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Review

Are there volumetric brain differences associated with the use of cocaine and amphetamine-type stimulants?

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ABSTRACT

While a large number of studies have examined brain volume differences associated with cocaine use, much less is known about structural differences related to amphetamine-type stimulant (ATS) use. What is known about cocaine may help to interpret emerging information on the interaction of brain volume with ATS consumption. To date, volumetric studies on the two types of stimulant have focused almost exclusively on brain differences associated with chronic use. There is considerable variability in the findings between studies which may be explained in part by the wide variety of methodologies employed. Despite this variability, seven recurrent themes are worth noting: (1) loci of lower cortical volume (approximately 10% on average) are consistently reported, (2) almost all studies indicate less volume in all or parts of the frontal cortex, (3) more specifically, a core group of studies implicate the ventromedial prefrontal cortex (including the medial portion of the orbital frontal cortex) and (4) the insula, (5) an enlarged striatal volume has been repeatedly observed, (6) reports on volume differences in the hippocampus and amygdala have been equivocal, (7) evidence supporting differential interaction of brain structure with cocaine vs. ATS is scant but the volume of all or parts of the temporal cortex appear lower in a majority of studies on cocaine but not ATS. Future research should include longitudinal designs on larger sample sizes and examine other stages of exposure to psychostimulants.

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1. Introduction

Cocaine and amphetamine-type stimulants (ATS) are psychoactive compounds that have profound effects on brain and body, e.g. appetite suppression, intense feels of well-being, and increased energy, heart rate, and mental alertness. Amphetamine-type stimulants, which include l-amphetamine, d-amphetamine, methamphetamine, 3,4-methylenedioxymethamphetamine (MDMA), methylphenidate, methcathinone, ephedrine, and pseudoephedrine among others, share common elements in their chemical structure (Sulzer et al., 2005). Although cocaine has a markedly different chemical composition than ATS, both act on the nervous system by increasing the synaptic availability of catecholamines (e.g. dopamine, norepinephrine) and serotonin. Cocaine and methylphenidate specifically block the reuptake of neurotransmitters via transmembrane transporters. Most ATS, in addition, catalyze the release of presynaptically stored neurotransmitters into the synaptic cleft (Woolverton and Johnson, 1992). While the medical use of cocaine is limited to topical anesthesia, ATS are prescribed to treat a variety of neurological diseases ranging from attention deficit hyperactivity disorder (ADHD) to narcolepsy and obesity. Non-medical use of these drugs is widespread and the economic burden of abuse in terms of health and criminal service costs as well as lost productivity is substantial (Executive Office of the President, 2004). A significant number of individuals who experiment with stimulants will develop problematic patterns of use. For example, it is estimated that 15% of those who consume cocaine recreationally will become addicted within 10 years of first use (Wagner and Anthony, 2002). The National Survey on Drug Use and Health (2010) indicates that 1 million persons in the U.S. are currently dependent on cocaine in addition to 350 thousand persons who are dependent on some other type of stimulant. An understanding of how these drugs affect the brain is critical to the development of interventions which could address the negative consequences of non-medical stimulant use.

