MOTOR DEVELOPMENT AND SUBCORTICAL BRAIN VOLUMES IN CHILDREN PRENATALLY EXPOSED TO METHAMPHETAMINE AND TOBACCO

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Abstract

Introduction: Methamphetamine use is a significant health concern, and doubly so for pregnant women who expose their fetuses during the prenatal period. Such prenatal methamphetamine exposure (PME) is associated with neurological alterations with developmental deficits seen clinically. This study investigated subcortical brain volume and motor development in children who were prenatal tobacco exposed (PTE), and both prenatal tobacco and methamphetamine exposed (PTE+PME). As adults often abuse both drugs concurrently, this study explored the combined influence of prenatal methamphetamine and tobacco exposure.

Method: The Movement Assessment Battery for Children-2 was used to assess motor skills in three domains: Manual Dexterity, Aiming and Catching, and Balance. These three domains were then combined to calculate an overall global score. Scores of 32 PME+PTE, 26 PTE, and 116 unexposed control (CON) children were compared. A subset of participants was also evaluated with brain MRI Scans. 27 PME+PTE, 11 PTE, and 19 CON were scanned on a Siemens 3.0 Tesla TIMTrio MR System. Brain images were analyzed using FreeSurfer 5.1.

Results: PTE children scored poorer than CON on Manual Dexterity, especially on the trail making task. PME+PTE children scored poorer than CON on Balance domain, including two tasks, balance board and jumping. The three groups were not different on Aiming and Catching. On brain imaging, PME+PTE children had smaller caudates and tended to have smaller ventral diencephalon and right globus pallidus compared to CON. Smaller caudates and right globus pallidus were associated with lower balance scores.

Conclusions: Findings suggest that PME+PTE may negatively impact gross motor skill development, while PTE alone may negatively influence fine motor skill development. Smaller subcortical volumes in children with PME+PTE compared to unexposed CON are consistent with prior reports. Correlations between smaller brain structures and lower MABC-2 scores suggest that brain morphometry may predict developmental outcome.

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Introduction

Substance use during pregnancy continues to be a public health problem in the United States.[1] Nationwide, more women use methamphetamine than men; in 2011, the percentage of women ages 12-44 years old (child bearing ages) seeking treatment for methamphetamine dependence was approximately two times higher compared to men in the same age range.[2] Pregnant women seeking treatment for methamphetamine dependence tripled from 8% (n=1,457) to 24% (n=5, 312) between1994 and 2006,[3] and the number remains high at approximately 6,000.[4] Methamphetamine use in Hawaii is especially prevalent, ranking number one in the nation for the percentage of drug related treatment admissions that were methamphetamine related.[5] Additionally, methamphetamine use amongst Hawaii women seems to be particularly high demonstrated by having the highest percentage of female arrestees testing positive for methamphetamine (50%), with the second highest in San Jose (42.8%).[6]

Despite 69% of methamphetamine users in the United States reporting concurrent tobacco use,[4] co-morbid prenatal tobacco exposure (PTE) is often overlooked in studies of children with prenatal methamphetamine exposure (PME). In 2012-2013, 15% of pregnant women in the Unites States admitted to smoking cigarettes in the past 30 days while 0.3% of pregnant women admitted to using stimulants, which includes methamphetamine.[7] Although reports of methamphetamine use among pregnant women seem low, data on prenatal methamphetamine use remains difficult to capture due to social stigma, fear of legal action, or the desire of providers to maintain confidentiality.[8] The Infant Development, Environment, and Lifestyle (IDEAL) study is a longitudinal, multi-site study, which included research participants from Los Angeles, California, Des Moines, Iowa, Tulsa, Oklahoma, as well as Honolulu, Hawaii. The IDEAL study specifically investigated prenatal influence of methamphetamine exposure. Of their initial sample of 1632 eligible mothers, 5.2% reported using methamphetamine at least once during pregnancy and 22.8% of the total sample also reported smoking tobacco during their pregnancy.[9] Both methamphetamine and tobacco pose maternal and fetal complications

during and after pregnancy.[10]

Children exposed prenatally to methamphetamine or tobacco separately, have shown motor development deficits compared to unexposed control (CON) children.[11-15] Data from the IDEAL study showed newborns with PME had more stress and lethargy, lesser arousal, and poorer quality of movement compared to non-exposed controls.[12, 16] In addition, children with PME have been found to have problems with visual motor integration tasks, which is the ability to coordinate visual perception and fine motor output or movement.[17, 18] PME children have also shown poorer gross motor outcomes at ages 1 and 2 years old.[19] However, a portion of these PME children most likely had concurrent tobacco or other prenatal poly-drug exposures.

Studies of newborns with PTE consistently demonstrated that neurobehavioral deficits are already manifested by this period, including abnormal muscle tone, compared to non-exposed newborns.[20-22] The literature on children with PTE in early childhood and adolescence is controversial. Young children and adolescents with PTE had poorer visuomotor coordination and balance compared to controls;[14, 15] however, other studies found no motor deficits in children with PTE.[23, 24] Varying results in the PTE on motor development literature may be due to the lack of a consistent measure of motor development used across studies. These conflicting findings suggest further research is needed with more stringency placed on confounding variables.

Methamphetamine and tobacco are both known neurotoxins.[1] Prior neuroimaging studies have suggested that PME and PTE can alter brain structure and function in exposed children in areas of the brain that contribute to motor skill development.[17] Examples of motor associated areas linked to PME or PTE include the caudate in PME[18, 25] and cerebellum in PTE.[26] Compared to unexposed children, PME children had smaller brain volumes in the putamen, globus pallidus, hippocampus, thalamus, and caudate.[18, 25] PTE children had smaller globus pallidus, amygdala, and cerebellum volumes.[26-28] Thus, PME and PTE may have distinct influences on brain development. To our knowledge, only one study has attempted to parse the

consequences of PME and PTE on brain morphometry; no additive or interactive influences of PME and PTE were seen.[29]

Brain structures that have long been associated with motor development include basal ganglia (consisting of the caudate, putamen, globus pallidus, subthalamic nuclei, and substantia nigra) and cerebellum.[30] To our knowledge, no study examined the relationship between PME/PTE, motor development, and brain morphometry. However, one study that evaluated the relationship between PME, motor, and brain chemistry found that compared to controls, PME children had poorer visuomotor skills, which also correlated with lower myoinositol concentrations in the thalamus.[17] A similar study also found a negative relationship between anterior cingulate glutamate+glutamine levels and visuomotor integration, only in PTE children and not un-exposed controls.[31] These findings support a link between prenatal drug exposure, motor development, and abnormal brain development in early childhood. In the current study, a quantitative motor examination called the Movement Assessment Battery for Children-2 (MABC-2) was used to evaluate the motor function in children with PTE and PME. Although this test has not been used to assess children with drug exposure, it has been used to assess extremely low birth weight (ELBW) children and the possible relationship between brain structure and motor development. Preterm and ELBW children, like PME/PTE children, also experienced stressors in-utero and/or shortly after birth and have been consistently shown to have abnormal brain development and poorer motor outcomes compared to full-term controls.[32, 33] Furthermore, children exposed to illicit and non-illicit drugs have a slightly higher risk of being born prematurely.[34] In the study of ELBW children, smaller subcortical and white matter volumes were correlated with poorer motor exam test scores.[35] Therefore, this study of ELBW children serves as a good model for the current study.

