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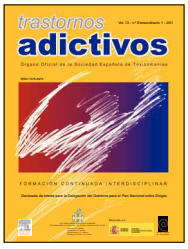

BRIEF REVIEW

Adolescent Brain and Drug Experimentation

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KEYWORDS
Population Neuroscience;
Adolescence;
Social Hierarchy;
Nicotine;
Drug Experimentation

Abstract Adolescence represents a major transition that takes place over most of the second decade of human life. In the shift from a caregiver-dependent child to a fully autonomous adult, the adolescent undergoes multiple changes in his/her physical growth, physiology, and cognitive and emotional skills. These changes are taking place in a social context dominated by peers. The adolescent brain (and behaviour) is the product of the interplay between genes and experiences taking place throughout development. The key question here is that of why: why do adolescents engage in "problem behavior". Some argue that this is part-and-parcel of risk taking and sensation seeking, which are "hard wired" in the adolescent brain. Rather than taking this biologically deterministic view, we and others argue that, for adolescents, problem behaviors are considered instrumental towards the attainment of goals". Specifically, in the case of adolescence, the main —adaptive and, hence, normative— goal in this context is that of establishing a new social hierarchy where same-sex and opposite-sex mates play a key role. Thus, the extent to which an adolescent experiments with drugs is likely to depend both on social context ("hierarchy" quest), his/her resistance to peer influences, his/her genes (e.g. nicotinic receptor) and other influences, such as prenatal exposure to maternal cigarette smoking. The latter factor is likely to influence substance-use behaviour through multiple (biological and psychosocial) pathways.

PALABRAS CLAVE
Neurociencia poblacional;
Adolescencia;
Jerarquía social;
Nicotina;
Experimentación con drogas

El cerebro adolescente y la experimentación con drogas

Resumen La adolescencia representa un período clave de transición que transcurre en su mayor parte durante la segunda década de la vida. En el proceso entre la dependencia del niño y la plena autonomía del adulto, el adolescente experimenta múltiples cambios en su crecimiento físico, su fisiología y sus destrezas cognitivas y emocionales. Estos cambios ocurren en un contexto social dominado por los iguales. El cerebro adolescente y su conducta es el producto de la interacción entre genes y experiencias que se expresan durante este período de desarrollo. La cuestión clave es: por qué los adolescentes se involucran en conductas

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problemáticas. Algunas teorías defienden que se debe a un predominio de los rasgos de búsqueda de sensaciones y riesgos que estarían incrustados en la arquitectura cerebral del adolecente. De manera alternativa a esta visión determinista, nuestra aproximación es que las conductas problemáticas pueden considerarse funcionales, propositivas e instrumentales para la consecución de las metas propias de este período. Específicamente, serían instrumentales al objeto de establecer una nueva jerarquía social donde los iguales del mismo sexo y del sexo opuesto ocupan un lugar prioritario. Por tanto, el grado en que los adolescentes experimenten con drogas dependerá, tanto del contexto social (la búsqueda de jerarquía), como de su resistencia a la influencia de los pares y otras influencias genéticas y biológicas (por ejemplo, el consumo de nicotina de la madre durante la gestación). Estos factores impactarían en la conducta de experimentación con drogas a través de múltiples vías biológicas y psicológicas.

Adolescence represents a major transition that takes place over most of the second decade of human life. In the shift from a caregiver-dependent child to a fully autonomous adult, the adolescent undergoes multiple changes in his/her physical growth, physiology, and cognitive and emotional skills. These changes are taking place in a social context dominated by peers. The adolescent brain (and behaviour) is the product of the interplay between genes and experiences taking place throughout development, from conception to the present[1]. Over time, the various internal (genes and their products) and external (environment, experience) factors affect different levels of the organism in a complex manner-hence, the relevance of the concept of developmental cascades: "The cumulative consequences for development of many interactions and transactions occurring in developing systems that result in spreading effects across levels, among domains at the same level, and across different systems or generations"[2]. Keeping this concept in mind, I will touch briefly on a few issues relevant for our understanding of drug experimentation during adolescence, focusing on the role of peers and parents.

