

Invited Review

A literature review of the consequences of prenatal marihuana exposure An emerging theme of a deficiency in aspects of executive function

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Abstract

In spite of marihuana being the most widely used illegal drug among women of reproductive age, there is a relative paucity of literature dealing with the neurobehavioral consequences in offspring — particularly the longer-term effects. However, there is a degree of consistency in the limited data, both across cross-sectional reports and longitudinally, where offspring have been followed for a number of years. Two cohort studies fall into the latter category; one involving a low-risk sample and, the other, a high-risk sample. Global IQ is not impacted by prenatal marihuana exposure but aspects of executive function (EF) — in particular, attentional behavior and visual analysis/hypothesis testing — appear to be negatively associated with in utero cannabis exposure in children beyond the toddler stage. This hypothesized influence of prenatal marihuana on EF is examined and discussed relative to effects (or lack of effects) across different ages in the offspring, cannabinoid receptors, and the extant general marihuana and prefrontal literature. © 2001 Elsevier Science Inc. All rights reserved.

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In recent years, there has been a notable increase in the public media's focus on marihuana. Numerous converging factors are contributing to this attention including the extent of use among young people, a vigorous debate about possible medical benefits of the drug, the increase in potency due to higher levels of Δ^9 -tetrahydrocannabinol (THC) content, and a sustained lobby for legalization or decriminalization of marihuana. From the scientific viewpoint, critical advancements have been made in recent years in such areas as the identification and pharmacological properties of marihuana receptors (recently reviewed in Refs. [7,72]), carefully controlled evaluation of cognitive outcomes following acute and chronic use (comprehensively reviewed in Refs. [49,85]), and neurological measures following marihuana using procedures, such as evaluation of brain glucose metabolism (e.g., Ref. [94]),

cerebral blood flow (CBF) [64], and electrophysiological measures (e.g., Ref. [86]).

Many of the above topics described in press and addressed in recent research have a direct bearing upon the question of putative long-term cognitive and behavioral outcomes on offspring of women who use marihuana during pregnancy, yet, in spite of the obvious critical nature of this issue, scientific data on this topic is sparse. Contributing to this paucity of work are numerous, complex pragmatic, logistic, and interpretative difficulties inherent in conducting such longitudinal, behavioral teratological research [23]. However, the extent of use of marihuana by both pregnant women and women of childbearing age emphasizes the need for the gathering and dissemination of data derived from well-controlled studies.

Only two longitudinal cohort studies with very different sample characteristics have focused upon the possible consequences of prenatal marihuana in offspring beyond early school age. In our own work, the Ottawa Prenatal Prospective Study (OPPS), the objective has been to examine the association between marihuana (and other

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socially used drugs) consumed during pregnancy and effects upon offspring in the areas of growth, cognitive development, and behavior. This longitudinal work has been underway since 1978, with the sample consisting of low-risk, white, predominantly middle-class families. During the pregnancy, neonatal, childhood, and adolescent time frames for which data have been published, the OPPS has collected over 4000 variables. Details of the repeated interview procedures during pregnancy, drug ascertainment, and general protocol have been described elsewhere [23,33]. The Maternal Health Practices and Child Development Study (MHPCD) [43] was initiated in 1982 at Pittsburgh and has focused upon the consequences of prenatal use of marihuana, alcohol, and cocaine. The subjects in this high-risk cohort are of low socioeconomic status and just over half are African American. Growth, cognitive development, temperament, and behavioral characteristics have been reported in offspring up to the age of 10.

1. Executive function (EF)

In the following review, a theoretical perspective that will be proposed (admittedly, somewhat speculatively at this stage of knowledge) is that the findings, particularly beyond the infancy stage, may be interpreted [22,23] as falling under the behavioral/cognitive construct termed EF.

EF is a term that connotes “top-down” mental control processes [15] reflected in future oriented behaviors that include cognitive flexibility in problem solving, focused attention, inhibition of prepotent responses, monitoring, evaluating, and adjusting self-directed responses, and working memory (the temporary storage of information while processing incoming data). Thus, EF may be considered a shorthand, describing a multiple, nonunitary set of cognitive/behavioral abilities critical in effortful, nonroutine, goal-oriented situations.