The purpose of this study was to investigate the influence of prenatal methamphetamine and tobacco exposure on motor performance and subcortical brain volume. Based on prior studies reviewed above,[13-15, 17, 19] children with PME and PTE should have deficits in motor task

performance. Additionally, based on prior studies,[18, 25-27] children with PME and PTE should also have smaller brain volumes compared to non-drug exposed controls, especially in the striatum, which includes the caudate and putamen subcortical structures. Furthermore, smaller brain volumes would be associated with lower scores on motor tasks.

Method

Study Design and Research Participants

The study protocol was approved by the University of Hawaii and the Queen's Medical Center Institutional Review Boards. Informed consent was obtained from the parent of legal guardian of all participants, and child assent was additionally obtained from participants older that 7 years old. Participants were recruited from the local community through flyers, internet advertisements, and word of mouth referrals. Upon passing an initial telephone screen, families were invited to the research facility for further screening by a physician to ensure the children fulfilled the following study criteria.

Inclusion criteria for the children included: 1) any child ages 3-16 years old; 2) male or female child of any ethnicity; 3) parental willingness for their child to participate; 4) child is able to understand study instructions in English and meets study hearing and vision requirements; 5) maternal self-reported methamphetamine or tobacco use during pregnancy of the child or positive meconium toxicology screen at birth (for methamphetamine-exposed or tobacco-exposed groups only).

Exclusion criteria included: 1) congenital or genetic neurological disorder; 2) preterm birth (gestational age <36 weeks); 3) failure to thrive within first year of life; 4) overt TORCH (Toxoplasmosis, Other, Rubella, Cytomegalovirus, and Herpes) infections or major neurological disorder at or since birth; 5) diagnosis of an autism spectrum disorder, mental retardation, bipolar disorder, or schizophrenia; 6) history of head trauma with loss of consciousness >30 minutes. A child was also excluded if the mother: 1) was non-English speaking; 2) was low

cognitive functioning (defined by an estimated verbal IQ score <80) or institutionalized for retardation; 3) was seropositive for HIV-1 during pregnancy; 4) had a history of psychiatric illness (e.g. schizophrenia, bipolar disorder with psychosis) that could confound analysis of study 5) had a confounding medical condition (e.g. severe pre-eclampsia, sickle cell anemia, cardiac, renal, or liver failure) during pregnancy; 6) had a history of other drug dependence during pregnancy (including cocaine, alcohol, opiates, inhalants, LSD, PCP, and barbiturates).

The children were recruited to three groups: prenatal methamphetamine and tobacco exposed (PME+PTE), prenatal tobacco exposed (PTE), and healthy non-drug exposed controls (CON). Participants were grouped into their respective cohort based on self-reported maternal drug use during pregnancy and if available, birth record toxicology reports. Birth records for 58% CON children, 81% PTE children, and 75% PME+PTE children were obtained.

Motor Assessment

The Movement Assessment Battery for Children-2 (MABC-2; Pearson Assessment; Strand, London) was used to assess motor skill ability in 32 children with PME+PTE (7 with only PME) children, 26 with PTE, and 116 CON. The MABC-2 is a comprehensive motor developmental examination measuring motor competence in Manual Dexterity (MD), Aiming and Catching (A&C), and Balance (BAL). Each domain contains 2-3 tasks related to the motor skill assessed. The MABC-2 has three age bands (ABs): AB 1 (3-6 years), AB 2 (7-10 years), AB 3 (11-16 years). The participants were administered the age appropriate MABC-2 exam to assess motor skill ability. The tests were conducted by trained research staff, in an environment with minimal distractions.

Magnetic Resonance Imaging

Fifty-seven children, including 27 PME+PTE (6 PME only), 11 PTE, and 19 CON, also underwent brain Magnetic Resonance (MR) imaging. Imaging was conducted on a Siemens 3.0 Tesla TIMTrio MR System (Siemens Medical Solutions, Erlangen, Germany) using a 12-channel phased-array radio frequency coil. Following a short reference scan, a high resolution 3D

Magnetization Prepared Rapid Gradient Echo (MP-RAGE, TR/TE/TI 4.9ms/2.2s/1s, 12 degrees flip angle, image matrix 256x256x144; IPAT factor = 2; 1x1x1 mm^3) was acquired and the MRI scans were analyzed using FreeSurfer 5.1 (http://surfer.nmr.mgh.harvard.edu). The skull was removed from the MRI brain images and the brain was transformed in Talairach space. Semi-automated segmentation of the whole brain, cortical, and subcortical white and deep gray matter structures were completed using a standardized atlas. These images were visually assessed for accuracy of the segmentation and manually edited for errors as needed by trained research staff blinded to the status of the participants.

Statistical Analysis

Statistical analysis was performed using SAS Enterprise Guide 5.1 (SAS Institute Inc.; Cary, North Carolina). Group demographic differences were determined using Chi-square or Fisher's exact test and analysis of variance (ANOVA). Kruskal Wallis statistical test was used for non-parametric data. Group differences on the MABC-2 exam and subcortical brain volumes were conducted using ANOVA and analysis of co-variance (ANCOVA), co-varying for Index of Social Position (ISP) and Intracranial Volume (ICV) when appropriate. As an exploratory analysis, significant MABC-2 scores were correlated with amount of drug exposure. Logistic regression was used to obtain odds ratio estimates to compare group risk of having a clinically significant movement difficulty. Repeated measures ANOVA was performed to determine if the subcortical structures in right and left hemispheres were different; if not, they were combined for the group analyses. To reduce type-1 errors from multiple comparisons, correlations between in the MABC-2 scores and subcortical brain volumes were performed only on those that showed significant ($p \leq 0.05$) or trends for ($p < 0.1$) group differences. Two-way ANCOVA, co-varying for ICV, was used to evaluate group-by-brain volume interactions on the MABC-2 scores. Partial correlation analysis was used to examine the relationship between MABC-2 scores and brain volumes while accounting for ICV and ISP. Simes correction was used to correct for multiple comparisons.

