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Review article

Prenatal marijuana exposure impacts executive functioning into young adulthood: An fMRI study

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ABSTRACT

Understanding the potentially harmful long term consequences of prenatal marijuana exposure is important given the increase in number of pregnant women smoking marijuana to relieve morning sickness. Altered executive functioning is one area of research that has suggested negative consequences of prenatal marijuana exposure into adolescence. Investigating if these findings continue into young adulthood and exploring the neural basis of these effects was the purpose of this research. Thirty one young adults (ages 18–22 years) from the longitudinal Ottawa Prenatal Prospective Study (OPPS) underwent functional magnetic resonance imaging (fMRI) during four tasks; 1) Visuospatial 2-Back, 2) Go/NoGo, 3) Letter 2-Back and 4) Counting Stroop task. Sixteen participants were prenatally exposed to marijuana while 15 had no prenatal marijuana exposure. Task performance was similar for both groups but blood flow was significantly different between the groups. This paper presents the results for all 4 tasks, highlighting the consistently increased left posterior brain activity in the prenatally exposed group compared with the control group. These alterations in neurophysiological functioning of young adults prenatally exposed to marijuana emphasizes the importance of education for women in child bearing years, as well as for policy makers and physicians interested in the welfare of both the pregnant women and their offspring's future success.

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Contents

1. Introduction

The most frequently used illicit drug during pregnancy is marijuana (Substance Abuse and Mental Health Services Administration [SAMHSA], 2013; Day et al., 2011; Porath-Waller, 2015. It has been

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used during pregnancy recreationally and also to attenuate symptoms of morning sickness (Westfall et al., 2006; Roberson et al., 2014). Exposure to marijuana in utero has been shown to have a detrimental effect on many aspects of cognitive development, behavioral repertoire and lifestyle outcomes. These results come mostly from 3 prospective studies that have followed groups of mothers and children over long periods of time. These include the Ottawa Prenatal Prospective Study (OPPS: Fried, 1982; Fried, 1995) in Canada, the Maternal Health Practices and Child Development Project (MHPCDP; Goldschmidt et al., 2000; Day et al., 1994) in the US and the Generation R study in Europe (El Marroun et al., 2011; Jaddoe et al., 2012).

The longitudinal nature of these cohort studies allows for more control than cross-sectional studies over the many lifestyle variables that might contribute to cognitive deficits and subsequent outcomes. Each of these studies has investigated prenatal marijuana exposure in varying samples with different testing protocols and for these reasons all results are not comparable. However, the significant results that are consistent across the OPPS and MHPCDP, the two that have tested children for the longest period of time, include neurocognitive challenges in the areas of short-term memory, verbal outcomes, aspects of attention, impulsivity and abstract visual skills (Leech et al., 1999; Goldschmidt et al., 2000; Fried and Watkinson, 2000; Fried et al., 1992, 1998, 2003). These deficits appear after age 3 and continue into young adulthood (Day et al., 1994; Smith et al., 2004, 2006). Most significantly, at 6 years of age, children exposed prenatally to marijuana showed more impulsive and hyperactive behaviour (Fried et al., 1992; Leech et al., 1999). This continued into adolescence and was accompanied by problems in abstract and visual reasoning, as well as visuo-perceptual functioning (Goldschmidt et al., 2004; Richardson et al., 2002; Wilford et al., 2010; Fried and Watkinson, 2000; Fried et al., 1998, 2003). Subsequent neuroimaging findings of the OPPS sample at ages 18 to 22 years, suggest an even longer term impact of the prenatal marijuana exposure on the neurophysiological underpinnings of these areas of cognition (Smith et al., 2004, 2006). The types of skills impacted in both the MHPCDP and OPPS samples are those required to perform top down processing, including working memory (the temporary storage of information before further processing), focused attention, inhibiting salient responses to stay focused on a task, monitoring self-progress, evaluating and adjusting behaviour and flexibility in problem solving (Fried and Smith, 2001).

