

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  $\Delta 9$ -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 marijuana, 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 marijuana 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 marijuana 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 subservise 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 marijuana 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].