Results

Participant Characteristics

The three groups of children were not different in sex proportion, age, handedness, and their average height, weight, and BMI at the time of the study. Children with PME+PTE had lower birth weight compared to CON, but the groups did not differ on birth length, birth BMI and gestational age at birth. CON had more races represented compared to the other groups, which were mostly mixed (more than one race reported). In addition, the PTE and PME+PTE groups had higher percentages of self-reported Hispanic ethnicity compared to the CON group. PME+PTE children tended to have higher DuPaul ADHD Rating Scale-IV percentiles (reported by primary caregiver) compared to CON (ANOVA, p=0.06, post-hoc p=0.02). The primary caregivers of CON children had lower ISP scores (indicating higher socioeconomic status based on years of education and occupational position) and higher household income compared to the primary caregivers of PTE and PME+PTE children. Groups were not different on prenatal exposure to alcohol, tobacco, and any other illicit drugs, based on the mothers' or primary caregivers' self-reports (Table 1).

Amongst the children who underwent MR imaging, more Hispanics were in the PME+PTE group, and the CON group also had lower ISP scores (indicating a higher socioeconomic status) and higher household income compared to the other groups (Supplementary Table 2).

Group Differences and Logistic Regression on the MABC-2

On overall test scores, the children with PME+PTE (-12.4%, p=0.04) and PTE only (-14.3%, p=0.03) performed worse than CON (Figure 1a). On the MD domain, the PTE children scored poorer than CON children (-19.6%, p=0.007), especially the subdomain MDIII (Drawing Trail, -33.9%, p=0.002; Figure 1b). Furthermore, lower scores on this Drawing Trail task were associated with higher number of maternal cigarettes smoked throughout the pregnancy (R=-

0.372, p=0.02; Figure 2). On the BAL domain, PME+PTE children performed worse than CON (-19.7%, p=0.001, Figure 1a). The lower BAL scores in the PME+PTE children were attributed to lower performance scores on subdomains BAL I (Balance Board, -10.1%, p=0.04) and BAL III (Jumping, -14.2%, p=0.01) compared to CON (Figure 1d). No group difference was seen on the A&C domain (Figure 1c). All findings remained significant after Simes correction.

Since the ISP was higher in CON than the two stimulant-exposed groups, the ISP score was added into the statistical model as a co-variate, and the group differences in the MD and BAL domains were no longer significant. However, on the subdomains PTE children still tended to perform worse compared to CON children on MD III Drawing Trail task (ANOVA p=0.06, post-hoc p=0.01). MD II Sewing task became significant (ANOVA p=0.05), with PME+PTE children performing worse compared to CON children (post-hoc p=0.006).

Logistic regression revealed children with PTE were approximately four times more likely to score at or below the 15th percentile in the manual dexterity domain compared to CON (p=0.0007, OR: 4.8, 95% CI 1.9-11.7) and PME+PTE (p=0.01, OR: 4.2, 95% CI 1.4-12.5; Figure 3A). Furthermore, children with PTE were approximately 3 times more likely to score below the 5th percentile in the manual dexterity domain compared to both CON (p=0.01, OR: 3.1, 95% CI 1.3-7.8) and PME+PTE (p=0.05, OR: 3.2, 95% CI 1.0-10.3; Figure 3B).

Groups Differences on Subcortical Brain Volumes

Repeated measures ANCOVA, co-varying for ICV, revealed no differences between right and left hemispheres for most subcortical structures; thus, left and right volumes were averaged for the group analysis, except for the globus pallidus since the left was larger than the right.

Children with PME+PTE had smaller caudate volumes (ANCOVA p=0.008, with ICV as a co-variate) than CON (-10.5%, post-hoc p=0.0008) and those with PTE (-13.3%, post-hoc p=0.001). Similarly, the ventral diencephalon showed group difference (ANCOVA p=0.01, with

ICV as a co-variate), with PME+PTE children showing smaller volumes compared to CON (-8.1%, p=0.005; Figure 4).

When ISP was additionally included as a co-variate in the ANCOVA, the significant group differences remained for smaller caudates in the children with PME+PTE (ANCOVA p=0.02) compared to PTE (p=0.01) and a trend remained in comparison with CON children (p=0.08). There was also a trend for smaller right globus pallidus in PME+PTE children (ANCOVA p=0.07), 5.8% smaller than CON (p=0.08) and 10.0% smaller than PTE (p=0.07). The ventral diencephalon became only a trend for group difference (ANCOVA p=0.08) but the posthoc analyses continued to show smaller volumes in PME+PTE compare to CON (p=0.02). After Simes correction, none of the group differences on the brain volumes remained significant, possibly due to the relatively small sample size of the children who had brain imaging.

Partial Correlations between MABC-2 Scores and Brain Volumes

No significant interactions by group were seen on the two-way ANCOVA. Therefore, all children were analyzed together for the partial correlations analyses. When comparing subcortical volumes and MABC-2 scores of all children, regardless of prenatal stimulant-exposure status, smaller caudate volume was associated with lower BAL standard scores (R=0.29, p=0.03) and BAL III Jumping scores (R=0.26, p=0.05). Smaller right globus pallidus was also associated with lower BAL I Balance Board scores (R=0.42, p=0.0002; Figure 5).

Discussion

In the current study, compared to the unexposed controls, both PME+PTE and PTE children had poorer performance on the motor tasks but in different domains, which suggests that the prenatal exposure to methamphetamine or the combination of methamphetamine and tobacco may lead to unique influence on motor development. Results also showed that the children with PME+PTE had smaller than normal caudate volumes, which suggest that the combination of methamphetamine and tobacco may be neurotoxic to the developing brain.

Furthermore, children with smaller caudate and right globus pallidus volumes had lower scores on balance tasks, which suggest that the abnormal brain development may lead to movement difficulties in these children.

