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Brain Crosstalk in Puberty and Adolescence

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Introduction

Puberty and adolescence are key developmental processes occurring in the transition period between childhood and adulthood. They involve profound physical and behavioral changes that share dependency on maturational events in the central nervous system (CNS). The neurobiology of puberty and adolescence has made important progress during the past decade through finely tuned studies on behavior, CNS imaging, and molecular neurobiology.

The aim of the symposium on which these proceedings are based was to provide the attendants with a pathophysiological perspective on the role of CNS in puberty and adolescence, starting from genetic/molecular aspects, going through structural/imaging changes, and leading to physical/behavioral characteristics. Renowned investigators involved in both animal and human research convened and shared with the participants their recent data as well as overall appraisals of relevant questions around CNS control of puberty and adolescence.

Among other findings, some contributors have underscored that adolescence is a critical phase for risk of addiction and mental illnesses in adulthood. Such a critical period may be longer than commonly expected, since brain imaging studies indicate that the final maturational changes associated with adolescence can occur as late as between 25 and 30 years.

Others have emphasized the importance of the prepubertal period that is crucial for the effect of testosterone on male sexual behavior, the gender dimorphic androgen effects on executive functioning, the epigenetic control of transcriptional repression of the neuroendocrine regulators of the onset of puberty, and the interactions between leptin- and kisspeptidergic-permissive effects on the onset of puberty.

Finally, some factors arising in the fetal and perinatal periods have emerged as possible new players in the early control of the onset of puberty. They involve microRNAs, rabconnectin-3alpha, and endocrine-disrupting chemicals.

No doubt the present book will inspire those involved in either scientific research or clinical practice or both in the fascinating field of puberty and adolescence.

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Drugs and the Adolescent Brain

Anne L. Wheeler and Paul W. Frankland

Abstract Adolescence is a developmental stage that is associated with increased risk-taking, novelty-seeking and greater vulnerability to peer pressure. Given this, it is perhaps not surprising that adolescence is also a time that is associated with drug experimentation. In some cases, drug experimentation progresses to drug dependence, a state commonly referred to as addiction. As the adolescent brain is still developing, how does drug dependence impact brain development? Imaging studies suggest that cocaine dependence is associated with abnormalities in brain structure in humans. However, it is unclear whether these differences in brain structure predispose an individual to drug use or are a result of cocaine's action on the brain. We have addressed this issue by studying the impact of chronic cocaine exposure on brain structure and drug-related behavior in mice. In our studies, mice were exposed to cocaine at two developmental time periods: adolescence (27–46 days-old) and young adulthood (60–79 days-old). Following 30 days of abstinence, either fixed brain T2 weighted MRIs were acquired on a 7T scanner at 32 μm isotropic voxel dimensions or mice were assessed for sensitization to the locomotor stimulant effects of cocaine. Three automated techniques (deformation-based morphometry, striatum shape analysis and cortical thickness assessment) were used to identify population differences in brain structure in cocaine vs. saline-exposed mice. We found that cocaine induced changes in brain structure, and these were most pronounced in mice exposed to cocaine during adolescence. Many of these changes occurred in brain regions previously implicated in addiction, including the nucleus accumbens, striatum, insular cortex, orbital frontal cortex and medial forebrain bundle. Furthermore, exposure to the same cocaine regimen caused sensitization to the locomotor stimulant effects of cocaine, and these effects were again more pronounced in mice exposed to cocaine during adolescence. These results suggest that altered brain structure following one month of abstinence may

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contribute to these persistent drug-related behaviors and may identify cocaine exposure as the cause of these morphological changes.

Introduction

An estimated 205 million people in the world use illicit drugs, and around 25 million of these can be described as having a drug use disorder (UNODC 2009). Of course, these numbers balloon if legal drugs such as alcohol and nicotine are additionally considered. At the outset, people take these drugs of abuse to benefit from their short-term effects, which include pleasurable sensation, the alteration of mental state and, in some instances, improved performance (Volkow and Li 2004). These acute effects are mediated by relatively short-lived changes in brain chemistry and physiology that are largely related to the molecular pharmacology of the drugs themselves (Nestler 2005). While the five major classes of abused drugs – psychostimulants, opiates, alcohol, cannabinoids and nicotine – have different mechanisms of action in the brain, ultimately they all act either directly or indirectly on dopamine function in the mesolimbic pathway. The mesolimbic circuitry consists of dopaminergic neurons that project from the ventral tegmental area (VTA) in the midbrain to the limbic system via the nucleus accumbens (NAc) to produce reinforcing effects (Pierce and Kumaresan 2006).

A portion of individuals who take drugs will progress to a pattern of repeated drug use that is typified by an intense desire for the drug and impaired ability to control urges to take that drug, even at the expense of serious adverse health and social consequences. This state is known as substance dependence and is often referred to as addiction. Substance dependence is not due solely to the physical dependence that underlies the withdrawal symptoms following cessation of drug use because, even after withdrawal symptoms subside, the risk of relapse remains very high (Milton and Everitt 2012). This increased relapse risk suggests that repeated drug use permanently alters the brain, producing persistent changes in brain circuits that favor learned drug-associated behaviors at the expense of adaptive responding for natural rewards (Kalivas and O'Brien 2008).

