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Investigating Maternal Brain Structure and its Relationship to Substance Use and Motivational Systems

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Substance use during pregnancy and the postpartum period may have significant implications for both mother and the developing child. However, the neurobiological basis of the impact of substance use on parenting is less well understood. Here, we examined the impact of maternal substance use on cortical gray matter (GM†) and white matter (WM) volumes and whether this was associated with individual differences in motivational systems of behavioral activation and inhibition. Mothers were included in the substance-using group if any addictive substance was used during pregnancy and/or in the immediate postpartum period (within 3 months of delivery). GM volume was reduced in substance-using mothers compared to non-substance-using mothers, particularly in frontal brain regions. In substance-using mothers, we also found that frontal GM was negatively correlated with levels of behavioral activation (i.e., the motivation to approach rewarding stimuli). This effect was absent in non-substance-using mothers. Taken together, these findings indicate a reduction in GM volume is associated with substance use and that frontal GM volumetric differences may be related to approach motivation in substance-using mothers.

INTRODUCTION

Maternal substance use represents a considerable public health concern, as many women who use substances during pregnancy continue into the postpartum period [1]. Although substance-using mothers demonstrate difficulties during interactions with their children [2-5], the underlying neurobiological basis of this is less well understood. Converging neuroimaging studies of parents report that brain regions critical to reward, emotion, and stress regulation are recruited when parents engage with infant stimuli [6-8]. In these same regions, a reduction in brain activity has been observed when substance-using mothers engage with infant stimuli [9]. This finding resonates with theoretical models that caretaking difficulties faced by substance-using mothers may reflect the dysregulation of reward and stress neurocircuitry [8,10]. This study investigated the impact of substance

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†Abbreviations: BIS, behavioral inhibition system; BAS, behavioral activation system; GM, gray matter; MRI, magnetic resonance imaging; WM, white matter; NIDA, National Institute on Drug Abuse; MPRAGE, magnetization prepared rapid gradient echo; ABC, Atlas Based Classification; CSF, cerebrospinal fluid; BG, background; ICV, intracranial volume; OFC, orbitofrontal cortex.

Keywords: substance use, addiction, maternal brain, gray matter, behavioral inhibition/behavioral activation

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use on maternal brain structure and examined whether individual differences in motivation were associated with structural differences between substance-using and non-substance-using mothers.

Parents contribute critically to their child's development [11]; therefore, adaptation of neural architecture to facilitate parenting may have an adaptive value from evolutionary and other perspectives. While functional MRI studies have begun to interrogate the maternal brain, to our knowledge, only one previous study has measured maternal brain structure, examining gray matter (GM) volume changes during the postpartum period [12]. This study found GM volume increased from 2 to 4 weeks postpartum to 3 to 4 months postpartum in multiple regions, including prefrontal and parietal cortex. Additionally, increases in GM volume in midbrain regions were related to mothers' self-reported positive thoughts related to their babies. These findings support the potential for neurobiological reorganization at a structural level in motherhood.

Substance dependence has been associated with changes in frontal-striatal circuitries. Reductions in GM, but not white matter (WM), volume have been observed in orbitofrontal, temporal, anterior cingulate, and insular regions in cocaine dependence [13]. Cocaine dependence also has been associated with reductions in ventral striatal GM [14], and methamphetamine dependence is associated with GM reductions in the medial frontal gyrus and insula [15]. A meta-analysis reported decreased GM volume in substance-dependent participants in the prefrontal cortex [16], with GM volumes in the inferior and middle frontal gyri associated inversely with longer histories of substance use. These structural findings converge with other data illustrating that frontal cortical function is associated with multiple components of addiction [17,18].