Consistent with past studies that used different motor assessments, such as the Bayley Scales of Infant Toddler Development (BSID),[13, 19] Peabody Developmental Motor Scales (PDMS),[14] and bimanual coordination task,[15] our children with PME+PTE and PTE performed worse on motor tasks compared to unexposed CON. Specifically, our PTE children performed worse the manual dexterity, indicating poorer fine motor skills, while PME+PTE children had poorer balance, indicating poorer gross motor skills. Past studies assessing children with PTE or PME showed variable findings on motor function (i.e., for both gross versus fine motor skills).[14, 15, 17, 18] The Infant Development Environment and Lifestyle (IDEAL) study found that infants in the United States cohort with heavy PME showed fine motor deficits at one year of age, while PME children of the same age in the New Zealand cohort exhibited gross motor deficits.[13, 19] The latter study suggested that the variability in motor outcomes found in PME children may be due to different prenatal or perinatal stressors eliciting varying responses from the monoaminergic system, which modulate behavior and is associated with abnormal motor development.[36] Influences from PME+PTE and PTE only could potentially explain the difference in motor domains that were associated with prenatal drug use in our study population. Both methamphetamine and tobacco were found to have neurotoxic effects on the developing brain.[1] However, methamphetamine acts on neurons in the striatum, by blocking the reuptake and reversing the flow of dopamine at the dopaminergic transporters;[37] whereas nicotine, the major addictive component of cigarettes, acts on nicotinic cholinergic receptors found throughout the cortex, hippocampus, striatum, midbrain, and brainstem.[38] Nicotinic cholinergic receptor's widespread distribution compared to methamphetamine's action on the dopaminergic neurons concentrated within the striatum may lead to different motor outcomes. PME children in past studies had concurrent PTE or other poly-drug exposures that might have confounded their

findings.[13, 17, 19] In our study, children comorbid for PME with PTE were compared to a PTE only group to explore the additional influence of PME. Furthermore, the IDEAL study used the BSID and PDMS to assess motor development, which showed low sensitivity in the detection of mild motor deficits in children.[39-41] In contrast, the MABC-2, used in the present investigation, has been validated as a reliable assessment of motor ability.[42, 43]

In addition, a dose-dependent relationship between more cigarettes smoked by the mother throughout the prenatal period scored poorer on the drawing trail task, while the motor performance was not dependent the on amount of maternal methamphetamine use throughout pregnancy suggesting that mothers who discontinue or reduce cigarette use may decrease the severity of adverse motor outcomes of their children. Prenatal cocaine exposure studies show high rates of concurrent maternal cocaine and tobacco use throughout pregnancy (~80-90%).[21, 44] Studies on prenatal cocaine exposures have found maternal cigarette use to be a better predictor of muscle tone abnormalities and motor performance after birth compared to maternal cocaine use.[21, 45] Pre-clinical studies further indicate that continuous low-dose nicotine exposure may be more neurotoxic compared to intermittent cocaine use.[46] Since methamphetamine and cocaine both influence the striatal structures, maternal tobacco cigarette use also might have a greater impact on child motor outcomes. Further evidence supporting the greater toxicity of tobacco than methamphetamine on motor development is seen in our data showing a 3 times greater risk for PTE children to perform below the 5th percentile on the manual dexterity domain, indicating these children had a clinically significant motor deficit. Furthermore, in addition to nicotine, tobacco cigarettes contain 3,000-4,000 toxic chemicals,[1, 21] which may further contribute to the motor deficits and the brain volume abnormalities.

Consistent with past findings, our study demonstrated the important role of socioeconomic factors on motor development in children.[47] However, other studies emphasize encouragement of autonomy/exploration and nurturing home environment are most important to motor development, rather than typical SES factors such as maternal education and IQ.[48, 49]

Future studies should further investigate the complex relationship between motor development, SES, and other factors in the home environment.

Methamphetamine is most neurotoxic in the striatum in animal models.[50, 51] Human studies have further shown that children with PME (and concurrent PTE) have smaller caudate or striatal volumes compared to unexposed controls,[18, 25] which is consistent with the current findings. Our findings are also consistent with another neuroimaging study that found PME children (95% with concurrent PTE) had smaller caudate volumes compared to non-PME children (47% with concurrent PTE); however, in the same cohort that was distributed differently, the subcortical volumes were not different between PTE children (73% with concurrent PME) and non-PTE children (11% with concurrent PME).[29] Overlapping poly-drug exposure is a major challenge in the attribution of each drug to subcortical volume differences. However, the current study tried to improve on the past study by including a PTE-only group with no concurrent PME.

Our finding of smaller ventral diencephalon volumes in PME+PTE children is difficult to interpret. Freesurfer defines the ventral diencephalon to include regions that cannot be individually delineated on MRI, including the: hypothalamus, mammillary body, subthalamic nuclei, substantia nigra, red nucleus, lateral geniculate nucleus, and medial geniculate nucleus. It is not possible with the current technology to discern which specific structure within this large region is contributing to the smaller volumes in PME+PTE children. Nevertheless, it is interesting to note that the subthalamic nuclei and substantia nigra both have reciprocal connections with the caudate and right globus pallidus,[30] which tended to be smaller in our PME+PTE children. Together, these structures comprise the basal ganglia, the system that largely controls voluntary movement.[52, 53] Therefore, it is not surprising that smaller caudate and right globus pallidus volumes were associated with lower scores on the balance tasks. Smaller subcortical volumes may indicate neuronal damage or abnormal development in these brain regions, which in turn may contribute to deficits in motor skill ability. Parkinson's disease

patients have decreased dopamine levels in the caudate and smaller caudate volumes,[54] with subsequent motor deficits.[55] The four cardinal signs of Parkinson's Disease include: bradykinesia/akinesia, hypertonia, resting tremor, and most consistent to our results, loss of balance. Although the sample was too small to examine by group, it would be of interest to note exposure to methamphetamine, a known neurotoxin, also leads to loss of dopaminergic fibers and cell bodies.[50] Studies also suggest that adult methamphetamine users are predisposed to developing Parkinson's Disease.[56, 57]

There are several limitations in this current study. First, only a subset of the children had useable imaging data, which limited our ability to correlate the brain volumes with the MABC-2 across the cohorts. Therefore, our findings regarding the imaging data are considered preliminary. The relatively small sample size also might have contributed to the lack of group differences in brain volumes of the PTE children, who were found to have smaller subcortical brain volumes in previous studies.[26-28, 58] Second, the data on maternal substance use during the pregnancy was self-reported by mothers, which may not be completely accurate. However, a study found that self-reported maternal drug use throughout pregnancy was more sensitive at predicting prenatal amphetamine and cannabis use than meconium testing, which was attributed to the study's assurance of confidentiality and the additional educational and medical resources for families.[59] Lastly, there was no PME only group for comparison since the majority of mothers (~80%) used methamphetamine and tobacco concurrently; future studies with a larger sample size should include a PME only group to further clarify the findings in the current study.