Each of these cognitive processes can be grouped under the umbrella of executive functioning. Executive functions are a fundamental requirement to allow us to adapt to constantly changing environments, perform appropriate behaviours, create (and execute) plans and persevere in a task until completion. These are necessary skills for success in school, work, relationships and everyday life. Prenatal neural development lays the foundation for these skills to flourish later in adolescence and into adulthood. Exposure to marijuana during this critical in utero period hijacks this development and can have far reaching implications for successful executive functioning, even into young adulthood. Regular, weekly, marijuana use during pregnancy is thus cause for concern.

Functional magnetic resonance imaging (fMRI) has been used to reveal the long term consequences of prenatal marijuana exposure on executive functioning. Imaging the OPPS sample at ages 18–22, Smith et al. (2004, 2006), revealed a significant relationship between amount of prenatal marijuana exposure and brain activity in several regions. The imaged OPPS sample was randomly contacted in 2000 from an available list of 116 participants (only those who were right handed). Funding allowed for the imaging of 35 participants. The participants performed 4 executive functioning tasks while in the scanner and results from a response inhibition task and a visuospatial working memory task have been published (Smith et al., 2004, 2006). Data from these 2 tasks were reanalysed with more rigorous and up to date methods and are gathered together in this paper with results from the two additional fMRI tasks that have not been previously published. These included a letter n-back working memory task and an interference Counting Stroop task. This new analysis was also performed to allow for a comparison of all 4 tasks and to identify an actual group difference between prenatally exposed and non-exposed participants rather than only a correlation. This paper summarizes the outcomes from all 4 tasks highlighting the similarities and presenting the consist results.

2. Materials and methods

2.1. Sample

Thirty five participants from the OPPS (aged 18–22, mean age 21 years; 16 female, 19 male) were imaged and data are included from 31 as structural anomaly, positive Axis I diagnosis (from the DSM-IV) and positive urine tests for cocaine and amphetamine excluded 4 participants. Prenatal marijuana exposure was defined as regular maternal use of marijuana cigarettes (at least one joint/week) throughout the whole of the pregnancy (not just in one trimester). This resulted in 16 exposed (mean age 21; 6 males, 10 females) and 15 non-exposed (mean age 21; 10 males, 5 females) participants. The range for the 16 prenatally exposed participants was 0.33–53 joints/week with a mean of 8.27 (SE 3.24) joints/week). The 15 non-exposed participants had no prenatal marijuana exposure. Measures of IQ (Wechsler Adult Intelligence Scale (WAIS: Wechsler, 1997) full scale IQ), socioeconomic status (parental income and education), education (participants' number of years of education) and behaviour (Neuroticism-Extraversion-Openness Personality Inventory (NEOI: Costa and McCrae, 1989) and the Connors' Parent Rating Scale (Goyette et al., 1978) were considered and shown not to be significantly different between the groups (Table 1). Prenatal and current offspring drug exposures were also not different between the groups (Table 2). Current drug use of the offspring was confirmed with a urine sample upon completion of the imaging session. The urine sample was tested for cannabis, amphetamines, opiates, cocaine, creatinine and cotinine. All metabolite concentrations were adjusted for creatinine to control for urine dilution. A drug questionnaire was administered following scanning and assessed current and past drug exposures. This was the same questionnaire that had been administered at each OPPS testing session since participants were adolescents and thus they were familiar with it and answers were compared with the urine sample results to ensure validity.

Table 1
Demographic data.

Variable	Prenatally Exposed to Marijuana n = 16[a] Mean (SE)	Prenatally Nonexposed to Marijuana n = 15[b] Mean (SE)
Family income[c]	31,904.5 (4962)	32,833 (3901)
Average parental education[d]	2.78 (0.22)	2.57 (0.22)
Years of schooling[e]	11.1 (0.26)	11.8 (0.35)
WAIS full scale IQ	117.8 (3.8)	112.8 (3)
NEO neuroticism	44.7 (3.6)	48.25 (3)
NEO extraversion	52.9 (3.7)	55.3 (2.9)
NEO openness	55.5 (2)	52.6 (2.9)
NEO agreeableness	50.7 (3.1)	50.5 (3.5)
NEO conscientiousness	50.2 (3.7)	51.8 (3.9)
Connors (conduct problems)	0.14 (0.34)	0.02 (0.27)
Connors (learning problems)	0.24 (0.17)	0.26 (0.26)
Connors (Impulsivity-hyperactivity)	0.17 (0.25)	0.07 (0.26)
Connors (anxiety)	0.11 (0.27)	0.02 (0.23)

No significant differences were observed between the groups for any variable. The exposed group consisted of 6 males and 10 females while the non-exposed group had 10 males and 5 females.