In hypothesizing a relationship between this construct and the consequences of prenatal marihuana exposure, it is important to recognize that EF is an overarching domain describing the organization and integration of specific cognitive and output processes over some interval of time. These on-line, integrative processes are, by the very nature of their function, comprised of subordinate cognitive operations. Thus, in evaluating EF adequacy in the offspring of marihuana users, consideration must be given to the competency in the underlying specific domains that are to be mentally manipulated [23].

Three additional aspects of EF merit a brief discussion. Clinical and empirical evidence indicate that EF is primarily subserved by the prefrontal region of the brain (e.g., Refs. [38,59]) although many cognitive tasks that require the prefrontal cortex also involve other structures, such as the hippocampus and cerebellum (e.g., Refs. [17,23,59]). The prefrontal region has various subregions

with reciprocal connections to other regions of the frontal lobe, posterior association cortices, and subcortical structures [38]. These anatomical pathways subserve the integrative nature of EF and its involvement with subordinate cognitive processes.

One characteristic of the prefrontal lobes is that morphologic development continues well after birth with full maturation being achieved around puberty. Importantly, for the present paper, different areas within the prefrontal cortex mature at different times (e.g., Refs. [42,91]) and, functionally, can be differentiated (e.g., Refs. [38,59]). Using a factor analytic approach to examine the developmental course of EF in children, it has been reported [16,58,96] that, in a battery of tests of this construct administered to a normative sample of children of different ages, three independent factors were revealed. One factor reflected planning, another reflected verbal fluency and complex problem-solving skills, while a third reflected visual hypothesis testing and impulse control. Later in this paper, the argument will be presented that it is quite feasible for certain facets (or factors) of EF to be vulnerable to prenatal marihuana use and other aspects of the construct not to show any impact of the drug.

Thus, EF is a multistage process, with various functions maturing at different times and the construct ought not to be considered a domain of a singular nature; rather it encompasses a number of distinct cognitive processes. These distinct facets of EF have a developmental trajectory. Precursors or rudimentary aspects of EF are present in infants and toddlers (e.g., object search and object permanence behavior), however, most spheres of EF are not apparent until the children approach or reach school age and continue to develop at least until puberty.

Both in clinical studies in which injury to the frontal lobes has occurred (e.g., Refs. [38,90]) and in studies examining the normative developmental course of EF in children (e.g., Refs. [58,96]), researchers have reported that this construct is not associated with typical measures of intelligence. As discussed elsewhere [23], EF may serve to distinguish between intelligence required in carrying out adaptive, goal-directed behavior from intelligence as measured by global performance on standardized psychometric intelligence tests. As many of the subtests in traditional intelligence tests are structured in such a way as to set up specific objectives, the assessment of such key aspects of EF as integration of domains of functioning, goal setting, planning, and self-monitoring is somewhat problematic. Furthermore, global IQ tests evaluate, to a large degree, well-learned information and established (“crystallized intelligence”) cognitive sets, which may not require facets of EF. This however, does not mean that there is no shared variance between general IQ and EF, particularly when the subtests involve ability to reason logically and abstractly (“fluid intelligence”) in timed problem-solving tasks and tasks that do not involve familiar, well-learned information [23].

2. Use of marihuana in the population of interest

Marihuana is the most commonly used illicit drug among women of reproductive age [54,55]. In NIDA's most recently completed National Pregnancy and Health Survey [69], self-reported marihuana use during pregnancy was 2.9%, which is approximately three times the frequency of cocaine/crack use. In NIDA's 1994 Monitoring the Future Survey [54], 10.4% of women between the ages of 19 and 32 reported using marihuana in the past month, in contrast to an 8.3% rate among women of the same age in the 1990 survey. Although these are the most recent figures available, they are based on 1992 data and likely represent a conservative estimate of current use as reversing a downward trend noted in the late 1980s and early 1990s, the use of marihuana is increasing among women of reproductive age [69]. In addition, among both heavy (e.g., Ref. [53]) and social (e.g., Ref. [46]) maternal cocaine users, marihuana is frequently smoked and therefore, in order to disentangle cocaine's potential effects, marihuana's role must be understood. Also of note is the fact that among high school seniors (those entering reproductive years), the annual use of marihuana increased between 1992 and 1993, from 22% to 26% (sexes not differentiated), reversing a previous declining trend seen since the early 1980s [54]. A December 1999 Monitoring the Future press release (www.isr.umich.edu/src/mtf/) noted that 23% of US high school seniors reported marihuana use in the past 30 days. These figures, using a survey approach, may well be conservative. In our own work (the protocol of which is described briefly below), among the predominantly middle-class, 18–20-year-old OPPS offspring, the rate of smoking at least one joint in the past week (ascertained by self-report and verified by urine analysis) was 32% and smoking at least that amount of marihuana on a regular basis in the past 5 years was 52% (unpublished data).