Conclusion

Prenatal exposure to methamphetamine+tobacco or to tobacco only may have distinct influences on motor skill outcomes and subcortical brain volumes. The current study also showed that children with PTE, might actually be more at risk for developing problems with fine

motor skills compared to their PME+PTE and CON peers. These finding could help guide clinicians to assess and develop interventions for at risk stimulant-exposed children. The smaller striatal volumes were associated with poorer performance on balance tasks, which demonstrate that the abnormal brain development, especially those with PME, led to negative motor function. Future studies with larger sample sizes are needed to validate these preliminary observations.

Table 1 Clinical characteristics of the research participants administered the MABC-2 (mean ± standard errors, unless otherwise specified)

	Controls (*n*=116)	PTE (*n*=26)	PME+PTE (*n*=32)	*p* value
Characteristics of the Children				
# of children (boys / girls)	61 / 55	15 / 11	18 / 14	0.86
Age (years) (range)	8.1 ± 0.3 (3.1 - 15.8)	7.5 ± 0.6 (3.2 - 15.8)	7.7 ± 0.4 (3.2 - 11.5)	0.48
Handedness (right / left)*	102 / 14	22 / 4	29 / 3	0.89
Race* (AS / MX / NHOPI / WH)^	22 / 66 / 10 / 13	0 / 21 / 5 / 0	5 / 24 / 3 / 0	**0.01**
Ethnicity (Non-Hispanic / Hispanic)*	93 / 23	16 / 10	19 / 13	**0.02**
ADHD Rating Scale Total Score (%tile)	42.7 ± 3.0	49.8 ± 7.0	58.1 ± 6.3	0.06
Height at Study Visit (cm)	128.3 ± 1.6	122.7 ± 3.6	123.5 ± 2.2	0.18
Weight at Study Visit (kg)	31.4 ± 1.4	29.8 ± 2.8	27.8 ± 1.6	0.40
BMI at Study Visit	18.1 ± 0.4	19.1 ± 1.0	17.9 ± 0.6	0.51
Gestational Age (weeks)	40.0 ± 0.1	38.5 ± 0.3	38.6 ± 0.4	0.26
Birth Length (cm)	51.3 ± 0.3	50.8 ± 0.4	49.9 ± 0.6	0.09
Birth Weight (kg)	3.4 ± 0.1	3.2 ± 0.1	3.1 ± 0.1	**0.01**
Birth BMI	13.0 ± 0.2	12.3 ± 0.3	12.5 ± 0.3	0.11
Estimated Maternal Drug Use During Entire Pregnancy				
Methamphetamine (grams used) (median / range)	N/A	N/A	98.8 ± 37.5 (22.7 / 0.4-931.0)	N/A
Tobacco (# cigarettes smoked) (median / range)	N/A	2821.0 ± 826.5 (600 / 9-14,000)	3118.3 ± 471.9 (2800 / 378-11,200)	0.78
Alcohol (# drinks) (median / range)	0.3 ± 0.0 (0 / 0-18)	1.8 ± 0.9 (0 / 0-20)	5.1 ± 3.1 (0 / 0-94)	0.33
Cannabis (# joints) (median / range)	5.1 ± 5.1 (0 / 0-518)	4.0 ± 2.5 (0 / 0-58)	15.0 ± 13.2 (0 / 0-420)	0.63
Characteristics of the primary caregiver (parent or legal guardian)				
Household Income Scale**	5.8 ± 0.2	3.2 ± 0.3	3.3 ± 0.4	**<0.0001**
Total Index of Social Position	32.9 ± 1.7	53.5 ± 2.6	56.0 ± 2.3	**<0.0001**

* p-values obtained using chi-square or fisher's exact (handedness and race) statistical test
**Values based on scale of 1-7
Household Income Range: 1 (<$5,000) – 7 (>$50,000)
^ Abbreviations: AS=Asian, MX=Mixed (more than one race), NHOPI=Native Hawaiian/Other Pacific Islander, WH=White

Table 2 (Supplementary) Clinical characteristics of the research participants with MR Imaging data (mean ± standard errors, unless otherwise specified)

	Controls (*n*=19)	PTE (*n*=11)	PME+PTE (*n*=27)	*p* value
Characteristics of the children				
# of children (boys / girls)	11 / 8	7 / 4	16 / 11	0.95
Age (years) (range)	8.3 ± 0.4 (6.3 - 12.8)	7.2 ± 0.5 (4.0 - 9.6)	7.5 ± 0.3 (3.8 - 11.5)	0.17
Handedness (right / left)*	19 / 0	9 / 2	24 / 3	0.15
Race* (AS / MX / NHOPI / WH)^	4 / 13 / 1 / 1	0 / 8 / 3 / 0	5 / 20 / 2 / 0	0.24
Ethnicity (Non-Hispanic / Hispanic)*	17 / 2	8 / 3	15 / 12	**0.05**
ADHD Rating Scale %tile	38.2 ± 8.0	60.4 ± 9.4	54.9 ± 7.1	0.17
Height at Study Visit (cm)	128.8 ± 2.5	122.0 ± 3.4	122.4 ± 2.0	0.11
Weight at Study Visit (kg)	29.5 ± 1.9	27.8 ±2.2	27.6 ± 1.8	0.73
BMI at Study Visit	17.5 ± 0.7	18.4 ±0.9	18.0 ± 0.7	0.78
Gestational Age (weeks)	38.9 ± 0.3	38.7 ± 0.6	38.5 ± 0.4	0.71
Birth Length (cm)	49.3 ± 0.7	50.9 ± 0.7	49.5 ± 0.7	0.31
Birth Weight (kg)	3.2 ± 0.1	3.2 ± 0.1	3.1 ± 0.1	0.59
Birth BMI	13.1 ± 0.4	12.4 ± 0.4	12.4 ± 0.4	0.47
Estimated Maternal Drug Use During Entire Pregnancy				
Methamphetamine (grams used) (median / range)	N/A	N/A	50.3 ± 19.7 (17.5 / 0.4-315)	N/A
Tobacco (# cigarettes smoked) (median / range)	N/A	2082.2 ± 1042.8 (600 / 9-11,200)	3043.3 ± 568.2 (2800 / 280-11,200)	0.43
Alcohol (# drinks) (median / range)	0.3 ± 0.2 (0 / 0-2)	0.7± 0.4 (0 / 0-4)	6.1 ± 3.6 (0 / 0-94)	0.28
Cannabis (# joints) (median / range)	0.1 ± 0.1 (0 / 0-2)	8.0 ± 5.7 (0 / 0-58)	2.0 ± 1.9 (0 / 0-50)	0.14
Characteristics of the primary caregiver (parent or legal guardian)				
Household Income Scale**	6.3 ± 0.4	2.7 ± 0.4	3.3 ± 0.5	**<0.0001**
Total Index of Social Position	26.5 ± 3.8	57.2 ± 2.6	56..2 ± 2.6	**<0.0001**