[a] Exposed prenatally to marijuana (mean 8.27 (SE 3.24) joints/week).

[b] Prenatally not exposed to marijuana.

[c] Family income is in Canadian Dollars and was part of the early OPPS data collection.

[d] Education was coded as 1 — did not finish high school, 2 — graduated from high school, 3 — graduated from college or university, 4 — obtained a post graduate degree.

[e] Offspring's number of years of schooling.

Table 2
Drug exposure based on prenatal marijuana grouping.

Drug Exposure	Exposed n = 16[a] Mean (SE)	Nonexposed n = 15[b] Mean (SE)
Current marijuana (joints/week)	6.36 (2.7)	0.93 (0.67)*
Prenatal nicotine (cigarettes/day)	5.94 (2.8)	6.22 (2.2)
Current nicotine (cigarettes/day)	4.19 (1.6)	1.73 (0.87)
Prenatal alcohol (AA/day)[c]	0.23 (0.06)	0.18 (0.07)
Current alcohol (drinks/week)	3.39 (0.9)	2.96 (0.7)
Prenatal caffeine (mg/day)	57.91 (17.58)	115.97 (32.66)

[a] Exposed prenatally to marijuana (mean 8.27 (SE 3.24) joints/week).
[b] Prenatally not exposed to marijuana.
[c] Ounces of absolute alcohol per day.
* $F = 3.56$, $p = 0.069$.

2.2. Cognitive performance parameters and analyses

Commission and omission errors, as well as reaction times were recorded during each task. Reaction times were only considered for all accurate responses occurring within 900 ms of stimulus presentation. These data were analyzed with SPSS 18, separately for each task, using an ANCOVA with prenatal nicotine, alcohol and caffeine exposure and current nicotine, marijuana and alcohol use as covariates. These covariates were chosen as previous literature suggests a role for each in cognitive functioning.

2.3. Imaging parameters

All imaging was performed using a 1.5 Tesla Siemens Magnetom Symphony MR scanner. Participants lay supine with their head secured in a custom head holder. A conventional T1-weighted spin echo localizer was acquired to confirm that the anterior commissure–posterior commissure (AC–PC) line in the sagittal view was at right angles to the slice select direction. This localizer was also used to prescribe a subsequent 3D FLASH (TR/TE 22/9.2 ms, flip angle 30°, field of view (FOV) 26×26 cm^2, 256×256 matrix, slice thickness 1.5 mm) volume acquisition. Whole brain echo planar fMRI was performed using a gradient echo pulse sequence (TR/TE 3000/40 ms, flip angle 90°, FOV 24×24 cm^2, 64×64 matrix, slice thickness 5 mm, 27 axial slices, bandwidth 62.5 kHz).

