adolescent clients with mean age 8.38,  $SD = 2.80$ , (ages 4–13 years) seen at an outpatient mental health clinical in Knoxville, TN. Fourteen of the clients were exposed to drugs of abuse in utero without the presence of fetal alcohol syndrome (FAS) with mean age 7.86,  $SD = 2.79$ , (ages 4–13). All IUDE clients (7 female) would be classified as polydrug exposed. All IUDE clients had been removed from biological parents and had been adopted by family members or foster parents. 99% of the IUDE group had received a prior diagnosis of ADHD. The second group (3 female) were clients admitted for ADHD with three having comorbid generalized anxiety disorder (GAD) with mean age 10,  $SD = 2.29$  (ages 6–13). There were no reports or records to indicate the ADHD children had been exposed to drugs or alcohol during the prenatal period. The IUDE group on average was younger than the ADHD group. The differences did not reach significance in this study population with  $t(21) = -1.91$ ,  $p = .067$ . There was no difference for gender between groups,  $t(21) = -0.438$ ,  $p = .66$ , and medications showed no differences,  $t(21) = 0.249$ ,  $p = .806$ . The IUDE group was taking medications for ADHD symptoms, which included Clonidine, Adderall, Concerta, Tenex, Straterra, and combinations thereof. The ADHD group was taking Ritalin or Adderall. All assessment data were reviewed with parents and informed consent was reviewed and signed.

## Methods

This study was conducted with approval from an institutional review board (IRB) at Maryville College, Maryville, TN, to examine attention and drugs of abuse in utero. All clients completed a standard protocol for admission to the program, including a diagnostic interview, prior record review, and psychological and neurophysiological measures. This manuscript examines select components of this

protocol for contrasting the two clinical groups. The clients completed the Conners Kiddie Continuous Performance Test, 2nd Edition, (K-CPT 2); or the Conners Continuous Performance Test 3rd Edition (CPT 3). Both are computerized performance tests. The K-CPT 2 is a 7.5-min performance-based assessment that uses pictures of objects familiar to young children, whereas the CPT 3 is a 14-min, 360-trial administration in which respondents are required to respond when any letter appears, except the nontarget letter “X” (MHS Assessments, Tonawanda, NY).

The clients were prepared for EEG recording using a measure of the distance between the nasion and inion to determine the appropriate international 10–20 system cap size for recording (Blom & Anneveldt, 1982). The head was measured and marked prior to capping for placement of frontal electrodes. The ears and forehead were cleaned for recording with a mild abrasive gel to remove any oil and dirt from the skin. After fitting the caps, each electrode site was injected with an electrode gel and prepared so that impedances between individual electrodes and each ear were less than 10 K $\Omega$ . The data were collected and stored utilizing the Deymed TruScan amplifier and acquisition software (Deymed Diagnostics, Payette, ID) with a band-pass set at 0.5–64 Hz, and a sampling rate of 256 samples per second. Standard 6-mm tin cup ear electrodes were used. All recordings were carried out in a quiet, comfortably lit, clinical neurofeedback room at the clinic. Lighting and temperature were held constant for the duration of the data collection. We elected to use eyes-opened baseline recordings, as many of the IUDE population struggled to keep the eyes closed during this condition, while others could not maintain the condition of keeping their eyes closed for more than a few seconds at a time.

### Data Processing

The EEG stream was edited using Eureka 3 software (NovaTech EEG, Mesa, AZ). EEG editing and resampling was obtained by means of natural cubic spline interpolation (Congedo, Özen, & Sherlin, 2002). All active task conditions and baseline data were processed with particular attention given to eye movement and jaw tension in frontal and temporal leads. All episodic eye blinks, eye movements, teeth clenching, jaw tension, body or neck movements, and possible electrocardiogram (EKG) artifacts were removed from the EEG record. Fourier cross-spectral matrices were then computed and averaged over 75% overlapping 4-s artifact-free epochs, which

resulted in one cross-spectral matrix for each subject for each discrete frequency. The EEG data were analyzed utilizing the following frequency domains: delta (1.0–4.0 Hz); theta (4.0–8.0 Hz); alpha 1 (8.0–10.0 Hz), alpha 2 (10.0–13.0 Hz) and beta (13.0–32.0 Hz).