Let us begin by asking about the frequency of substance use during adolescence and the role of peers. As presented by Dr. Antonia Domingo-Salvany (in this issue), the lifetime experience of 14 to 18 year-old Spanish adolescents with the use of alcohol (92%) and cannabis (55%) point to the normative nature of this behaviour. This is also the case in other populations; for example, in the Saguenay Youth Study, 52% and 38% of 12-to-18 year-old adolescents have tried alcohol and cannabis in their lifetime[3]. And yet, the use of alcohol and drugs during adolescence is considered to be part of the "problem behaviour" defined by Jessor and Jessor[4], namely "behaviors that depart from the legal and social norms of general society" and include, in addition to cigarette smoking, problem drinking and drug use, sexual precocity and delinquent behavior. The key question here is that of why: why do adolescents engage in "problem behavior". Some argue that this is part-and-parcel of risk taking and sensation seeking, which are "hard wired" in the adolescent brain[5]. Rather than taking this biologically deterministic view, we would argue together with Jessor and Jessor[4] that, for adolescents, problem behaviors "are considered functional, purposive and instrumental towards the attainment of goals". We extend this argument to hypothesize that, in the case of adolescence, the main —adaptive and, hence, normative— goal in this context is that of establishing a new social hierarchy where same-sex and opposite-sex mates play a key role. Thus, in this view, risk-taking is not the consequence of an "imbalance" between the "reward" system and the "cognitive control" system, often thought as being related to the immaturity of the latter, but simply a tool for reaching a top position in the new social hierarchy. Some of the evidence supporting this contention comes from a Dunedin study that examined the predictive value of problem behaviour in late adolescence vis-à-vis involvement of those same individuals in a car crash three years later: marijuana use, unsafe sex and delinquent behaviour at 18 years predicted a car-crash at 21 years — but only in young women[6]. It is unlikely that this pattern is due to the differential maturation of brain systems involved in the processing of rewards and/or cognitive control; it is more likely that it reflects sex-specific dynamics in social groups of young men and women.

Of course, engaging in "problem behavior" is not the only way to establish oneself in a peer group. Furthermore, individuals may also differ in their resistance to peer influences, a capacity that appears to increase particularly between 14 and 18 years of age[7]. We have investigated differences in the brains of adolescents as a function of their self-reported resistance to peer influences and found that, during observation of angry hand actions, children with high resistance engage a set of regions (important for cognitive control, imitation and extraction of social cues) in a highly coordinated manner while those with low resistance engage the same regions but in a less coordinated way[8]. Thus, it appears that integration of various types of information in an emotionally charged situation provides an individual with the freedom to make a choice without the undue influence of group dynamics.

Let us now turn our attention to the role of parents. But we will do so by focusing on findings related to the possible (biological) impact of maternal smoking during pregnancy on the adolescent brain and behaviour, rather than on the parental roles vis-à-vis substance use. We wish to preface this section by pointing out that: *1)* the focus on the mother is simply due to the interest in the exposure of the fetus to cigarette smoke; we will not deal with the reasons why pregnant woman and, very often, their partners continue to smoke, and *2)* findings in human studies are confounded by many other factors associated with a particular behaviour

and can rarely establish a causal link with the exposure and outcome without complementary investigations carried out in experimental animals.

The impact of maternal smoking on the developing fetus is complex. Tobacco smoke may affect the foetus in several ways: *a)* inhaled nicotine induces vasoconstriction of the uteroplacental vasculature, leading to uteroplacental underperfusion and, in turn, a decreased flow of nutrients and oxygen to the foetus, *b)* increased levels of carboxyhemoglobin reduce tissue oxygenation of the foetus, *c)* nicotine suppresses the mother's appetite, leading to reduced energy intake by the mother and, hence, reduced energy supply to the foetus, and *d)* nicotine causes alterations in the cellular growth and activity of the central and peripheral nervous systems[9]. In addition, tobacco smoking is frequently associated with epiphenomena, such as risky behaviours, co-abuse of other substances (e.g. alcohol), poor prenatal care, and low socio-economic status[9].