* p-values obtained using chi-square or fisher's exact (handedness and race) statistical test
**Values based on scale of 1-7
Household Income Range: 1 (<$5,000) – 7 (>$50,000)
^ Abbreviations: AS=Asian, MX=Mixed (more than one race), NHOPI=Native Hawaiian/Other Pacific Islander, WH=White

Table 3 (Supplementary) MABC-2 results

				Uncorrected				Corrected for Index of Social Position			
MABC-2 Scores	**CON (n=116)**	**PTE (n=26)**	**PME+PTE (n=32)**	**p-value**	**CON vs. PME+PTE**	**CON vs. PTE**	**PME+PTE vs. PTE**	**p-value**	**CON vs. PME+PTE**	**CON vs. PTE**	**PME+PTE vs. PTE**
MD Standard Score	8.1 ± 0.3	6.5 ± 0.5 (-19.6%)	7.4 ± 0.4 (-7.9%)	0.02	0.23	0.007	0.18	0.30	---	---	---
MD I	8.5 ± 0.3	7.9 ± 0.5 (-7.2%)	7.8 ± 0.4 (-8.7%)	0.27	---	---	---	0.97	---	---	---
MD II	8.4 ± 0.3	7.6 ± 0.6 (-8.9%)	8.7 ± 0.4 (+3.9%)	0.41	---	---	---	0.05	0.006	0.43	0.18
MD III	7.7 ± 0.3	5.1 ± 0.8 (-33.9%)	6.7 ± 0.7 (-13.3%)	0.005	0.17	0.002	0.11	0.06	0.66	0.01	0.11
AC Standard Score	10.5 ± 0.3	10.4 ± 0.5 (-0.6%)	10.6 ± 0.5 (+0.8%)	0.98	---	---	---	0.57	---	---	---
AC I	9.7 ± 0.3	8.9 ± 0.3 (-7.9%)	8.9 ± 0.4 (-8.0%)	0.23	---	---	---	0.93	---	---	---
AC II	10.5 ± 0.3	11.1 ± 0.6 (+6.2%)	11.5 ± 0.6 (+9.8%)	0.23	---	---	---	0.10	---	---	---
Balance Standard Score	10.5 ± 0.3	9.5 ± 0.7 (-9.3%)	8.4 ± 0.5 (-19.7%)	0.004	0.001	0.16	0.19	0.23	---	---	---
BAL I	10.8 ± 0.3	9.7 ± 0.6 (-10.4%)	9.7 ± 0.5 (-10.1%)	0.04	0.04	0.06	0.97	0.67	---	---	---
BAL II	9.2 ± 0.3	9.1 ± 0.7 (-1.0%)	8.0 ± 0.7 (-13.5%)	0.21	---	---	---	0.28	---	---	---
BAL III	10.5 ± 0.3	9.7 ± 0.7 (-7.7%)	9.0 ± 0.6 (-14.2%)	0.03	0.01	0.21	0.39	0.36	---	---	---
Overall Standard Score	9.4 ± 0.3	8.0 ± 0.6 (-14.3%)	8.2 ± 0.4 (-12.4%)	0.03	0.04	0.03	0.81	0.89	---	---	---

Table 4 (Supplementary) MR Imaging Results

				Corrected for ICV				Corrected for ICV and ISP			
Brain Region	**Control (n=19)**	**PTE (n=11)**	**PME+PTE (n=27)**	**p-value (ICV)**	**CON vs. PME+PTE**	**CON vs. PTE**	**PME+PTE vs. PTE**	**p-value (ICV,ISP)**	**CON vs. PME+PTE**	**CON vs. PTE**	**PME+PTE vs. PTE**
Cerebellum	68.8 ± 1.5	70.9 ± 2.1 (+3.0%)	65.8 ± 1.1 (-4.3%)	0.33	---	---	---	0.37	---	---	---
Thalamus	7.9 ± 0.2	8.0 ± 0.2 (+0.8%)	7.5 ± 0.1 (-5.2%)	0.22	---	---	---	0.12	---	---	---
Caudate	4.4 ± 0.1	4.5 ± 0.2 (+2.7%)	3.9 ± 0.1 (-10.5%)	0.008	0.008	0.71	0.01	0.02	0.08	0.94	0.01
Putamen	6.3 ± 0.1	6.1 ± 0.3 (-2.7%)	5.9 ± 0.1 (-6.0%)	0.26	---	---	---	0.19	---	---	---
Left Pallidum	2.0 ± 0.05	2.0 ± 0.05 (+2.7%)	1.9 ± 0.04 (-1.5%)	0.91	---	---	---	0.65	---	---	---
Right Pallidum	1.9 ± 0.04	2.0 ± 0.06 (+5.2%)	1.8 ± 0.05 (-5.8%)	0.12	---	---	---	0.07	0.08	0.50	0.07
Hippocampus	4.3 ± 0.07	4.4 ± 0.2 (+2.2%)	4.1 ± 0.09 (-4.8%)	0.64	---	---	---	0.62	---	---	---
Amygdala	1.5 ± 0.03	1.5 ± 0.07 (+0.7%)	1.5 ± 0.03 (-4.7%)	0.79	---	---	---	0.96	---	---	---
Accumbens	0.6 ± 0.02	0.6 ± 0.04 (+2.4%)	0.7 ± 0.02 (+3.5%)	0.17	---	---	---	0.29	---	---	---
Ventral DC	4.1 ± 0.1	4.1 ± 0.1 (-1.7%)	3.8 ± 0.06 (-8.1%)	0.01	0.005	0.17	0.21	0.08	0.02	0.15	0.16