### Data Analyses

In order to assess the electrophysiological differences between groups, sLORETA was employed to localize the sources of scalp EEG power spectra. The sLORETA solution space is restricted to the cortical gray matter in the digitized Montreal Neurological Institute (MNI) atlas with a total of 6,329 pixels with 5mm<sup>3</sup> spatial resolution (Pascual-Marqui et al., 2002; Pascual-Marqui et al., 1999). To test the specific hypotheses of the differences in cortical activity between groups, independent *t*-tests were used. The average common reference was computed prior to the sLORETA estimations. The calculated tomographic sLORETA images correspond to the estimated neuronal generators of brain activity within each frequency domain (Frei, Gamma, Pascual-Marqui, Lehmann, Hell, & Vollenweider, 2001). This procedure results in one 3D LORETA image for each subject for each frequency range. The significance threshold is based on a randomization test utilizing 5,000 data randomizations.

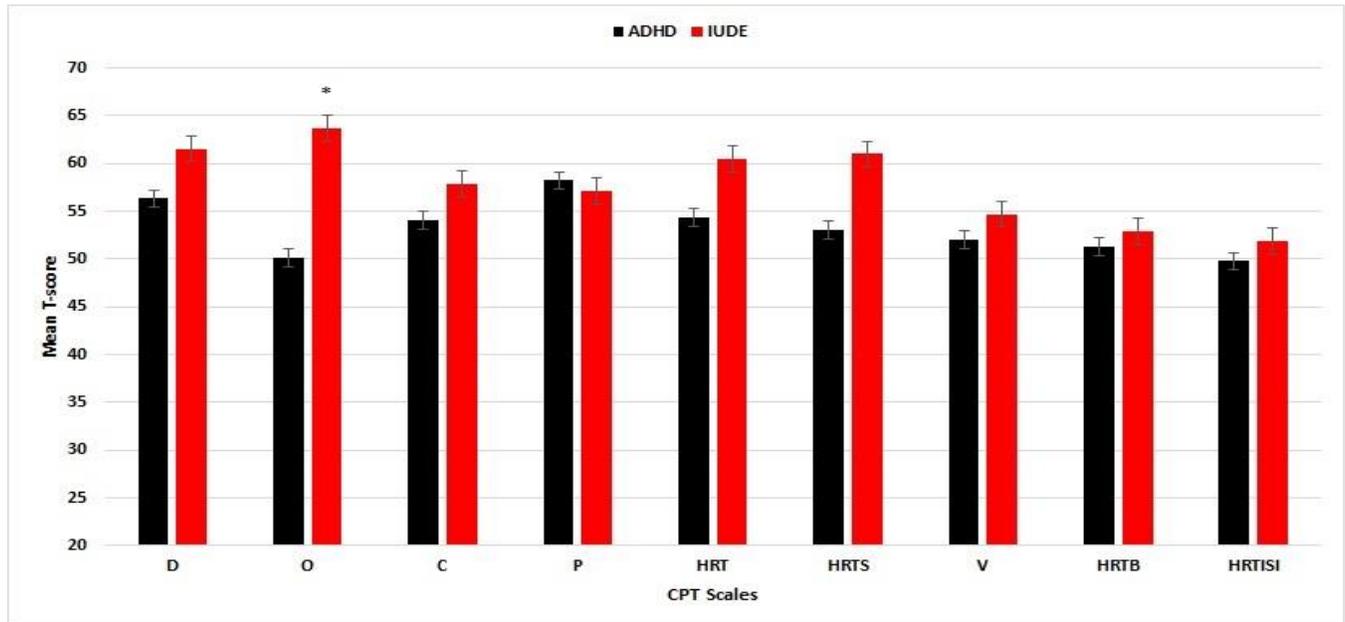
The Conners CPT assessment includes nine scales to measure distractibility, omissions, commissions, perseverations, reaction time, reaction time standard deviation, variability, reaction time block change, and reaction time for interstimulus intervals. The scores are expressed in *T*-scores with higher scores indicating greater severity. We utilized independent *t*-tests to contrast the nine scales of the CPT between groups.