A recent model of parenting suggests a central role for motivation in guiding caretaking behavior in parents [8]. Therefore, understanding variability in motivational tendencies may provide insight into individual differences in caretaking in substance-using and non-substance-using parents. Converging work suggests two motivational systems underscore emotion and behavior: an approach system that drives behavior *toward* stimuli and an avoidance system that drives behavior *away* from stimuli [19]. These systems may map onto a behavioral activation system (BAS) and a behavioral inhibition system (BIS) that guide goal-directed behaviors [20][1]. The BAS is implicated in reward responding, guiding behavior toward desirable outcomes or stimuli. The BIS is implicated in responding to punishment, guiding behavior away from undesirable outcomes or stimuli. Notably, a recent study of non-parents evidenced BIS and BAS were associated with the neural response to infant stimuli [21] — supporting the value of examining motivational tendencies as they relate to parenting.

Carver and White [22] developed an assessment to capture variability in behavioral inhibition and activation with behavioral activation consisting of three components: 1) persistence pursuing goals (BAS-Drive); 2) engagement in seeking rewards (BAS-Fun Seeking); and 3) anticipation or response to reward receipt (BAS-Reward). The BAS is relevant to substance use, given that individuals high in BAS may be more likely to seek out and have a positive response to rewards (including drugs and alcohol) [23]. Consistent with this notion, cocaine- and heroin-dependent participants report higher BAS scores (BAS-Drive and BAS-Fun Seeking) than do healthy control subjects [23]. Furthermore, substance use in college students positively correlated with BAS scores, specifically BAS-Fun Seeking, while only a weak correlation was found between substance use and BIS scores [24]. BAS-Drive scores also have been associated with an increased desire and intent to drink, as well as an expectation to feel relief from drinking, in participants receiving inpatient alcohol treatment [25]. Elevated scores on the BIS and all BAS subscales have been associated with hazardous drinking in a community sample [26]. These studies suggest there may be an important coupling between substance use and motivational behavioral tendencies, particularly those relating to behavioral activation.

We examined GM and WM volumes in substance-using and non-substance-using mothers and whether structural brain differences would relate to general motivational behavioral tendencies (BIS/BAS). Given the potential damage from substance-use exposure to the developing or newborn infant, we broadly defined substance use to include any addictive substance used during pregnancy and/or postpartum. The purpose of this study was to investigate structural volumes and motivational tendencies in response to the presence (and absence) of an addictive process rather than the neurochemical effect of any one specific substance [9,27]. We hypothesized that perinatal (i.e., during pregnancy and/or up to 3 months postpartum) substance use would be related to differences in maternal brain structure, specifically decreased GM volume. Further, given the associations previously reported between BAS and substance use, we also hypothesized that GM volumes would be associated with BAS motivation in the substance-using mothers.

MATERIALS AND METHODS

Participants

The Human Investigations Committee at Yale School of Medicine approved all procedures, and the National Institute on Drug Abuse (NIDA) approved a Certificate of Confidentiality for this study. Sixty-six mothers were recruited through drug treatment and rehabilitation facilities, maternity wards, and posted flyers. All participants provided informed consent, and data were collected approximately 3 months (range 1-3 months) postpartum. Each

[1]A fight-flight system is also recruited in the presence of threat stimuli in the immediate environment [20].

mother was reimbursed $80 and given a gift for her baby. Substance-use status was determined by self-report and urine toxicology. Women were considered substance using (n = 31; mean age approximately = 25.77 years; SD = 4.89; 9 first-time mothers) if they used any substance of abuse during pregnancy and/or within the past 30 days at time of recruitment and/or positive toxicology screen at the time of visit. Substance-using mothers reported using only tobacco (n = 15), tobacco and other substances (n = 10, including marijuana, amphetamine, cocaine, heroin, alcohol, and/or other opiates), and marijuana only (n = 4). One mother self-reported using substances but did not disclose details, and one mother was in rehabilitation. Twenty-six mothers were single, two were married, two divorced, and one mother did not report marital status. Eight were Caucasian, 18 were African American, and five were Hispanic/Latino.

Non-substance-using mothers (n = 35; mean age approximately = 28.88 years; SD = 5.70; 27 first-time mothers) were free from tobacco or other substance use. Fourteen were single and 21 were married. Twenty-one were Caucasian, eight were African American, two were Asian American, two were Hispanic/Latino, and two mothers did not report race or ethnicity. Consistent with evidence that there are age-related effects on brain matter volume [28] and the age difference between groups reported here ($t(62) = 2.21$, $p = .03$), age was entered where appropriate as a covariate in analyses.