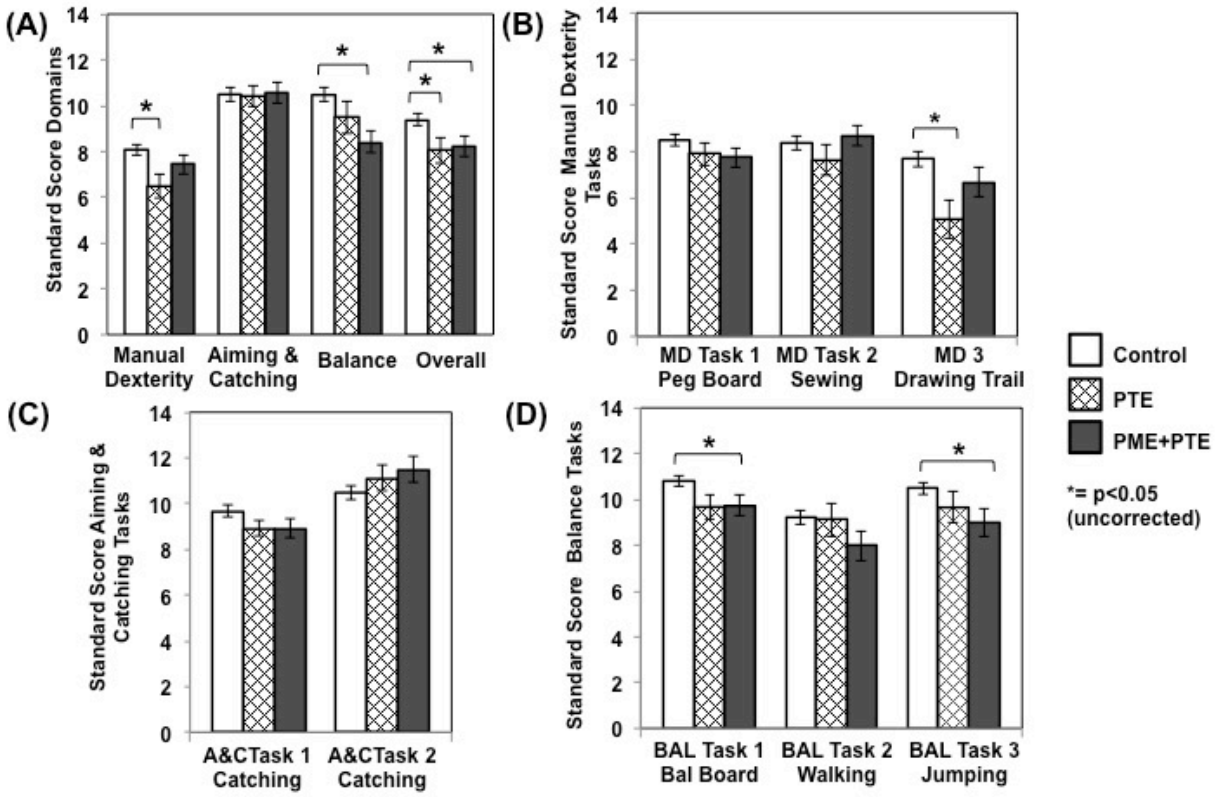

Fig. 1 **(a)** Movement Assessment Battery for Children-2 scores showed that compared to CON, children with PTE had lower manual dexterity domain scores, while PME+PTE children had lower balance domain scores. **(b)** On the subtasks children with PTE scored worse than CON on the drawing trail task in the manual dexterity domain. **(c)** No group differences were found on Aiming & Catching domain and the corresponding subtasks. **(d)** Children with PME+PTE scored worse than CON on balancing and jumping tasks in the balance domain.

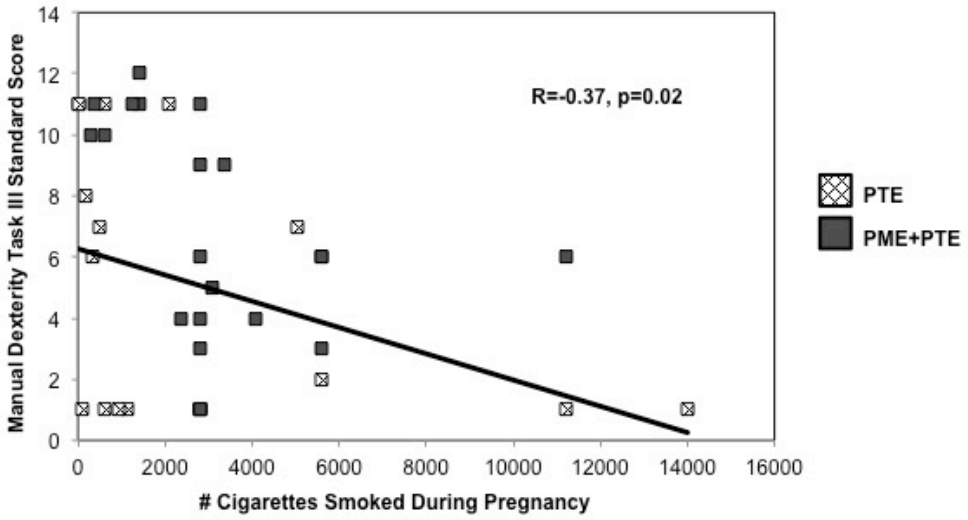

Fig. 2 Correlation Between Movement Assessment Battery for Children-2 Scores and Prenatal Tobacco Exposure showed that more cigarettes smoked during pregnancy was associated with lower standard scores on Manual Dexterity Task III (Drawing Trail).

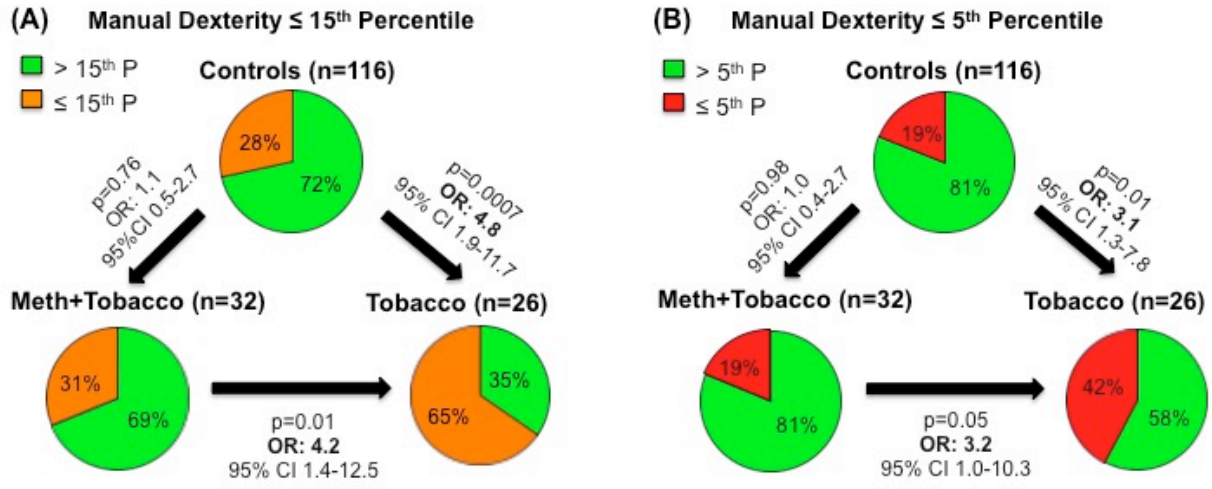

Fig. 3 (A) Prenatal tobacco exposed children were approximately 4 times more likely to score at or below the 15th percentile compared to prenatal meth+tobacco and control children. Indicating these children were either at risk for developing or they have a clinically significant movement difficulty. (B) Prenatal tobacco exposed children were also approximately 3 times more likely to score in 5th percentile or below (clinically significant for movement difficulty) compared to prenatal meth+tobacco exposed and controls.