### Results

Figure 1 shows the mean *T*-scores and standard deviation for each CPT scale, side by side for each group. The test results show elevations on nearly all scales for the IUDE group as contrasted with the ADHD group except for perseverations. The only scale that showed significance between IUDE and ADHD groups was omissions, yet results of all scale differences are important to the overall description. The results show distractibility (D),  $t(21) = 1.65$ ,  $p = .113$ ; omissions (O),  $t(21) = 2.62$ ,  $p = .016$ ; commissions (C),  $t(21) = 0.917$ ,  $p = .370$ ; perseverations (P),  $t(21) = -0.195$ ,  $p = .847$ ; reaction time (HRT),  $t(21) = 1.66$ ,  $p = .111$ ; reaction time

standard deviation (HRTS),  $t(21) = 1.57, p = .130$ ; variability (V),  $t(21) = 0.361, p = .722$ ; reaction time block change (HRTB),  $t(21) = 0.220, p = .828$ ; and reaction time for interstimulus intervals (HRTISI),  $t(21) = 0.570, p = .575$ . The results show clear

differences between the two groups with IUDE performing with less accuracy and speed than the ADHD group on most measures except for perseverations.



**Figure 1:** Contrast results between groups for scales on the Conners CPT. Red is the IUDE group and black the ADHD group. From left to right the measures are distractibility (D), omissions (O), commissions (C), perseverations (P), reaction time (HRT), reaction time standard deviation (HRTS), variability (V), reaction time block change (HRTB) and reaction time for interstimulus intervals (HRTISI). \*Only the omission scale was statistically significant at  $p = .016$ .

Table 1 shows the sLORETA statistical contrasts between groups (IUDE > ADHD). In the table from left to right are the frequency range, sLORETA x, y, and z coordinates, hemisphere, anatomical label/Brodmann area (BA),  $t$  value for the IUDE

versus ADHD contrasts, and its probability. From top to bottom are the frequency domains and coordinates for both the maximum and minimum levels of current source density (CSD) at specific regions of interest for sLORETA findings.

**Table 1**  
sLORETA Results for Contrasts IUDE > ADHD

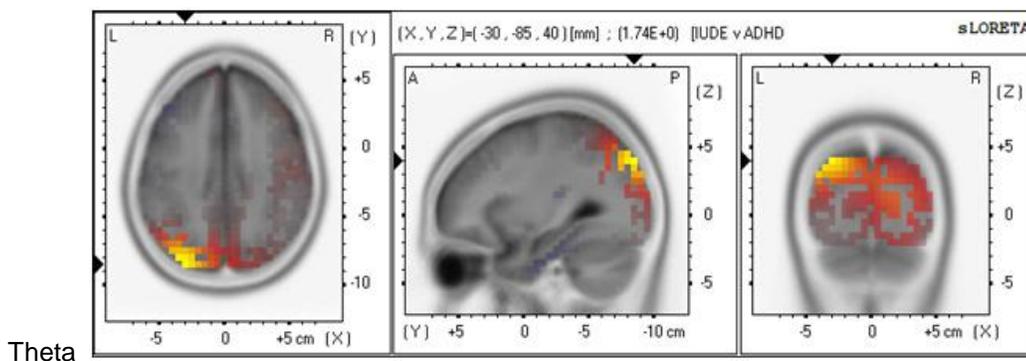
Frequency Range		X, Y, Z Coordinates	Hemisphere	Anatomical Label	t Value	p
Delta		–		–	–	ns
Theta	Max	–30, –85, 40	L	BA 19, precuneus, parietal	1.74	.096
	Min	–35, –15, –35	L	BA 20, uncus, limbic	–0.74	ns
Alpha 1	Max	–30, –85, 40	L	BA 19, precuneus	2.11	.047*
	Min	–40, 35, 35	L	BA 9, superior frontal gyrus	–1.65	.113
Alpha 2	Max	70, –35, –5	R	BA 21, middle temporal gyrus	0.048	ns
	Min	–50, –70, 35	L	BA 39, angular gyrus	–2.37	.027*
Beta	Max	–40, 35, 35	L	BA 9, superior frontal gyrus	2.16	.042*
	Min	15, –100, 15	R	BA 18, cuneus	2.32	.030*

Note: \*p values are statistically significant.