The present article will review data collected by magnetic resonance imaging (MRI) on the interaction of brain structure with cocaine and ATS consumption and will concentrate primarily on differences in regional grey matter. It should not be assumed that cocaine and ATS have entirely identical effects on the brain. However, multiple independent lines of investigation point to several convergent a priori regions-of-interest for both cocaine and ATS. This review will emphasize commonalities between cocaine and ATS because the limited amount of volumetric data available and the high degree of variability between studies make it difficult to identify differences reliably at this time. Acute cocaine and ATS intoxication produces an increase in intracellular dopamine in the striatum, especially in its ventral anterior part (Di Chiara and Imperato, 1988; Drevets et al., 1999; Volkow et al., 1996). These acute effects are believed to mediate the reinforcing properties of stimulants but are unlikely the sole factor in the development of compulsive drug-taking behaviors (Volkow et al., 2009). Neural activity may be impaired in other parts of the brain which, in healthy individuals, would otherwise protect against substance abuse (Everitt et al., 2008; Goldstein et al., 2009). Such impairments could either be the result of stimulant use or could predate substance use in a population of individuals at-risk. In animal models, chronic exposure to cocaine and ATS produces long-lasting alterations in markers of dopamine, norepinephrine and serotonin activity in many parts of the brain, including the striatum, thalamus, hippocampus, midbrain and cortex (Gould et al., 2011; Krasnova and Cadet, 2009; Porrino et al., 2004). Similarly in humans, in vivo positron emission tomography (PET) studies have shown alterations of catecholamine and serotonin signaling in association with chronic cocaine and ATS use (Ding et al., 2010; McCann et al., 1998; Sekine et al., 2003, 2006; Volkow et al., 2001, 1993). Markers of dopamine activity are decreased in the striatum of chronic methamphetamine users postmortem (Kitamura et al., 2007; Wilson et al., 1996) and lower levels of dopamine transporter availability in cocaine and ATS users correlates with glucose metabolism in the orbitofrontal cortex (Volkow et al., 2001, 1993). fMRI studies further indicate that there is abnormal activity in the frontal, parietal, and insular cortex of chronic stimulant users (Paulus et al., 2003, 2002, 2005). Taken together, the diversity of findings suggest that extensive neuroadaptations occur throughout the brain in response to stimulant intoxication (Koob and Volkow, 2010).

The time course of these neuroadaptations may be reflected in the volume of the brain at several stages of interest: (1) prenatal exposure, (2) differences in brain structure before initial use that might bias at-risk individuals toward use or abuse/dependence, (3) effects of occasional/recreational use which represents the most prevalent pattern of drug consumption, (4) effects of chronic use associated with abuse/dependence, (5) structural markers that could predispose individuals to relapse after rehabilitation, and (6) the effects of abstinence. To date, the literature on the interaction of brain structure with stimulants has focused almost exclusively on stage 4, the effects of chronic use. Studies on the effects of chronic cocaine use are catalogued in Sections 2.1 (current or recent chronic use) and 2.2 (more than 2 months abstinence). The few studies pertaining to the other stages of interest of cocaine use are grouped together in Section 2.3. Since more studies have examined volumetric effects associated with cocaine, these studies provide a framework to interpret the smaller number of studies that have examined ATS (Section 3). Studies that have examined regional volumetric differences associated with chronic ATS use are catalogued in Section 3.2 (current or recent chronic use) and 3.2 (more than 2 months abstinence) while studies on the other stages of interest are grouped in Section 3.3. One goal of Sections 2 and 3 is to draw attention to the variability of results that have been reported in the literature. Most parts of the brain have been implicated in at least one study. In order to properly interpret of the significance of individual findings, it is necessary to view them against this background of variability. Awareness of variability in the literature is also a precondition of understanding its source. Methodological considerations which could account for some of the differences in findings between studies are considered in Section 4. Despite a large number of apparent contradictions, many consistent findings do emerge when this body of work is considered as a whole. Seven recurrent themes in the literature are summarized in Section 5 and discussed at length in section 6. The summary and discussion sections are followed by speculation on future directions of the field.

2. Volumetric effects of cocaine use

2.1. Active or recently abstinent chronic users

Several magnetic resonance imaging studies have examined the relationship between brain volume and chronic cocaine use in populations that are either currently using the drug or recently abstinent (Table 1). Subjects in these studies on recent or active use meet the criteria for a clinical diagnosis of cocaine dependence according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (American Psychiatric Association, 1994) and a positive urine test is frequently required for inclusion. The substance dependent subjects described in this section have consumed cocaine at least once within the previous 20 days on average.

The earliest of these studies relied on manual identification of predetermined regions of interest and generated several conflicting