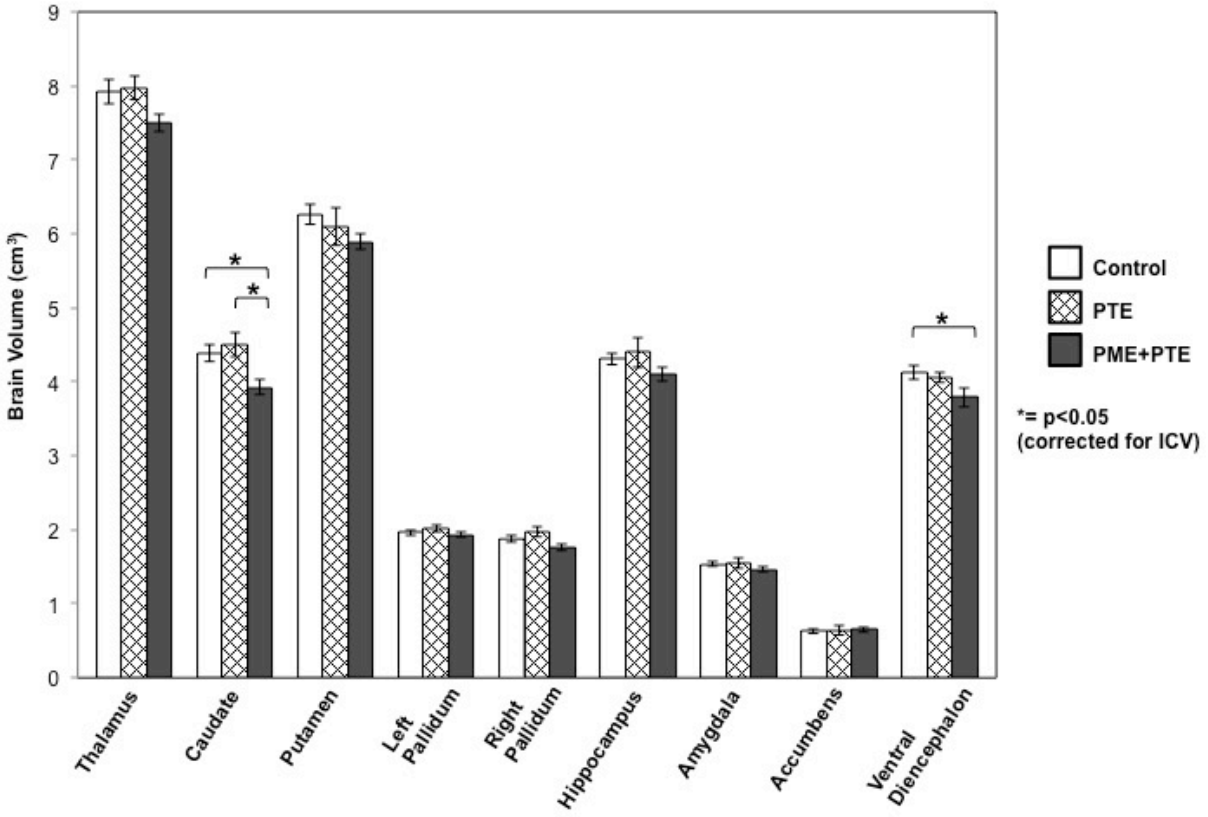

Fig. 4 Children with PME+PTE had smaller caudate and ventral diencephalon volumes compared to CON and children with PTE only. The cerebellum is not illustrated in the graph due to scaling issues.

	Caudate		Right Pallidum		Ventral Diencephalon	
	r-value	p-value	r-value	p-value	r-value	p-value
MD Standard Score	0.06	0.66	-0.03	0.80	0.11	0.43
MD III	0.24	0.08	0.12	0.40	0.26	0.06
BAL Standard Score	0.29	0.03	0.21	0.12	0.16	0.24
BAL I	0.19	0.17	0.42	0.002	0.18	0.20
BAL III	0.26	0.05	-0.04	0.80	0.10	0.46
Overall Standard Score	0.15	0.26	0.08	0.56	0.12	0.39

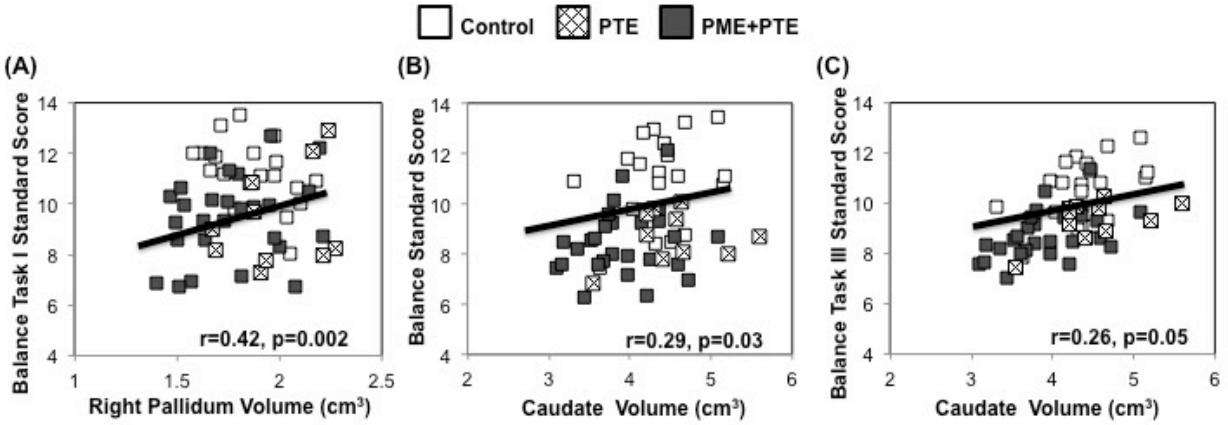

Fig. 5 Partial correlations analysis showed associations between balance domain subtasks and caudate and right pallidum subcortical brain regions. Adjusted MABC-2 scores are plotted.

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