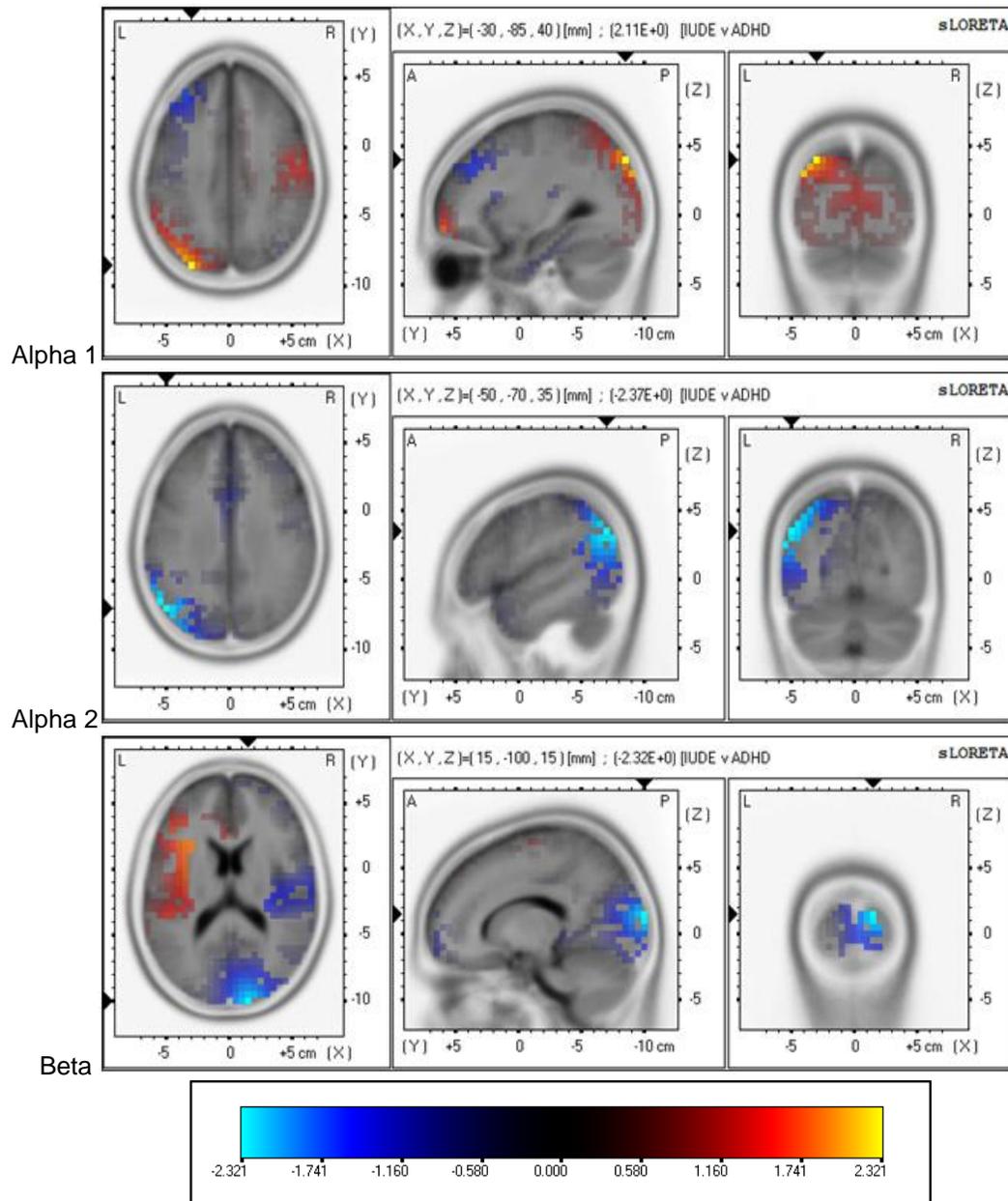
In Figure 2 the images shown are horizontal, sagittal, and coronal slices of the brain in MNI space. There were no significant effects for gender in any of the measures. CSD differences were not significant for the delta frequency bin. Theta CSD was elevated in the IUDE group in posterior parieto-occipital regions but did not reach statistical significance. The lower range of alpha 1 CSD did show significant elevations

in IUDE compared to ADHD in BA 19, posterior parietal regions, notably the same region of interest as theta power. Alpha 2 CSD showed significantly less CSD in IUDE as compared to ADHD at BA 39, angular gyrus. Beta CSD showed significant elevations in IUDE as compared to ADHD in left BA 9, superior frontal gyrus, and less CSD in right BA 18, cuneus.