Behavioral Inhibition System and Behavioral Activation System (BIS/BAS) Scale

The BIS/BAS scale [22] is a valid and reliable 24-item self-report measure designed to capture individual variability in behavioral inhibition and activation [20]. Each item is rated on a 4-point likert scale, from "1 - strongly disagree" to "4 - strongly agree." Seven items capture behavioral inhibition, including, "If I think something unpleasant is going to happen, I usually get pretty worked up." Behavioral activation consists of three subscales: BAS-Drive ("When I want something, I usually go all-out to get it"), BAS-Fun Seeking ("I'm always willing to try something new if I think it will be fun"), and BAS-Reward ("When I get something I want, I feel excited and energized"). A BAS-total score indicates the sum of all BAS subscale scores.

Image Acquisition

Magnetization prepared rapid gradient echo (MPRAGE) images (176 slices, 256 x 256 mm field of view, 256 x 256 data acquisition matrix, 2.530 s repetition time, 2.77 ms echo time, 7° flip angle, bandwidth 179 Hz/pixel) were acquired with a Siemens Trio 3T scanner (Siemens AG, Erlangen, Germany).

Automatic Tissue Segmentation

Several methods have been developed for automatic segmentation of adult brain MRI data [29-31]. Pohl et al. [32] additionally augments tissue class segmentation by a detailed parcellation of neuroanatomical structures. We used a modified version of an atlas-moderated expectation-maximization method [31]. The tool, named Atlas Based Classification (ABC), was written in ITK (Insight Consortium, 2004) and made freely available to the scientific community via the NITRC platform [33,34]. The ABC tool takes single or multi-modal MR images as input and performs registration of a probabilistic atlas that serves as a spatial prior, bias correction, brain stripping, user-selected non-linear filtering, and multivariate classification combined into one integrated tool. Results include tissue probability maps p(category|x) for the categories of WM, GM, cerebrospinal fluid (CSF), and background (BG) and binary label maps of the maximum posterior classification, defined at each voxel location x. An additional category, the intracranial volume (ICV), is defined as the sum of WM, GM, and CSF. Subdivision into lobar regions was obtained by non-linear registration of a parcellation template to each subject's brain image, resulting in WM, GM, and CSF volumes per lobe. The ABC segmentation methodology previously has been applied in large clinical studies (e.g., of schizophrenia [35]) and validated in a multi-site human traveling phantom study that demonstrated coefficients of variation for GM and WM in the 1 percent range [36].

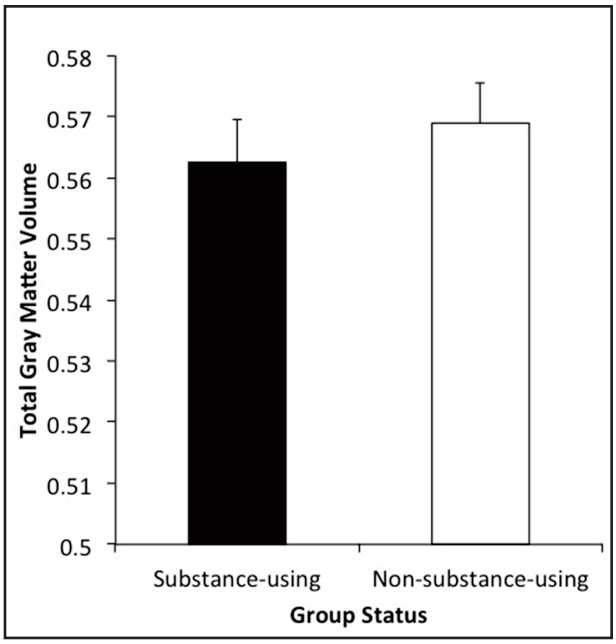

Figure 1. Mean normalized gray matter volume as a function of substance-use group, with error bars indicating one standard deviation from the mean.