3. Course of pregnancy and fetal effects

Historically, at an anecdotal level, marihuana has been associated with an increase in frequency and intensity of contractions [1]. Consistent with this folk medicine are observations from the OPPS that among mothers who used marihuana on approximately a daily basis, compared to appropriate controls, precipitate labor was significantly more frequent [47], and a shortened gestation length of approximately 1 week was observed [37]. Although a 1-week shortened gestation length has little clinical significance, the finding that the effect was dose-related may be of significance given the increased THC content in marihuana today as contrasted to the typical marihuana of two decades ago. Although two reports have noted a relationship between preterm delivery and marihuana [40,50], most investigators (including reports based on both the OPPS

and MHPCD cohorts) have not noted such an association (e.g., Refs. [12,24,92]).

In neither the OPPS [20,24] nor the MHPCD [12] cohorts was maternal marihuana use associated with increased miscarriage rates, types of presentation at birth, Apgar status, nor the frequency of complications or major physical abnormalities at birth. In the OPPS sample, there was no significant association with prenatal marihuana exposure and either an increased frequency of particular minor anomalies or a specific pattern of such anomalies [70]. However, two anomalies associated with the visual system, true ocular hypertelorism and severe epicanthus, were observed only among children of the heaviest users of marihuana [70]. The lack of a clear relationship in the OPPS sample between minor physical anomalies and maternal marihuana is consistent with the few investigators who have reported data on this subject [12,60,92]. There are however two possible exceptions. One is a large study [52], and the other involves two reports of five individual cases [74,75]. In both instances, the anomalies related to prenatal marihuana use are part of the diagnostic criteria of the fetal alcohol syndrome. These findings may reflect a lack of control for confounding factors and/or the relative risk status of the women in the study. A comprehensive review of the animal and human literature related to prenatal marihuana use and morphologic abnormalities in offspring is presented elsewhere [10].

4. Growth

Most studies have failed to find a negative relationship between prenatal marihuana exposure and fetal growth (reviewed in Refs. [9,18]). However, others [12,13,92] have found a small but significant negative relationship between first trimester marihuana use and birth length but not other growth parameters. In a sample of primarily minority women, there is one report [97] of decreased birth weight and length significantly associated with marihuana use. Intriguingly, in the MHPCD and OPPS cohorts, prenatal marihuana use was associated with an increased weight: Day et al. [12] found this association at birth between heavy third trimester use and birth weight in a minority, high-risk sample (although it was not found with a combined marihuana and alcohol cohort [13]), and Fried and O'Connell [27] reported a positive relationship between marihuana use during each trimester and weight at 24 months in the low-risk, middle-class OPPS sample.

A limited number of studies have examined growth in offspring of marihuana users beyond the neonatal stage. Those studies, which noted a negative association between birth length and prenatal marihuana exposure, reported that this association was no longer significant by 8 months [13], 1 year [92], or 6 years [14]. In a recent report [36] based on the OPPS sample, extending the positive association between the weight of children at 24 months born to women

who smoked marihuana on a regular basis during pregnancy, there was a similar trend in both weight and height noted in this low-risk sample at 3 and 4 years of age. Growth at these ages, as indicated by ponderal indices, was relatively symmetrical. Caution must be exercised in generalizing this observation to a high-risk population for, as reviewed elsewhere [21], a high-risk environment may well exacerbate the effect of prenatal cannabis exposure.

A further observation among the OPPS sample [36] was that, in contrast to the positive tendencies observed with respect to weight and height, prenatal marihuana use is significantly, negatively associated with the children's head circumference at 9–12 years of age. This trend was present in a nonsignificant dose response fashion at each of the earlier ages assessed.

5. Neurobehavioral/cognitive outcomes: a developmental view

5.1. Newborn, infants, and preschoolers

The literature describing the neurobehavioral effects of prenatal marihuana use on the newborn, although provocative, is far from definitive. In the Ottawa sample, at less than 1 week of age, prenatal marihuana exposure was associated with increased tremors, typically accompanied by exaggerated and prolonged startles, both spontaneous and in response to mild stimulation [20,26]. In the same sample, maternal marihuana use was associated with relatively similar observations in 9- and 30-day-old infants [32]. Although these particular indicants of impairments in nervous system state regulation were not detected by some researchers [79,92], reports of altered autonomic arousal in other outcome measures have been reported. Neonates of maternal cannabis users have been noted as having an increased likelihood of exhibiting a high-pitched cry [57] and to spend less time in quiet sleep [82].