In 2002, we initiated The Saguenay Youth Study (SYS) asea cross-sectional study funded by the Canadian Institutes of Health Research; it investigates the effects of prenatal exposure to maternal cigarette smoking (PEMCS) on the brain & behaviour as well as cardiovascular & metabolic health during adolescence[9]. Adolescents and their biological parents are recruited from a region with a known genetic founder effect, namely the Saguenay Lac-Saint-Jean region of Quebec, Canada. Both the maternal and paternal grandparents of the adolescents are of French-Canadian ancestry born in the region; as such, all adolescents are of a single ethnicity. The SYS employs a family-based design where only children with one or more siblings and with both biological parents available are included. Exposed adolescents must have a positive history of maternal cigarette smoking (> 1 cigarette/day in the 2nd trimester of pregnancy). The non-exposed adolescents are matched to the exposed adolescents based on the level of maternal education and the school attended. For both the mothers of exposed and non-exposed adolescents, we require a negative history of excessive alcohol use during pregnancy (< 210 ml/week). Cigarette smoking before and during pregnancy is ascertained retrospectively by a research nurse during a structured telephone interview with the mother. We assessed the overall agreement between the exposure status noted in the medical records at the time of pregnancy and the maternal report during the telephone interview using Kappa statistics, and found a value of 0.69 ± 0.04 indicating ''good'' agreement. Structural magnetic-resonanc scans have been collected in over 900 adolescents (12 to 18 years of age; 50% females). Psychopathology is assessed with the Diagnostic Interview Schedule for Children Predictive Scales (DPS) and several other instruments. In the DPS, a total of 15 questions concern the use of and problems associated with alcohol (4 questions), marijuana (3 q) and other substances (8 q). To provide an index of drug exposure complementary to the DPS, we also collect information about adolescent drug experimentation by asking 15 questions about the use of drugs, including alcohol, cigarettes, and marijuana as well as other illicit drugs, namely stimulants, psychedelics, PCP, ecstasy, prescribed drugs, inhalers, cocaine, opiates, tranquilizers, heroin, anabolic steroids and other drugs-not-listed; these questions have been used previously and, for the SYS study, were incorporated in the "GRIPado" questionnaire. In the biological parents, we assess cigarette smoking and substance use (alcohol, drugs) at present and during their adolescence. In addition, the parents self-report symptoms of depression and anxiety, as well as any family history of alcohol abuse. DNA is acquired in both biological parents and in adolescent siblings. The full protocol is described in[9] and on the SYS website (www.saguenay-youth-study.org).

To date, we have made several observations about PEMCS and the adolescent brain and behaviour. First of all, we have shown that "exposed" adolescents have smaller corpus callosum[10] and thinner orbitofrontal cortex[11], as compared with non-exposed adolescents. Given the role of the orbitofrontal cortex (OFC) in reward processing, the latter finding prompted us to assess differences between the exposed and non-exposed adolescents in substance use and drug experimentation. We found that exposed adolescents show slightly greater drug experimentation and that this appears to be related to the degree of OFC "thinning" (Lotfipour et al. 2009[3]; model 1 in fig. 1). Another brain structure important for appetitive motivation is the nucleus accumbens; in the exposed adolescents only, genetic variation in the alpha 6 nicotinic acetylcholine receptor influences the size of this nucleus and the probability of drug experimentation and cigarette smoking[12]; we speculated that this finding may reflect PEMCS-induced nicotine-mediated modulation of the dopamine system.

In non-exposed adolescents, we have shown that the number of *different* drugs an adolescent ever experimented with was related positively to the thickness of the orbitofrontal cortex[3]. We hypothesized that this might be related to an experience-driven plasticity and tested this hypothesis using the known functional polymorphism in brain-derived neurotrophic factor, a gene known to mediate activity-related structural changes. As predicted, only the val66val homozygotes (and not the met carriers) showed a function-structure relationship (model 2 in fig. 1). This moderating effect of the brain-derived neurotrophic factor polymorphisms was not observed in the exposed adolescents, perhaps due to the "inactivation" of a brain-derived neurotrophic factor promotor through DNA methylation[13].

Based on the above results from our human study and those from relevant studies examining the effects of prenatal exposure to nicotine in experimental animals[14], we hypothesize that PEMCS interferes with the developmental of the OFC and, by raising a reward threshold, increases drug experimentation during adolescence (model 1 in fig.1). On the other hand, in non-exposed adolescents with the val66val brain-derived neurotrophic factor genotype, drug experimentation leads to structural changes in the OFC via experience-related plasticity (model 2 in fig. 1).