Data Analysis

Dividing the individual structural values by the ICV for each participant was performed to normalize the data. Data from two mothers (one substance-using; one non-substance-using) were excluded after boxplots of the structural data confirmed they were outliers. Analysis first focused on com-

Table 1. Means and standard deviations for GM volume parcellation for each maternal group.

	Lobe Parcellation				
	Prefrontal	**Frontal**	**Parietal**	**Temporal**	**Occipital**
Non-SU mothers	.034 (.001)	.049 (.001)	.055 (.002)	.053 (.002)	.027 (.002)
SU mothers	.034 (.001)	.047 (.002)	.055 (.003)	.052 (.002)	.027 (.001)
p value	.33	< .001*	.77	.19	.22

Note. Standard deviations presented in parentheses. * Indicates statistically significant differences between groups.

Table 2. BIS/BAS scores (means and standard deviations) as a function of substance use.

	BIS/BAS Subscale				
	BAS-Drive	**BAS-Fun Seeking**	**BAS-Reward**	**BAS-Total**	**BIS**
Non-SU mothers	11.17 (2.59)	11.00 (1.95)	17.50 (1.88)	39.67 (5.12)	20.15 (3.62)
SU mothers	11.77 (2.61)	11.88 (2.08)	17.23 (2.16)	40.87 (5.88)	19.34 (2.80)
p value	.45	.06	.84	.39	.33

Note. Standard deviations presented in parentheses.

parisons between total GM and WM volumes as a function of substance use. If group differences were found, the second analytic step was to examine lobe parcellation to probe the potential regional sources for substance-use differences. Greenhouse-Geisser corrections were used where applicable. The third and final analytic step was to examine associations between structural volumes where substance-use differences emerged with BIS/BAS measures. Data from the BAS subscales were not normally distributed; therefore, non-parametric analyses were used for these measures. The alpha level was defined as $p < .05$, and all data presented in figures and text are means and standard deviations.

RESULTS

Total GM and WM Volumes

Despite statistically significant age differences between substance-use groups, this variable did not correlate with GM and WM volumes and was not included as a covariate in this analysis. Substance-using mothers presented with less total GM volume ($t(62) = 3.71$, $p < .001$) than non-substance-using mothers (Figure 1). There was no difference ($t < 1$) in total WM volume between substance-using ($M = .353$; $SD = .008$) and non-substance-using ($M = .352$; $SD = .006$) mothers.

GM Parcellation

Table 1 presents the means and standard deviations for GM volume parcellation for each maternal group. To further examine GM differences, parcellated GM volume was examined using a 5 (Lobe: prefrontal, frontal, parietal, temporal, occipital) by 2 (Hemisphere: left, right) repeated-measures ANOVA with a between-group factor of substance-use status. Age was included as a covariate in the analysis after preliminary data analysis revealed age correlated with GM volume in some lobes. Age was not a significant covariate in the overall model ($F(1,61) = 2.22$, $p = .14$), but substance-use status was a significant between-group factor ($F(1,61) = 8.58$, $p < .01$). There was a main effect of lobe ($F(3,171) = 169.42$, $p < .001$), evidencing variability in GM volume and the smallest GM volume in occipital and prefrontal regions (Table 1). There was a marginal interaction between lobe and substance-use status ($F(3,171) = 2.67$, $p = .05$). With no main effect of hemisphere ($F < 1$) or any interaction between lobe, substance-use status, and hemisphere ($F < 1$), the data were averaged across hemispheres for analysis. Independent samples t-tests showed non-substance-using mothers had more frontal cortical GM volume than substance-using mothers ($t(62) = 4.60$, $p < .001$). Across the other lobe regions, GM volume was comparable between the groups. Therefore, the overall reduction in total GM volume in substance-using mothers reported here seems driven by differences in GM volume in the frontal lobe.