sLORETA Regions of Interest Contrasts IUDE > ADHD



## sLORETA Regions of Interest Contrasts IUDE &gt; ADHD



**Figure 2.** sLORETA contrast images for IUDE group compared to ADHD group. From left to right are horizontal, sagittal, and coronal slices from the MNI atlas. The brighter the colors the greater the CSD amplitude difference between groups (red, yellow, orange) whereas the darker the colors indicate less CSD amplitude between groups (light blue, blue). Delta showed no differences between groups. Theta CSD levels between groups neared significance with  $p = .096$ . The lower end of alpha power showed significantly elevated CSD in IUDE as compared to ADHD with  $p = .047$ . Alpha 2 showed significantly less CSD in IUDE as compared to ADHD with  $p = .027$ . Beta CSD showed differences between groups with elevated CSD in left BA 9 superior frontal gyrus (SFG) with  $p = .042$ , and less CSD in right cuneus, BA 18 with  $p = .030$ . The last row in the figure shows the scale for the contrast results for IUDE compared to ADHD.

## Discussion

The present findings are the first of their kind showing differences between children with IUDE compared to children with ADHD using sLORETA. The current data show children with IUDE perform less well than children with ADHD on the Conners CPT. Specifically, IUDE children showed more omissions, to a statistically significant degree. Given the CPT and classification procedures *T*-scores of 60 or above would produce atypical results for the test and increase the likelihood of positive classification in the ADHD index. With the pattern of results, it is not surprising that 99% of the IUDE population had received a prior diagnosis of ADHD at or before the age of 5, even though 96% of the IUDE population was taking medications for ADHD at the time of admission to the program. These medications included Clonidine, Adderall, Concerta, Tenex, Straterra, and combinations thereof. Prior research has shown that IUDE children exhibit extreme difficulties with self-regulation across numerous domains associated with attention including arousal, emotional reactivity, sustained attention (Accornero et al., 2007; Gabriel & Taylor, 1998; Garavan et al., 2000; Gendle et al., 2003; Jaeger et al., 2015; Noland et al., 2005; Slinning, 2004; Willford et al., 2018), and in some cases at our clinic a lack of understanding about the importance and significance of giving an appropriate effort on these types of tests. Close monitoring during test administration in these children and clear instructions are good clinical practice to increase the accuracy of the results. It is also important to consider that the IUDE children will not meet all criteria for ADHD, and in many cases the more pronounced issues are impulsivity and emotional reactivity, motor slowing (reaction time), and difficulties with sustained attention (Nygaard et al., 2016).

The sLORETA contrasts show significant CSD differences between IUDE and ADHD groups in the alpha and beta bands. Theta (4.0–8.0 Hz) showed a nonsignificant trend toward elevated CSD in IUDE as contrasted with the ADHD group at BA 19 and associated posterior regions. This is an important finding given the indications that excess theta power has been associated with a higher likelihood of having ADHD and the potential comodulated slowing between theta and alpha power (Bink et al., 2015; Gloss, Varma, Pringsheim, & Nuwer, 2016; Koehler et al., 2009; Tye, Rijdsdijk, & McLoughlin, 2014). Mazaheri and colleagues (2010) found a functional disconnection between frontal and occipital regions in children with ADHD as contrasted with normal

controls and suggested a deficit in top-down regulated attentional processes. Cannon (2014) showed specific inverse correlations between posterior alpha and frontal theta in children with ADHD.