In conclusion, the extent to which an adolescent experiments with drugs is likely to depend both on social context ("hierarchy" quest), his/her resistance to peer influences, his/her genes (e.g. nicotinic receptor) and other influences, such as prenatal exposure to maternal cigarette smoking. The latter factor is likely to influence substance-use behaviour through multiple (biological and psychosocial) pathways.

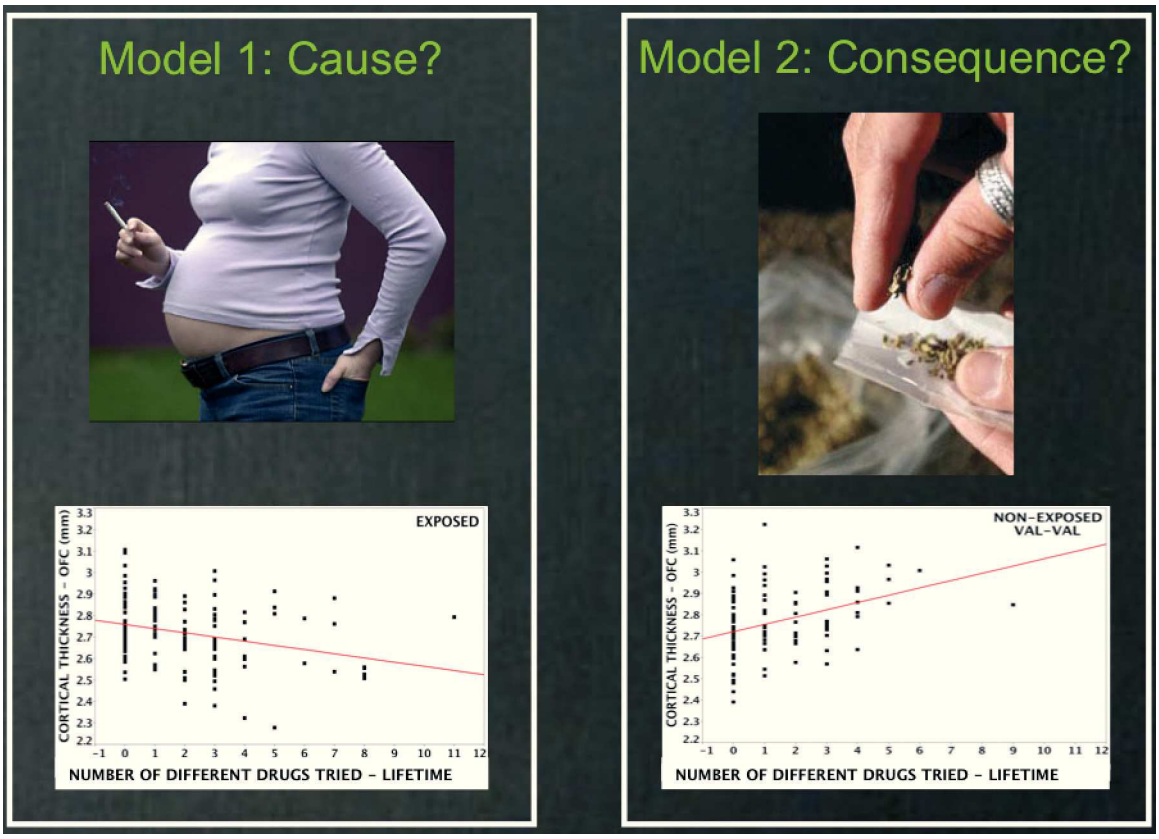

Figure 1. Relationship between the number of drugs ever tried and the thickness of the orbitofrontal cortex in adolescents exposed (left) and not-exposed (right) to maternal cigarette smoking during pregnancy. Note that only individuals with the val66val brain-derived neurotrophic factor genotype are shown for non-exposed adolescents. From Lotfipour S, Ferguson E, Leonard G, Perron M, Pike B, Richer L, et al, 2009.

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