This omnibus analysis also showed a lobe GM volume and age interaction ($F(3,171) = 7.60$, $p < .001$). Age did not correlate with frontal ($r(64) = -.16$, $p = .22$) or occipital ($r(64) = .23$, $p = .06$) GM volumes. There were significant inverse correlations between age and parietal GM volume ($r(64) = -.32$, $p = .01$) and prefrontal GM volume ($r(64) = -.28$, $p = .02$). There was also a positive correlation between age and temporal lobe GM ($r(64) = .25$, $p = .04$). A lobe by hemisphere interaction was also found ($F(4,244) = 3.58$, $p < .01$), whereby the GM volume was larger across all lobes in the right versus left hemisphere, with the exception of the parietal lobe in which this volumetric asymmetry was reversed. There were no other statistically significant interactions between any of the remaining variables of lobe, hemisphere, substance-use group and age (F's < 3.16, p's > .08).

BIS/BAS and Frontal GM Volume

Table 2 presents BIS/BAS scores (means and standard deviations) as a function of substance use. Although

there was a non-significant trend to suggest that substance-using mothers had higher BAS-Fun Seeking scores than non-substance-using mothers, no other statistically significant differences were found between the other BAS subscales or the BIS scale as a function of substance-use group. However, we examined the relationship between BIS/BAS within each group, given the statistically significant frontal GM volume differences. In substance-using mothers, we found an inverse correlation between frontal GM volume and BAS-Fun Seeking ($r(30) = -.44$, $p = .02$) and BAS-Reward ($r(30) = -.39$, $p = .03$). There was a comparable, but not statically significant relationship, between frontal GM volume and BAS-Drive ($r(30) = -.34$, $p = .06$). Figure 2 illustrates the relationship between frontal GM volume and the total BAS score ($r(30) = -.38$, $p = .04$). No relationship between frontal GM volume and BIS was observed ($r(30) = .07$, $p = .73$). We found no relationship between frontal GM volume and BIS, or any BAS subscale, in non-substance-using mothers (r's, < -.16, p's > .36).

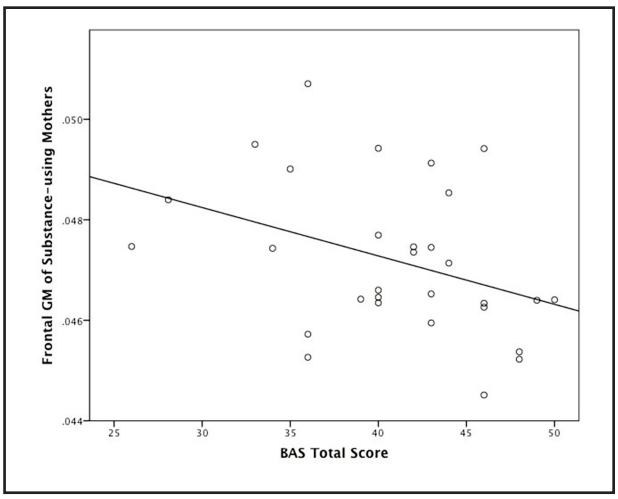

Figure 2. The relationship between frontal gray matter volume and BAS-Total Score for the substance-using mothers, $r(30) = -.38$, $p = .04$.

DISCUSSION

Recent work has suggested that substance use may affect maternal neural responses to infant stimuli [9]. Critically, individual differences in maternal brain structure and motivation may underlie functional correlates of substance use and infant cue perception. Past research has evidenced an important role for GM volume in maternal brain development [12]. Our finding of reduced GM volumes in substance-using mothers, particularly in the frontal lobes, converges with other studies that have reported abnormalities in frontal regions associated with substance use [13,15,16]. While we found substance use-related differences in overall frontal GM, understanding whether there are regional variants in the frontal cortex will be valuable for future research. For instance, decreased GM in the orbitofrontal cortex (OFC) has been reported in substance-dependent participants [13]. The OFC contributes to reward-related processes [37,38] and is recruited in fMRI studies where parents engage with infant stimuli [39-41]. Therefore, an important extension of this work will be to relate these structural findings to maternal cognitions and behavior. While maternal behavior is likely underpinned by multiple complex neurophysiological systems [42], frontal cortical functioning may be of particular interest owing to the complexity of human parenting [43]. Our finding of structural differences in frontal GM volume will be important in guiding research questions specifically targeting the role of functions mediated by the frontal cortex in parenting. Indeed, executive functions may be associated with observable parenting behavior during parent-child interactions [44].