Repeated Drug Use Has a Long-Term Impact on Brain Circuitry

How do drugs of abuse permanently alter the brain? Pre-clinical and clinical research suggest that repeated use of drugs changes the brain of the user at the molecular, cellular and circuit organizational levels. These changes likely underlie a shift toward behaviors that are more reflexive and, consequently, much less

amenable to cognitive interference. Brain alterations have been studied in most detail in the neurocircuits responsible for reward, motivation, cognitive control and memory. These circuits are directly or indirectly modulated by dopamine and are highly connected to each other through glutamatergic and GABA-ergic projections that allow them to interact to generate behavioral output in response to reinforcing stimuli (Baler and Volkow 2006).

The rewarding properties of drugs are mediated by dopamine, and enduring alterations in dopaminergic signaling following repeated drug use are thought to contribute to drug dependence (Diana 2011). For example, dopamine release in the NAc is decreased in drug-dependent rodents (Diana et al. 1999; Rossetti et al. 1992), and human imaging studies have shown a reduction in dopamine receptors (Volkow et al. 1996) accompanied by reduced release of endogenous dopamine in the ventral striatum of drug-dependent subjects (Martinez et al. 2005).

Motivation is thought to be regulated by the orbital frontal cortex (OFC), which is responsible for processing the motivational value of rewarding stimuli (Tremblay and Schultz 1999). For example, the OFC is activated upon presentation of cocaine-associated stimuli in humans (Garavan et al. 2000) and rodents (Thomas et al. 2003). Furthermore, OFC dysfunction persists even following long periods of drug abstinence in drug-dependent individuals (Goldstein and Volkow 2002).

The frontal cortex is responsible for cognitive control. The compromised ability of cocaine users to reign in uncontrollable urges has been linked to reduced activity in the anterior cingulate gyrus (ACG) and in the prefrontal cortex (PFC; Hester and Garavan 2004). Additionally, a significant aspect of drug dependence is the pathological narrowing of goal selection to those that are drug-related. The representation of goals, assignment of value to them, and selection of actions based on the resulting valuation depend on the PFC (Hyman 2005).

Neuroadaptations in learning and memory processes have been proposed to play an essential role in drug dependence as they can account for its persistence. First, chronic drug exposure causes strong associations to develop between drugs and the environmental stimuli and contexts in which they are encountered. Exposure to these drug-associated cues often precedes drug relapse even after long periods of abstinence (Torregrossa et al. 2011). This is consistent with drug-associated cues producing limbic activation and craving (Childress et al. 1999), with associated dopamine release (Volkow et al. 2006) in cocaine addicts. Second, changes in the dorsal striatum underlie the learning of specific motor actions to receive rewards that are linked to the rituals of drug consumption (Porrino et al. 2004). Shifting from voluntary drug use to more habitual and compulsive drug use represents a transition at the neural level from prefrontal cortical to striatal control over drug-seeking and drug-taking behavior, as well as a progression from ventral to more dorsal domains of the striatum (Everitt and Robbins 2005).

Initiation of Drug Use Often Occurs During Adolescence, Which May Increase Vulnerability to Drug Dependence

The onset of drug use often occurs during adolescence, a developmental transition from childhood to adulthood during which the brain continues to develop and change. Indeed, in Canada, 60 % of illicit drug users are between the ages of 15 and 24 (Statistics Canada 2003). Adolescence is thought of as a period when risk-taking and novelty-seeking are typical and individuals are hyper-responsive to peer pressure (Spear 2000); clearly, these factors may contribute to a propensity to experiment with drugs during adolescence, a prerequisite for drug dependence.

The effects of drugs on behavior may also differ in adolescence. For example, preclinical studies have shown that adolescent rodents are less sensitive than adult animals to many of the negative effects of alcohol such as alcohol-induced sedation and motor impairment (Little et al. 1996), as well as alcohol withdrawal-induced social depression and anxiety (Varlinskaya and Spear 2004). Additionally, adolescent rodents are subject to greater reinforcing properties of alcohol (Pautassi et al. 2008) and have increased sensitivity to its social-facilitation effects compared to adult animals (Varlinskaya and Spear 2002). Similar studies have demonstrated that adolescent rodents show increased sensitivity to the rewarding effects of nicotine (Natividad et al. 2013). This 'enhanced' sensitivity may lead to prolonged periods of drug experimentation during adolescence and promote excessive consumption. Epidemiological studies indicate that, when drug use is initiated during adolescence (rather than during adulthood), there are higher lifetime rates of drug use and faster progression to dependency (Anthony and Petronis 1995; Grant and Dawson 1998; O'Brien and Anthony 2005). Together these data suggest that the adolescent brain may contribute to drug experimentation and excessive consumption and, at the same time, drug experimentation and excessive consumption at this age likely impact ongoing development of the brain.

Brain Development Throughout Adolescence and Its Susceptibility to the Effects of Drug Use

The structural and functional development of the brain is remarkably complex during infancy and childhood and continues on a dynamic trajectory throughout adolescence. Magnetic resonance imaging (MRI) studies indicate that white matter volume increases into the third decade of life whereas the volume of gray matter in the brain follows an inverted U-shaped trajectory, peaking in late childhood and decreasing through adolescence (Giedd et al. 1999; Giedd 2008). The increase in white matter volume may be associated with continued myelination of white matter tracts or increases in the caliber of axons (Paus et al. 2008). The decline in gray matter is thought to reflect the reorganization and refinement of synaptic connections through the process of synaptic pruning (Petanjek et al. 2011), or it may be