In the OPPS sample, newborns of less than a week of age born to marihuana users had poorer habituation to visual, but not auditory, stimuli [20,26]. It may be noteworthy that these observations are consistent with the findings of some of the older animal literature. In a primate study [44], the behavior that distinguished the marihuana offspring from controls was a failure to habituate to novel stimuli. In rodents, visual developmental milestones also were delayed in the offspring of marihuana-treated dams [6,19,25]. However, no negative relationship between human infant visual habituation and maternal marihuana use has been reported in other studies (e.g., Refs. [79,92]).

Although the literature is quite sparse, reports examining infants and preschoolers born to marihuana users have a degree of consistency that is intriguing. At 1 year of age, the OPPS cohort [29], as well as in other studies [2,92], all of whom used the Bayley Scales of Infant Development [4], report no association between marihuana use during preg-

nancy and infant mental or motor development. In the MHPCD cohort, third trimester use of one or more joints a day was associated with a lowered mental score on the Bayley scale at 9 months of age but not at 18 months [81]. In children in the OPPS cohort, the consistent lack of effect persisted for a few years beyond infancy. At 2 years of age [29], prenatal marihuana exposure was found to be negatively associated with scores on a test of language comprehension, but this relationship did not persist after the influence of home environment was taken into account. When 36-month-old offspring were assessed [30], after controlling for confounding factors, prenatal marihuana exposure was neither significantly associated with tests of language expression and comprehension nor decreased cognitive scores.

However, at 48 months of age, a number of cognitive variables appeared to distinguish the children of regular marihuana users (more than five joints per week) from the remainder of the OPPS sample [30]. In particular, memory and verbal outcome measures (based primarily on the McCarthy Scales of Children's Abilities [67]) were negatively associated with prenatal daily marihuana use, and this statistical association remained after controlling for confounding variables. These observations are strikingly similar to findings reported from the MHPCD cohort [11] in which the 3-year-old children of daily marihuana users were impaired on the short-term memory, verbal, and abstract/visual reasoning subscales of the Stanford–Binet Intelligence Test [93]. An additional report [48] using the Stanford–Binet test also noted, in 3-year-old offspring of polydrug users, that maternal marihuana use (the amount not specified) was predictive of poorer performance on abstract/visual reasoning. It is noteworthy that in all three studies, when the total cohorts were considered, there were no overall effects of marihuana on the composite, intelligence scores.

Reports focusing upon the behavioral and cognitive effects of prenatal marihuana exposure in offspring older than 36 months are limited to data derived from the OPPS and MHPCD. Although convergence might be too strong a term to describe data derived from just two research centers, there appears to be, as with the children at a younger age, at least a confluence of findings. Furthermore, equally important is that this seeming confluence extends to two other facets of the data. First, the outcomes reported from the two cohorts as the offspring get older are, in many ways, consistent with those observed at earlier stages of development and, secondly, the range of findings may be collectively, as falling under the construct of EF, described at the beginning of this review.

The case for considering prenatal marihuana exposure as impacting upon aspects of EF can begin with the observations summarized earlier in which it was noted that no effects of the drug upon the offspring beyond the neonatal period were observed until the children were 3 [11,48] or 4 [30] years of age. The absence of such an association is

consistent with the developmental course of executive functioning. Furthermore, the absence of a lowering of IQ and, in contrast, the nature of the tasks (memory, verbal outcomes, and abstract/visual reasoning), which were negatively impacted in the 3- and 4-year-old offspring of marihuana users also is consistent with the hypothesis that in utero marihuana exposure may impact, in a negative manner, on aspects of EF.

5.2. School-aged children

In considering the data available on school-aged offspring born to women who used marihuana during pregnancy, an interesting, but certainly incomplete picture is emerging. In the OPPS sample, at 5 and 6 years of age, no differences were noted in the exposed and nonexposed children when assessed with global tests of cognition and language [28]. As mentioned above with respect to EF and intelligence, it is possible that the instruments used in this work [28] provide a general and broad description of cognitive abilities and may not be capable of identifying nuances in neurobehavior that discriminate between marihuana-exposed and nonmarihuana-exposed children. Tests that assess specific cognitive characteristics and strategies may be needed to differentiate between these groups.