We investigated whether individual differences in BIS/BAS would be associated with structural brain measures. Higher levels of behavioral activation may be associated with seeking and using substances [23]. Unlike previous reports, we did not find that BAS scores differentiated substance-using from non-substance-using participants. One explanation for this null BAS finding may be that in past samples where this distinction was found, participants were typically substance-dependent [23,25] rather than substance-using, as in the sample recruited here. However, there was a trend-level difference between groups on the BAS-Fun Seeking subscale, a measure that has previously been implicated in substance-use behaviors [24-26]. Nevertheless, owing to significant differences between groups in frontal GM volume, we assessed the relationship between structural volumes in this region and BIS/BAS. Frontal GM volumes were negatively correlated with BAS scores, specifically the BAS-Fun Seeking and BAS-Reward scales, with the correlation between GM volume and BAS-Drive not reaching statistical significance ($p = .06$). Thus, in our substance-using group, reductions in GM volume were associated with higher levels of behavioral activation (an effect absent in non-substance-using mothers). One interpretation is that the decreased integrity of frontal cortical regions may be associated with increased approach motivation to rewarding stimuli and events. This resonates with prior findings that impulsivity levels were negatively associated with GM volume in the left superior frontal gyrus [15]. We did not find associations between GM volume and behavioral inhibition. The role of the BIS in differentiating individuals as a function of substance use has not been consistently reported [24,26], and the current findings further suggest the value of examining behavioral activation in substance-use research.

One of the important next steps in this work will be to understand the role of BAS motivation to components of caretaking. One previous non-mother fMRI study [21] found relationships between BIS/BAS measures and neural responses to infant emotional stimuli. For instance, BAS-Drive was positively associated with activity in the right superior occipital gyrus while women viewed sad relative to neutral infant faces. A replication of this fMRI study in a maternal sample will afford the opportunity to build on the current structural findings. However, the present study adds an important component to neurobiological accounts of ad-

diction and parenting. It has been proposed that the dysregulation through addiction of reward and stress neurocircuitry may be associated with potential difficulties many substance-using women face in caring for their children [8,10]. Specifically, caring for infants may be relatively less rewarding and more stressful for addicted adults. Our findings suggest frontal GM reductions are associated with increased behavioral activation; therefore, approach motivation more generally may not be compromised in these women, although the specificity of this to the caretaking role (as opposed to other activities that may interfere with parenting), as well as other social and non-social rewards, should be established.

These findings should be considered in light of limitations. There was heterogeneity in maternal substance use without measures assessing frequency and duration of use. Although differences may exist in the effects of varying substances at a neurochemical level, the nature of addiction encompasses habitual responding underpinned by dysregulation in stress and reward systems [45,46] consistent with a syndrome model of addiction [27]. It is also unclear when differences in GM volume emerge between substance-using and non-substance-using mothers, and whether this difference will continue across the postpartum period. A recent study reports substance-dependent individuals and their non-substance-using siblings show commonalities in brain structure and behavioral inhibition relative to unrelated control subjects, suggesting potential familial vulnerability to substance use [47]. Here, our sample consisted only of mothers, and considering existing studies examining substance use and GM volume [13,15,16], it is likely these results may generalize to non-parent samples, although this should be empirically tested. Further, understanding what underscores differences in GM volume is critical, given that this may not be related to changes in the number of neurons in GM. Finally, the maternal samples were not well matched with respect to demographics characteristics. These potential confounds represent a challenge to fully understanding the generalizability of the findings. However, with larger samples, these variables may be more tightly controlled.

In summary, we found that GM volume, particularly in frontal regions, was reduced in substance-using mothers relative to non-substance-using mothers. In substance-using mothers, we also found frontal GM negatively correlated with behavioral activation. These findings add to an emerging neuroscience of human parenting and addictive behaviors, highlighting the importance of individual differences in motivational tendencies.

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