Maturation of the alpha rhythms is associated with an increase in frequency and reduction in amplitude between ages of 3 and 10. The significant difference between IUDE and ADHD groups in lower alpha CSD is found at BA 19 (precuneus and associated posterior areas). Interestingly, alpha and theta power showed elevations in the same area with differing effects in a hypothesized self-regulation network (SRN) ipsilateral and contralaterally (Cannon, 2014; Cannon, Strunk, Carroll, & Carroll, 2018), although not reaching significance. Alpha rhythms are suggested to perform as other EEG phenomena and exhibit an opposite relationship between amplitude and frequency. For example, the higher the amplitude the slower the signal becomes. One can think of this in terms of information being carried along a signal. The greater the peaks and valleys, the slower the information travels. This carrier signal and these patterns are important to numerous processing speed and learning processes (Cannon, 2015). Certain drugs of abuse and conditions may cause reductions of alpha frequencies together with increased amplitudes, while others may be more associated with increased amplitude of low-frequency beta activity superimposed on scalp alpha rhythms (Nunez, 2006; Sokhadze, Cannon, & Trudeau, 2008). Although it is difficult to ascertain specific EEG patterns related to exposure to drugs of abuse in children, adolescent and adult populations provide replicable information concerning these patterns. Alpha 2 (10–13 Hz) shows a significant deficit in IUDE children as contrasted with the ADHD group in BA 39 and associated cortex. The angular gyrus (BA 39) has broad implications associated with receptive language, perceptual, memory, and sensory processes as well as learning (Bonnici, Cheke, Green, FitzGerald, & Simons, 2018; Boylan, Trueswell, & Thompson-Schill, 2017; Bravo et al., 2017; Matchin, Liao, Gaston, & Lau, 2019; Thakral, Madore, & Schacter, 2017; van der Linden, Berkers, Morris, & Fernández, 2017; van Kemenade, Arikan, Kircher, & Straube, 2017). Studies have examined alpha EEG power in attentional, saccadic, and cognitive processes, although the higher band of alpha power is often described as having no association with the maintenance of attention (Babiloni et al., 2004; Dockree, Kelly, Foxe, Reilly, & Robertson, 2007; Jaime et al., 2016; Klimesch, Doppelmayr, Russegger, Pachinger, & Schwaiger,

1998; Kornrumpf, Dimigen, & Sommer, 2017; Sauseng et al., 2005) and therefore may play a more important role in encoding the stream of information being attended to (e.g., related to learning; Fell et al., 2011; Lenartowicz et al., 2016; Molle, Marshall, Fehm, & Born, 2002; Wang, Kamezawa, Watanabe, & Iramina, 2017), and associated language and working memory indices.

Beta CSD shows elevations in IUDE as compared to ADHD in left superior frontal gyrus (SFG) and insular cortex, and in the right cuneus (BA 18). The SFG and associated cortex has been implicated in motor, language integration, impulse control, and speech production, as well as executive and social functions (Fujii et al., 2015; Hu, Ide, Zhang, & Li, 2016; W. Li et al., 2013; Ookawa et al., 2017; Tsujii, Sakatani, Masuda, Akiyama, & Watanabe, 2011; Vogel et al., 2016). BA 18 and associated regions are implicated in visual and perceptual processes, as well as symptoms of anxiety, panic, posttraumatic stress, and other psychiatric issues (Heesink et al., 2017; Lai & Wu, 2013; Parise et al., 2014; Whitford et al., 2012; Yu et al., 2018).

The insular cortex is typically divided into three subsections—the anterior, middle, and posterior. The anterior insula is proposed to be associated with subjective intensity and self-awareness concerning experience and perception. The middle insula is suggested to be associated with polymodal integration and may also play an important role in motor processes and regulation. The posterior insula is proposed to be associated with interoceptive processes and awareness of the bodily state, as well as potential in attention, sensory, and social processes (Di Cesare, Pinardi, et al., 2018; Duval, Joshi, Russman Block, Abelson, & Liberzon, 2018; Schiff et al., 2018; Wang et al., 2018; Zhang et al., 2019). It is of note that most differences, even those not reaching significance, were found in the left hemisphere. In prior research it has been shown that important interactions exist between frontal theta and posterior alpha power distributions in ADHD (Cannon, 2014). It appears that IUDE children show an inverse pattern of EEG CSD levels as contrasted with ADHD samples, distinct parietal and associated network and parieto-frontal interactions, and associated social and emotional issues found in ADHD samples (Castellanos, 2015; Castellanos & Elmaghrabi, 2017; Castellanos & Hyde, 2010; Castellanos & Proal, 2012; Cortese et al., 2012; Petrovic & Castellanos, 2016).

Further, data have shown that prenatal exposure can alter development of opioid and dopaminergic systems in striatal and mesocorticolimbic areas given there is a rapid and massive growth and organization process during prenatal development (Wang, Dow-Edwards, Anderson, Minkoff, & Hurd, 2006). Data have reported reductions in bilateral caudate and left anterior insula connections with the cerebellum, as well as right caudate connectivity disruptions with occipital and fusiform regions in IUDE as contrasted with nonexposed infants (Grewen et al., 2015; Salzwedel et al., 2016). Additional data have shown disruptions in connectivity amongst frontal, amygdala, insula, thalamus, and anterior cingulate regions. These functional associations involving the thalamus are important to arousal regulation, sustained attention, detection of salient qualities of stimuli, and working memory (Salzwedel et al., 2016).