This approach was the subject of two reports arising from the OPPS cohort when the subjects were between 9 and 12 years of age. In the first [35], a neuropsychological battery was administered that included tests that assessed various aspects of EF, as well as tests designed to assess global intelligence. The second was a direct investigation of the possible influence of prenatal marihuana exposure on 'top-down' visuoception [31].

In the cognitive report [35], the assessment battery included the Weschler Intelligence Scale for Children-III (WISC-III) with its subscales, composite, and derived scores [95], a Continuous Performance Task (CPT), and a delay task [45], the category test — a visual concept formation task [78], working memory assessment [84], a measure of oral fluency [87] and a timed, difficult tactile, self-monitoring task [78]. The WISC-III was used as a measure of general intelligence with the subscales measuring various cognitive abilities. The other tests assess aspects of behavior that, traditionally, are considered to be indicants of EF. The CPT and the delay tasks examine sustained attention and inhibition of prepotent responses, respectively. The category test involves visually deducing abstract categories and the ability to adjust behavior on the basis of negative and positive feedback. The tactile performance task required a blindfolded subject to put wooden blocks of varying shapes in their proper place on a formboard first with their dominant hand, then with their nondominant hand and finally, with both hands. This task purports to assess the ability to recall previous information, as well as the ability to monitor and correct self-directed responses.

As with the data collected from the OPPS sample at earlier ages, there was no association between the Full Scale IQ and in utero marihuana exposure. Among the 13 WISC-III subtests, only two, the Block Design and Picture Completion subtests, differentiated among levels of prenatal marihuana exposure suggesting that in utero marihuana affects particular, rather than global, aspects of intelligence.

In the Block Design subtest, subjects are directed to assemble blocks to form a design identical to one presented in a picture. This nonverbal concept formation task requires the ability of perceptual organization, spatial visualization, and abstract conceptualization. The Picture Completion subtest requires the subject to identify a missing portion of an incompletely drawn picture and tests the ability to differentiate essential from nonessential details.

These two subtests of the WISC are multifaceted, involving basic visuospatial and visuomotor abilities, as well as higher order cognitive processes. The latter likely include planning, impulse control, visuoconstruction and visuoanalysis. The marihuana findings on the two WISC subtests persisted after statistically controlling for basic spatial and motor abilities, thus supporting the interpretation that the impact of prenatal marihuana exposure on these WISC subtests is upon 'higher-order' cognitive processes. Although not the subject of this review, it should be noted that these findings are in considerable contrast to those found among the offspring of cigarette smokers as both the IQ scores and virtually all of the WISC subtests (particularly those with a verbal aspect) served to discriminate across levels of prenatal cigarette exposure [35].

The negative relationship between the two subtests and maternal marihuana use in the present work is consistent with the finding of poorer abstract/visual reasoning in 3-year-olds exposed in utero to marihuana in the MHCPD cohort [11] and elsewhere [48]. At that age, the assessment consisted of the child having to do a formboard puzzle and replicate different block designs. At approximately 10 years of age, prenatal marihuana use in the MHCPD cohort was reported (abstract [80]) to continue to be a significant predictor of poorer abstract/visual reasoning [80]. At this age, the score was derived from performance on a block-design task, a progressive design matrices task, and the ability to copy geometric shapes. It may also be noteworthy, with respect to the proposed vulnerability of aspects of visual functioning, that when the children in the OPPS were less than a week old, prenatal marihuana exposure was associated with poorer habituation to visual stimuli.

Among the 9–12-year-olds in the OPPS cohort [35], the results of the non-WISC outcome measures, which assessed aspects of EF, were consistent with the observations for the marihuana groups gleaned from the WISC tasks. The primary variables (in addition to the Block Design and Picture Completion subtests of the WISC) that maximally discriminated among the marihuana groups were the category test and measures of impulsivity.

Thus, of the six tests thought to assess aspects of EF, the two that were found to be associated with marihuana involve impulse control, visual analysis, and hypothesis testing. This is consistent with the WISC results as the two subtests in that battery associated with prenatal marihuana use — Block Design and Picture Completion — require visual analysis and hypothesis testing.