2.4. Executive functioning tasks

All tasks were presented in a block design with white stimuli on a black background. Lights were off during task completion. The tasks included, in order of presentation; 1) The Visuospatial 2-Back task (Smith et al., 2006), that involved the presentation of a circle in 9 different positions on the screen, one at a time for 75 ms every 2 s for a total of 16 stimuli per block. Instructions were to Press for Middle (baseline condition when the circle was in the middle position) or Press for 2 Back (working memory test condition when the circle was presented in the same position as 2 stimuli prior). The order of blocks were counterbalanced with 'Press for Middle' followed by 'Press for 2 Back' for 3 alternations, a middle rest period, and then 3 alternations with 'Press for 2 Back' followed by 'Press for Middle' blocks. The contrast of interest was the Press for 2 Back condition minus the Press for Middle condition to yield the activity unique to visuospatial working memory. 2) The Go/NoGo task (Smith et al., 2004) included the presentation of letters in the middle of the screen, one at a time for 75 ms with an interstimulus interval of 925 ms and a total of 12 stimuli per block. Fifty percent of the letters presented were X while the other 50% were all other letters of the alphabet. Instructions were to Press for all letters except X (response inhibition condition) or to Press for X (baseline condition) with the contrast of interest subtracting the baseline condition scans from those during the Press for all letters except X blocks. Four blocks of each condition were presented, interspersed with 21 s rest periods (not modelled). 3) The Letter 2-Back (Longo et al., 2014) was similar to the first task but included letters in the middle of the screen for 1500 ms with an interstimulus interval of 500 ms. There were 16 stimuli in each block and 6 blocks of each condition were presented with instructions to either Press for 2-Back or Press for X (baseline). Rest periods were interspersed between conditions for 21 s each. The working memory contrast subtracted the Press for X from the Press for 2-Back blocks. The final task was 4) the Counting Stroop (Hatchard et al., 2014). The interference or incongruent blocks included number stimulus words (i.e. one, two, three, four) and the baseline or congruent blocks presented common animal names (i.e. dog, cat, mouse, bird). Words were presented with 1 to 4 identical words printed horizontally one above another. The instructions were to press for the number of words observed for each group using the appropriate button on the response pad (index finger for one work, middle finger for two words, etc.). Stimuli were presented every 1.5 s for a total of 20 trials in a 30 s block. Eight blocks of congruent and eight blocks of incongruent stimuli were alternated. Number blocks minus animal blocks resulted in the contrast of interest. Full descriptions of each task can be found in previous publications (Smith et al., 2004; Smith et al., 2006; Hatchard et al., 2014; Longo et al., 2014).

2.5. Statistical analyses

Previously published results for the Visuospatial 2-Back and Go/NoGo tasks have used SPM99 and multiple regression with regions of interest analyses. To be consistent with analyses for the Letter 2-Back and Counting Stroop tasks, and to use a more up to date analysis tool, the data were analyzed with SPM8 and included whole brain analyses with *t*-tests only. This analysis is more indicative of group differences rather than the predictive nature of a multiple regression. The power of *t*-tests is also lower than that of regression analyses so a significant effect is more meaningful (Keith, 2015).

First level analyses for each participant and each task were performed following standard SPM8 realignment/motion correction, normalization to the MNI template and smoothing (with an 8 mm kernel; Friston et al., 1995). Contrast images for the contrast of interest (test condition minus baseline condition e.g. Press for 2-Back minus Press for X) were entered into the second level analyses to compare marijuana exposed with non-exposed participants. This was performed with a two sample *t*-test for each task separately. Multiple independent samples t-tests were conducted at a set threshold of $p_{uncoorr} = 0.001$, with a cluster-wise correction for multiple comparisons at $p_{FWE} = 0.05$. Seven comparisons were made for each of the four fMRI tasks before the final results were calculated. Other prenatal drug exposures (alcohol, nicotine), current use (alcohol, nicotine), errors and reaction times were not shown to impact the results so were not included in the analyses as covariates. Current marijuana use modified the results for all 4 tasks, specifically in the prefrontal cortex. Before controlling for current marijuana, there were prefrontal cortical regions that were significantly more activated for all 4 tasks in the prenatally exposed compared to non-exposed group. Including current marijuana as a covariate reduced this effect to non-significant. Thus, offspring marijuana use was included as a covariate in all results reported. Results from Smith et al. (2004) and (2006) were reported from multiple regressions rather than t-tests and are thus different from the results reported below.

3. Results

3.1. Performance measures

Table 3 reports the performance results for all task. No task revealed performance differences between the exposed and non-exposed groups for reaction times or errors of omission. Prenatally exposed participants did have significantly more errors of commission in the Go/NoGo task

for the Press for all letters except X condition, however, a large standard deviation and high percent accuracy rate for both groups reduced the relevance of this finding. The performance results did not alter the imaging analyses for any task so were not used as covariates.