The current data are in line with other neuroimaging data concerning IUDE and its effects on the brain and attentional processes. There have been numerous studies indicating substance exposure in utero impacts the developing brain in significant fashion. The orbitofrontal region has been implicated in learning, sensory processing, reward prediction, and behavioral responses (McDannald, Jones, Takahashi, & Schoenbaum, 2014; Sadacca et al., 2018; Wikenheiser, Marrero-Garcia, & Schoenbaum, 2017). Social cognition and the perception of social interactions and behavioral and emotional responses are also reported to involve orbitofrontal, insula, and default network engagement and potential integrity anomalies (Li et al., 2011; Weng et al., 2010) that persist into adolescent years. Social and emotional processes involve a complex interaction between brain regions and networks, and substance exposure creates a complex disruption in these processes that delays the maturation and adaptive development of these vital functions (Estelles, Rodríguez-Arias, Maldonado, Aguilar, & Miñarro, 2005; Fernandes, Rampersad, & Gerlai, 2015; Greenwald et al., 2011; Kabir, Kennedy, Katzman, Lahvis, & Kosofsky, 2014; Kully-Martens, Denys, Treit, Tamana, & Rasmussen, 2012; Sobrian & Holson, 2011). There are data suggesting IUDE impacts the maturation of the brain and its contributions to behavior and attentional processes (Chiriboga, Starr, Kuhn, & Wasserman, 2009; Church, Overbeck, & Andrzejczak, 1990; Hammer & Scheibel, 1981; Tamnes et al., 2010; Walhovd, Tamnes, & Fjell, 2014); however, there are few data providing behavioral and standardized assessment examples of what these deficits may resemble in the clinical setting.

In the clinical environment, one of the most prevalent issues reported by parents and teachers is the discrepancy between age-expectation of behavior and actual social/emotional regulation maturation which can differ by years in context. For example, a 10-year-old throwing tantrums, hitting, or breaking things in response to environmental demands and not getting what he/she wants is age inappropriate. Likewise, there may be behaviors present such as taking others' property, or performing acts that are dangerous with an impairment in understanding the inherent danger (e.g., why is it dangerous to play with fire in your bedroom? "It is against the rules and I am not 18 yet"). In future research paradigms it would be useful to attempt to determine the greatest common factors impacted by IUDE including regional brain differences, cognitive or attentional processes, and social and emotional delays. These issues are present in most studies examining the effects of IUDE. However, in order to begin the first step in planning interventions these commonalities across substances must be uncovered and targeted (McDannald et al., 2014; Morrow et al., 2006). In this study's sample, the first intervention in 99% of the IUDE children was for ADHD. This is an important finding due to the lack of specific criteria for diagnosis and treatment for this growing population with IUDE. It is also important to consider the increased risk in IUDE of cognitive deficits, antisocial behaviors, substance abuse, academic and educational failure, and emotional/mood disorders (Li et al., 2011), not to mention the side effects of medications on these children.

The current study has several limitations, which suggest steps for subsequent research. First, a larger sample size for both IUDE and ADHD groups will provide statistical tests with greater power to detect real differences between groups. Second, a healthy normal control group will also provide a contrast that shows the clinical significance of the IUDE group. Third, a contrast between subgroups of IUDE children with and without exposure to adverse childhood experiences (ACE) would be of interest. Last, eyes-closed resting states are relevant to evaluate.

Prenatal drug exposure is not a new problem; however, over the past few decades more attention has been directed to it. The numbers of children exposed to drugs prenatally is growing, not all of whom are born addicted. IUDE children do exhibit attentional difficulties that strongly increase the likelihood of an ADHD diagnosis. Sensory and auditory processing issues may also be present.

There are also major delays in social cognition and emotional regulation associated with a frontal, insula, and amygdala dysregulation that have been noted in numerous studies including this study data. The sLORETA findings in this study provide some insight into regions of the brain and frequency distributions that may serve as markers to monitor treatment methods or develop novel approaches to help this population including neurofeedback-based models (Cannon, Strunk, Carroll, & Carroll, 2018).

### Author Disclosure

Dr. Cannon directs a neurofeedback-based outpatient program for mental health and IUDE children. No other financial interests or financial support for this research exists.

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