The finding that only particular facets of EF appear to be associated with maternal marihuana use can be interpreted as consistent with substantial evidence, briefly described earlier in this review, suggesting that behaviors predicated upon successful executive functioning are not of a singular nature. This position arises from diverse findings one of which was based upon a factor analytical approach used by Welsh et al. [96] to examine the developmental course of EF in children. Three independent factors were revealed. One factor was labeled “Hypothesis Testing and Impulse Control.” This identified a convergence of cognitive processes that were strikingly similar to those associated with prenatal marihuana exposure in the cognitive assessment study just described [35]. This factor was defined by Welsh et al. [96] as requiring visual analysis and inhibition of prepotent responses. Of the other two factors identified by Welsh et al. [96], the first was referred to as a “Fluid and Speeded Response” factor and included verbal fluency and motor sequencing. The final factor was labeled as “Planning” and involved a spatial positioning problem-solving task relying heavily on working memory with no visual cues or alternatives to select from. In the assessment of cognition in the 9–12-year-old OPPS cohort, those tasks, which assessed cognitive processes contributing to what Welsh labeled as the “Fluid and Speeded Response” factor (verbal fluency, tactile performance task) and “Planning” factor (working memory, tactile performance task) were not found to be associated with maternal marihuana use.

It is noteworthy that in the examination of the development of EF findings [96], hypothesis testing and impulse control, in contrast to the other EF factors, were achieved at 10 years of age. This finding is consistent with the observation that marihuana’s negative effect on this dimension of EF manifested itself in the 9–12-year-olds.

A recent report based on the 9–12-year-old OPPS sample provides support for the hypothesis that prenatal marihuana may impact upon ‘top-down’ neurocognitive functioning [31], a key aspect of EF. In this work, visuo-perceptual tasks, some of which were part of the earlier cognitive assessment battery [35], ranging from those that required basic capabilities to those that required considerable integration and cognitive manipulation, were utilized. Further, in order to ascertain whether any change in visuo-perceptual functioning may in fact be due to demands upon nonvisual facets, such as attentional, memory, and/or motor components, tasks were included to assess and control for these underlying behaviors.

The tests included the Test of Visual–Perceptual Skills (TVPS) [39], a nonmotor task with an overall derived

summary score (Perceptual Quotient) and seven subscales that assess basic visuo-perceptual skills; the Trail Making Test [77] requiring visual scanning, visuospatial sequencing, attention, mental flexibility, and motor function; the Knox Cube [88] requiring visual attention, visual memory, and visual sequencing; and the WISC-III Perceptual Organization Index, its four subscales each of which require problem-solving abilities (Block Design, Object Assembly, Picture Completion, Picture Arrangement), and the subscales of Symbol Search, Mazes, and Coding [95], all requiring various aspects of visuo-perceptual functioning.

Abilities that might influence performance on visual tasks were also assessed. The WISC-Full-Scale was used as a measure of general intelligence, the WISC-Digit Span as a test of memory, the WISC-Freedom of Distractibility as a measure of attention, and the Developmental Test of Visual–Motor Integration [5] as a measure of visuo-motor coordination.

Overall, the effect of maternal marihuana on the 9–12-year-old offspring depended upon the nature of the visuo-perceptual task. No association was noted between prenatal marihuana exposure and any of the TVPS subtests or the overall Perceptual Quotient summary score of that test. Thus, in tasks that demanded little or no analytical or integrative skills but did require basic fixed, functional visuo-perceptual abilities, children exposed to marihuana in utero were not impacted. However, a contrasting picture emerged with prenatal marihuana exposure and the Perceptual Organization Index derived from the WISC-III. This composite score, based upon subtests that require skills in planning, integration, analysis, and synthesis in addition to basic visuo-perceptual abilities, was negatively associated with maternal use of this drug.

When the TVPS Perceptual Quotient Index was used as a covariate statistical control representing basic visuo-perceptual capabilities, the significant negative association between prenatal marihuana exposure and the Perceptual Organization Index remained. This suggests that the negative outcome was not mediated by a dysfunction in basic perceptual competencies (‘bottom-up’) but rather was due to marihuana’s impact upon the analytical and integrative demands of the tasks making up this composite Perceptual Organization Index.