3.2. Imaging results

Each task revealed significant differences between prenatally exposed and non-exposed participants when controlling for current marijuana use. Consistently, the exposed group required increased neural activity in posterior brain regions to perform the tasks. The Visuospatial 2-Back task results included more activity in the left posterior cingulate gyrus of the prenatally exposed offspring compared to controls. The left lateralized differences between groups continued to be observed in the Go/NoGo task where the left post central gyrus, left precentral gyrus and left superior frontal gyrus were significantly more activated in the exposed than non-exposed group. The Letter 2-Back task elicited more activity in the left middle occipital gyrus, cerebellum and also the right superior temporal gyrus in the exposed compared to non-exposed group. Similarly, the left cuneus and right superior frontal gyrus were both more active during the interference of the Counting Stroop for the prenatally exposed group. The results are summarized in Table 4 and Fig. 1.

Table 4
Most significant results from each task. L = left R = right. Coordinates (x y z) are reported in Montreal Neurological Institute (MNI) space. T represents the T score obtained during the *t*-tests to determine significant group differences. The only significance level for the first column that did not meet the cut off with control for multiple comparisons was the Visuospatial 2-Back task results (was p = 0.67 corrected at cluster level and p = 0.04 as a region of interest).

fMRI Task	Exposed ≥ Non-Exposed Most Significant Voxel Information	Exposed ≥ Non-Exposed Additional Regions
Visuospatial 2-Back	L posterior cingulate x y z = −12 −48 25 T = 3.90 cluster size 386 p = 0.028 uncorrected	
Go/NoGo	L post central gyrus −48 −18 55 T = 4.29 cluster size 1499 p = 0.003 corrected	L precentral gyrus −24 −15 65 T = 3.77 cluster size 1499 p = 0.003 corrected L superior frontal gyrus −24 54 10 T = 3.30 cluster size 1499 p = 0.003 corrected
Letter 2-Back	L middle occipital gyrus −42 −84 25 T = 4.03 cluster size 5515 p = 0.000 corrected	L cerebellum −18 −39 −25 T = 3.95 cluster size 5515 p = 0.000 corrected R superior temporal gyrus 42–33 5 T = 3.91 cluster size 5515 p = 0.000 corrected
Counting Stroop	L cuneus/lingual gyrus −9 −78 25 T = 3.62 cluster size 1580 p = 0.002 corrected	R superior frontal gyrus 18 39 25 T = 3.66 cluster size 700 p = 0.075 FDR corrected

4. Discussion

This paper summarizes the outcomes from 4 executive functioning fMRI tasks performed by a unique, well studied group of young adults from the OPPS. The results highlight the similarities and present the consist results. Capitalizing on the ability of fMRI to act as a window into the working brain and the wealth of information obtained from these young adults throughout their lives, the results endorse the findings that there are in fact long term neurophysiological consequences of prenatal marijuana exposure.

Results from all four executive functioning tasks identified significantly more brain activity in the prenatally exposed group compared to the non-exposed group. Although both groups were able to successfully perform the fMRI tasks, the increased activity of the prenatally exposed group suggests the need for a compensatory response whereby either additional brain regions are required to perform the tasks or more activity in typically activated regions is necessary. It is possible that the two groups had different strategic approaches to perform the tasks, however, this too is suggestive of a required compensation or altered blood flow pattern that correlates with prenatal marijuana exposure.

While the results were varied for each task, they were consistently observed in posterior brain regions. Each task was designed to test a

Table 3
Performance results for all 4 tasks performed in the scanner adjusted for prenatal nicotine, alcohol and caffeine exposure and offspring nicotine, marijuana and alcohol use.