Thus, consistent with the speculations described above, prenatal marihuana use appears to be negatively associated with performance in situations, which demand ‘top-down,’ integrative processing — the type of neurocognitive requirement underlying EF. This is in contrast to the association between prenatal cigarette smoking and performance on these tasks as the impact of cigarette use during pregnancy was negatively associated with the basic visuo-perceptual tasks — a ‘bottom-up’ impact.

The finding that complex visuo-perceptual tasks may be impacted by in utero marihuana exposure and that this may reflect impaired EF and prefrontal activity is supported, indirectly, by the clinical literature. Patients with damage to

the frontal region are not impaired on basic visuoperceptual tasks, but one of the most striking negative consequences noted among such subjects is in the performance of tests requiring visuoperceptual planning and integration [62,90].

A further line of evidence suggesting a link between prenatal marihuana exposure and aspects of EF can be derived from studies that have focused upon attentional behavior. Both the OPPS [34] and MHCPD [56] cohorts at age 6 were assessed in this domain. Attention, a complex, multifaceted behavior, encompasses processes that overlap with many aspects of EF [3], including the capability to withhold prepotent but inappropriate response tendencies, resistance to distraction and interference, and the ability to sustain a focus. Although different aspects of attention appeared to be impacted in the two cohorts, both studies found that prenatal marihuana use was associated with a negative effect upon attentional processes.

In both cohorts, a CPT was used to measure inattention and impulsivity. Essentially, the CPT involves a serial presentation of stimuli over a designated length of time. Typically, the subject is asked to press a response button or computer key when a particular stimulus (or sequence of stimuli) is presented and to withhold responding when nontarget stimuli occur. Measures that can be taken in this task include correct identification (hits), errors of omission (misses), and errors of commission (false alarms). In the OPPS [34], prenatal marihuana exposure was associated with increased omission errors and decreased number of hits in a dose-related fashion. Furthermore, as the CPT progressed, only the children in the regular (more than five joints per week) marihuana category increased their omission errors suggesting that sustained attention may be particularly vulnerable to prenatal marihuana exposure.

In the MHPCD cohort, prenatal marihuana exposure was also found to impact upon attentional processes [56] although, on a CPT, it was errors of commission (possibly reflecting impulsivity), rather than omission, that were related to the drug. It was speculated by the authors that prenatal marihuana may impact upon processing speed, and that this deficit would become more manifested over a longer task, particularly if there were time pressure demands upon the child. Furthermore, the authors interpreted their findings as suggesting that, in this domain, prenatal marihuana exposure impacts upon attention and impulsivity and, thereby, decreases the ability to plan and execute tasks; critical aspects of EF.

In the OPPS work [34], in addition to the CPT task carried out by the children, the mothers in the study were asked to rate their offspring using a behavioral symptom checklist [8]. Consistent with the findings on the experimental task, the children exposed prenatally to marihuana were rated as more impulsive and hyperactive. Paralleling the OPPS observations, a recent report of the MHPCD cohort at 10 years of age [43] noted an association between prenatal marihuana exposure in the first and third trimester

and increased parental reports of hyperactivity, inattention, and impulsivity.

In this MHPCD study [43], based on both maternal ratings of child behavior and teachers' reports, an association between increased levels of delinquency and externalizing behavior associated with prenatal marihuana exposure was observed. On the basis of a path analysis, it appeared that poor attentional skills mediated the association between the mothers' report of delinquency and prenatal marihuana use. This relationship between marihuana use during pregnancy and the behavioral problems in the offspring is similar to an earlier trend noted in the OPPS cohort when the children were between 9 and 12 years of age [71]. In that preliminary report, mothers who had used marihuana regularly during pregnancy rated their children as having a higher rate of conduct disorders. However, this difference did not retain significance after extraneous variables were controlled.

Taken as an overall picture, the somewhat limited literature on prenatal marihuana exposure does present a theoretically consistent picture — one that is supportive of the hypothesis of the drug impacting upon aspects of EF in the offspring. The question may be put as to whether marihuana research findings outside the world of pregnancy are, at least indirectly, supportive of the proposition put forth in this review. In fact, consideration of some of the extant literature suggests that there are several lines of evidence linking cannabis, frontal lobe activity, and EF.