Performance measure and task	Exposed n = 16 Mean (SE)	Non-exposed n = 15 Mean (SE)	ANCOVA Results
Visuospatial N-Back			
Errors of omission (match to centre)	0	0.13 (0.09)	F(1,30 = 2.3 p < 0.14
Errors of omission (press for 2-back)	4.27 (2.4)	3.38 (2.2)	F(1,30) = 0.007 p < 0.94
Errors of commission (match to centre)	0.13 (0.09)	0.62 (0.33)	F(1,30) = 2.0 p < 0.17
Errors of commission (press for 2-back)	0.87 (0.36)	0.69 (0.26)	F(1,30) = 0.14 p < 0.71
Reaction time (s) (match to centre)	0.48 (0.03)	0.48 (0.03)	F(1,30) = 0.05 p < 0.83
Reaction time (s) (press for 2-Back)	0.53 (0.04)	0.53 (0.03)	F(1,30) = 0.00 p < 1.0
Go/NoGo			
Errors of omission (press for X)	0.25 (0.14)	0	F(1,30) = 1.46 p < 0.24
Errors of omission (press for all letters except X)	0.38 (0.20)	0.27 (0.15)	F(1,30) = 0.03 p < 0.87
Errors of commission (press for X)	0.69 (0.24)	0.6 (0.16)	F(1,30) = 0.13 *p* < 0.72
Errors of commission (press for all letters except X)	5.56 (1.05)	2.8 (0.59)	F(1,30) = 6.24 *p* < 0.02*
Reaction time (s) (press for X)	0.387 (0.008)	0.397 (0.015)	F(1,30) = 0.33 p < 0.57
Reaction time (s) (press for all letters except X)	0.40 (0.007)	0.41 (0.16)	F(1,30) = 0.28 p < 0.6
Letter N-Back			
Errors of omission (press for X)	0.19 (0.14)	0	F(1,30) = 3.1 p < 0.1
Errors of omission (press for 2-back)	2.9 (1.2)	2.5 (1.1)	F(1,30) = 0.01 p < 0.92
Errors of commission (press for X)	0.13 (0.09)	0.93 (0.37)	F(1,30) = 3.1 p < 0.9
Errors of commission (press for 2-back)	0.73 (0.5)	0.5 (0.27)	F(1,30) = 0.01 p < 0.92
Reaction time (s) (press for X)	0.42 (0.01)	0.44 (0.02)	F(1,30) = 1.3 p < 0.27
Reaction time (s) (press for 2-back)	0.50 (0.03)	0.52 (0.03)	F(1,30) = 0.26 p < 0.61
Counting Stroop			
Errors of commission (congruent)	5.6 (1.3)	3.8 (0.67)	F(1,30) = 1.6 p < 0.22
Errors of commission (incongruent)	13 (2.2)	8.3 (1.7)	F(1,30) = 2.75 p < 0.11
Reaction time (s) (congruent)	0.71 (0.02)	0.68 (0.02)	F(1,30) = 0.65 p < 0.43
Reaction time (s) (incongruent)	0.79 (0.04)	0.72 (0.03)	F(1,30) = 2.4 p < 0.14

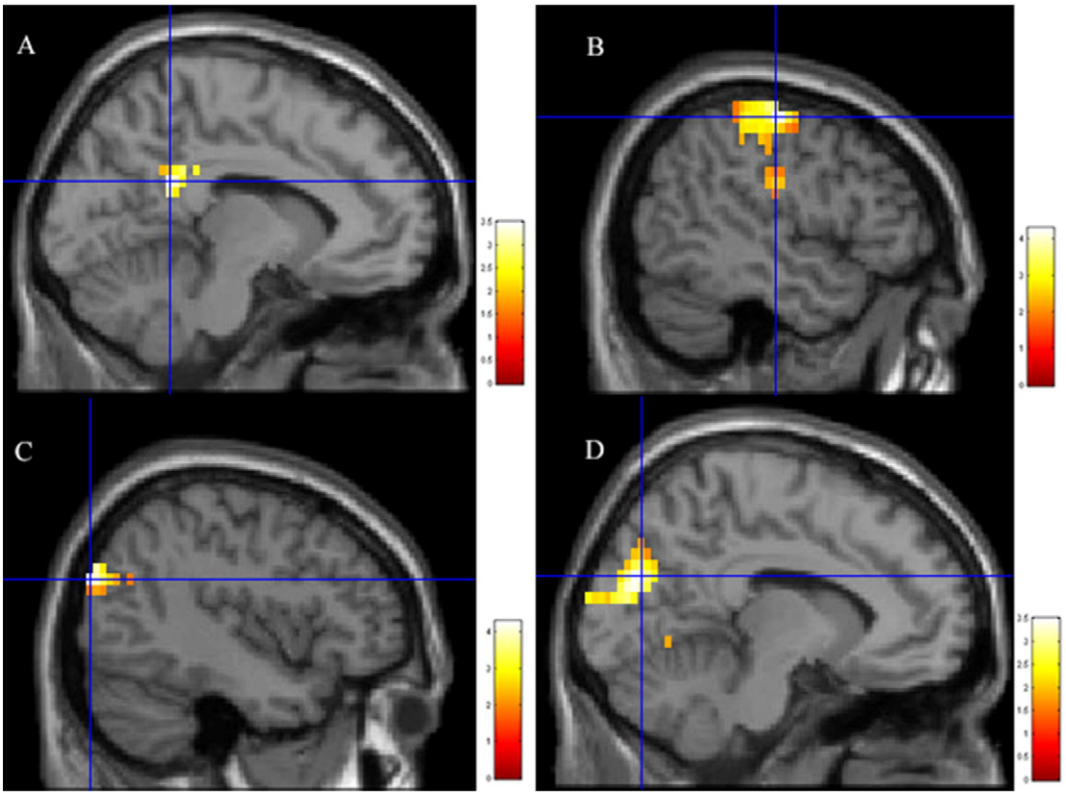

Fig. 1. Blue cross hairs represent the most significantly different voxel between groups for each task with the prenatally exposed group showing significantly more activity than the non-exposed group. A) Visuospatial 2-Back – left posterior cingulate gyrus, B) Go/NoGo task – left postcentral gyrus, C) Letter 2-Back – left middle occipital gyrus, D) Counting Stroop – left cuneus and lingual gyrus.

different type of executive functioning and thus commissioned distinct neural pathways. In general, it is thought that executive functions rely on the prefrontal cortex. However, these results reinforce the need for the integrity of the connections between more posterior brain regions and the prefrontal cortex to successfully perform these tasks. The specific regions with the greatest increased activity in the prenatally exposed participants were the postcentral gyrus in the Go/NoGo task, the cuneus in the Counting Stroop, the middle occipital gyrus in the Letter 2-Back task and the posterior cingulate in the Visuospatial 2-Back task.

The most significant imaging results were observed during the Go/NoGo task. The increased activity in the primary somatosensory cortex was part of a larger cluster that included the primary motor cortex. The left sided hyperactivity has been reported by Rubia et al. (2001) to represent a left fronto-parietal specialization for response selection. The participants responded with their right index finger and thus these regions would be active during the task but the increased activity for the prenatally exposed group suggests that they had to work harder to successfully perform the task, possibly due to dysfunction within the neural circuitry sub-serving response inhibition. Response inhibition is required for many aspects of everyday life and faulty development of the circuitry involved would impact the ability to suppress inappropriate behaviour.

This type of processing was also required during the Counting Stroop task, in addition to cognitive interference or the ability to allocate attentional resources when confronted with competing information (Bush et al., 1998). Interestingly, the Go/NoGo and Counting Stroop tasks were the only two tasks that showed significantly more activity in the superior frontal gyrus in the exposed group compared with the non-exposed group. This region is involved in mediating response selection and thus suggests, again, a compensation required for sufficient performance of these inhibition related tasks. By using more complex tasks, this compensation may not have been sufficient and further prefrontal cortex differences might have been observed in all tasks with subsequent performance decline.

The increased cuneus activity for the Counting Stroop task in exposed participants would suggest the requirement of additional visual processing. It would be of interest to investigate the functional connectivity between the posterior brain regions impacted during the Go/NoGo and Counting Stroop tasks and the prefrontal cortex activity to further understand their association and potential breakdown as a result of the prenatal marijuana exposure. Similarly, it would be relevant to use diffusion tensor imaging (DTI) to explore the integrity of the white matter tracts joining these regions in the prenatally exposed participants compared to controls.