6. Marihuana, frontal cortex, and EF

In work carried out in the early 1970s, injected, tritiated THC in the squirrel monkey [68] and in the rat [83], was found in high concentrations in the frontal regions of the cortex. Twenty years later, using autoradiographic procedures [51] to investigate the distribution of cannabinoid receptors in rodents, it was reported that, within the different regions of the rat's cortex, there was a rostral-to-caudal gradient density of receptors. Recently, the anatomical distribution and concentration of cannabinoid receptors in the fetal, neonatal, and adult human brain were examined by autoradiography following *in vitro* labeling with a synthetic cannabinoid agonist [41]. Cannabinoid receptor binding sites were identified throughout the regions of the adult neocortex with the greatest density being in the middle gyrus of the frontal lobe, cingulate gyrus, and temporal lobe. Unfortunately, frontal cortex from either fetal or neonatal tissue was not available for analysis. However, based on the material that was examined, the authors found that the receptor distribution was similar in the fetal and neonatal brain to the adult human brain except that the density of receptor binding was markedly higher in the developing brain. The researchers conclude that one of the major cannabinoid receptor sites in the human brain is in that part of the forebrain associated with higher cognitive functions.

The association between marihuana and the frontal lobes is also seen in a number of studies using physiological markers of neurological functioning. CBF is used as an index of brain activity [76], and this technique has been used by several researchers to examine brain function and marihuana (e.g., Ref. [66]). Paralleling the receptor literature, the frontal lobes appear to be markedly impacted by marihuana. Consistently across studies, among the most marked change in CBF following marihuana smoking or THC administration in experienced users was in the frontal region of the brain [63–65,94]. Using another physiological measure as an indicant of brain activity, chronic daily use of marihuana resulted in marked alteration of alpha activity derived from EEG recordings [89]. These changes were primarily in the frontal region and were noted even after prolonged cessation of use [89].

Perhaps the most obvious association between marihuana and EF can be found in the behaviors that appear impacted by the long-term use of cannabis. These include fragmentation of thought, difficulty in short-term memory tasks, and disturbances in attention, concentration, and judgment (e.g., Refs. [49,61,85]). Perseverative responding has also been reported as a residual EF effect in heavy users who had been abstinent for at least 24 h [73]. These findings strongly implicate marihuana as having an impact upon EF and, therefore, the prefrontal cortical regions. Finally, although beyond the scope of this review, it should be noted that observations on nonpregnant animal models using behavioral and/or histological measures have reported outcomes that are consistent with alterations in EF. This extensive literature has recently been comprehensively described and summarized [85].

7. Conclusion

The consequences of prenatal exposure to marihuana are subtle. Furthermore, longitudinal research that forms the basis of the bulk of the observations reported in this review is quasi-experimental in nature and as such, raises marked interpretative issues that must be recognized [23]. Perhaps most fundamental among these is the inability to manipulate the host of complex factors ranging from nonmarihuana drug use to caretaker variables that potentially influence outcomes of interest. Other problematic issues include the reliability of drug self-report, the relatively small sample sizes (particularly in the heavy drug using group) that are frequently dictated by pragmatic issues endemic to longitudinal research, and the recognition that the unique variance attributable to prenatal marihuana is typically less than 5% after the variance due to potentially confounding factors is partialled out. However, as discussed elsewhere [29], this latter statistical procedure, in which all shared variance is attributed to confounding variables, may be an overconservative view of marihuana's association with the offspring's behavior and cognitive functioning. Together,

these caveats, coupled with the relatively sparse literature, are a combination that makes any definitive statement problematic, presumptuous, and foolhardy. However, the available reviewed and synthesized data have led to the following observations and hypothesis. The impact during the course of pregnancy and upon the neonate appear to be considerably moderated by other risk factors with evidence from a number of cohorts suggesting limited (if any) effects upon fetal growth and central nervous system functioning. During the toddler stage, there is little evidence for a prenatal marihuana effect either upon growth or behavior. However, beyond the age of 3, there is a confluence of findings from widely differing cohorts suggestive of a putative association between prenatal marihuana exposure and aspects of cognitive behavior that fall under the umbrella of EF — a construct that is mediated primarily by the prefrontal region of the brain. The facets of this construct, which appears particularly impacted, are in the domains of attention/impulsivity and problem-solving situations requiring integration and manipulation of basic visuo-perceptual skills. Support for this hypothesized link can also be found in the general marihuana literature that clearly indicates an association between this drug and frontal lobe functioning. Although there is a degree of consistency in the prenatal literature, the very limited number of studies, which have followed children beyond the age of 3, coupled with the issues raised in the opening paragraphs of this review, emphasizes the need for further, well-controlled investigations in this area.

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