DTI methods would also be of interest to investigate those pathways that make up the distributed neural network related to working memory. The ability to encode, temporarily store and then retrieve visual and spatial information is invaluable for effective goal-directed behaviour. The two working memory tasks in this study both revealed significant differences between exposed and non-exposed groups (although the Visuospatial 2-Back task results were significant at an uncorrected p value). The posterior cingulate has been shown to be an important structure for attentional focus (Leech and Sharp, 2014). This might suggest that the exposed group required more blood flow in this region to be able to attend to the stimuli and the desired responses during the Visuospatial 2-Back task. Similarly, during the Letter 2-Back task, regions related to attention, visual processing and the homologue to the left language related areas were significantly more activated in the exposed participants, suggestive of a disrupted working memory network requiring increased blood flow to perform the task successfully.

The combined results from the four fMRI tasks suggest that prenatal marijuana exposure affects diverse neurophysiology. This coincides with the widespread endocannabinoid system within the brain. Cannabinoid receptors, specifically CB1 receptors, are abundant in prefrontal

cortex, anterior cingulate, basal ganglia, amygdala, hippocampus and cerebellum (Batalla et al., 2013; Burns et al., 2007). Activity at these receptors by the naturally synthesized endogenous cannabinoids, anandamide and 2-arachidonoylglycerol (2-AG), plays a key role in several fundamental prenatal processes, such as cell proliferation, neurogenesis, and migration (Wu et al., 2011). This contribution to maturational refinement of cortical neuronal networks lays the groundwork for these connections to develop to maximal levels during late adolescence when executive functioning abilities are notably reaching their potential. Exogenous cannabinoids, for example smoked marijuana, are able to cross the placental barrier (Gomez et al., 2003) and can interfere with this development, leading to dysregulation of the endocannabinoid system and potentially limiting executive functioning in the future.

In summary, prenatal marijuana affects neurophysiological processing in several distributed neural networks that underlie multiple types of executive functioning. The finding of left lateralized results may represent a vulnerability that requires further engagement of the dominant hemisphere to perform higher cognitive processes. Further fMRI investigation into different types of executive functioning, functional connectivity analyses, and DTI protocols would help elucidate the mechanisms of how prenatal marijuana impacts brain function and structure and in turn affects abilities related to executive functioning later in life.

There are limitations of this study that should be pointed out, including the use of a block rather than an event-related design. Although block designs have advantages, it is not possible to divide neural activity into correct and incorrect responses or in the case of the Go/NoGo task between go and no-go trials. Further use of event-related tasks should be considered. The sample size of the study, while sufficient to observe significant results, should be increased for future studies. Another consideration is the timing at which these OPPS participants were prenatally exposed to marijuana. The potency of marijuana in the 1980s was lower than it is currently (Volkow et al., 2014). Thus, the message of significant long term implications for offspring is now more important than ever. The use or exposure to multiple drugs can also introduce a synergistic effect on brain activity and although drug exposures were controlled for in this study, it is not possible to completely rule out the potentially combined effects of several drugs. Further caution must be taken in extrapolating the results to other ethnic or socioeconomic status populations as the OPPS is primarily a middle-class white population.

Despite the limitations, these results demonstrate that prenatal marijuana exposure does have long term effects on brain activity and this is important for policy makers, medical practitioners, and women of child bearing age. This is particularly important given the debates about the legalization of marijuana and the risks of marijuana use across the lifespan that are currently abundant worldwide. Benefiting from the ability of fMRI to non-invasively access the active brain in such a unique sample of participants strengthens the findings and provides novel empirical evidence of the impact of prenatal marijuana on the young adult brain.

5. Conclusions

These results, although only briefly presented, extend previously reported effects of prenatal marijuana exposure on neurophysiological processing during executive functioning. These long term effects highlight the importance of optimizing the prenatal environment. The observed negative long term transgenerational effects are avoidable with knowledge transfer, education and a wider appreciation for the harmful consequences of prenatal marijuana exposure.

Transparency document

The Transparency document related to this article can be found, in the online version.

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