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The acute effects of *d*-amphetamine and *d*-methamphetamine on ERP components in humans

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Abstract

While a number of behavioural studies have been conducted to investigate the acute effects of amphetamines on tasks of attention and information processing, there is currently a scarcity of research concerning their electrophysiological effects in healthy adults. It is also unclear as to whether amphetamines exert effects on stimulus evaluation or response selection. In two studies, independent groups of twenty healthy illicit stimulant users aged between 21 and 32 years were administered 0.42 mg/kg *d*-amphetamine versus placebo, and 0.42 mg/kg *d*-methamphetamine versus placebo respectively, and completed an auditory oddball task on two separate testing days. A 62-channel EEG was recorded during the completion of the task, and the effects of amphetamines on N200 and P300 ERP components were analysed. *d*-amphetamine significantly decreased reaction time, improved accuracy, and reduced the latency of the P300 component relative to placebo, while having no effect on the N200 component. *d*-methamphetamine had no effect on reaction time, accuracy or the P300 component, but reduced the amplitude of the N200 component, relative to placebo. It was concluded that there is tentative support to suggest that *d*-amphetamine at a dose of 0.42 mg/kg may enhance speed of information processing while *d*-methamphetamine at a dose of 0.42 mg/kg may reflect changes to stimulus evaluation.

1. Introduction

Amphetamines, with potent effects on noradrenalin and dopamine neurotransmission (Laruelle et al., 1995), have been found to have a number of dose-dependent acute effects on tasks of attention, psychomotor function and perceptual speed (Silber et al., 2006). However, there exists inconsistency

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in the literature as to whether a single therapeutic dose produces slight improvements in cognitive functioning (Hart et al., 2005; Johnson et al., 2000; Shappell et al., 1996; Silber et al., 2006) or causes detriment (Bakshi et al., 1995; Hutchison and Swift, 1999; Kennedy et al., 1990; Kumari et al., 1998; Silber et al., 2005; Solomon et al., 1981; Swerdlow et al., 2003; Weiner et al., 1988).

In contrast to cognitive and behavioural measures, the measurement of event-related potentials (ERPs) provides a more sensitive means of gauging the effects of amphetamines on perceptual and attentional processes, enabling the detection of effects that may be too subtle to be measured using standard cognitive measures. While considerable research has been conducted regarding the acute effects of amphetamines on electrophysiological parameters in animals, there is currently a lack of data addressing acute effects in healthy humans. The N200 is an attention-dependant ERP component that reflects stimulus evaluation processes (Näätänen, 1992) and provides a measure of selective attention (Hillyard and Hansen, 1986). The P300 is arguably the most prominent and extensively researched ERP component; providing an index of general cognitive efficiency (Donchin and Coles, 1988) and context updating (Patel and Azzam, 2005). In particular, the P300 is considered to be an index of working memory (Donchin and Coles, 1988; Donchin et al., 1986), as it reflects the allocation of attentional resources and speed of processing (Donchin and Coles, 1988; Johnson, 1986).

To date there has been a paucity of acute studies investigating the electrophysiological sequelae of amphetamine administration in non-clinical samples and of these the results have been mixed. In an investigation into the effects of noradrenergic drugs on early stimulus processing, Halliday et al. (1994) reported that 10 mg *d*-amphetamine brought about a decrease in reaction time as well as a decrease in the latency of the P300 components using single trial estimates. However, no change to the amplitude of the P300 component was reported. In contrast McKetin et al. (1999) failed to report any effects on P300 latency associated with 10 mg or 20 mg *d*-amphetamine administration, although increased P300 amplitude at CZ was reported following the 20 mg dose. In a more recent drug preference study by Gabbay et al. (2010), 15 mg *d*-amphetamine was found to bring about a significantly greater P300 amplitude increase in comparison to placebo using an oddball task with novel environmental sounds. 15 mg *d*-amphetamine was also found to bring about a significantly greater reduction in P300 latency in comparison to placebo using a three tone oddball task. No significant differences in P300 amplitude or latency were found between 10 mg *d*-amphetamine and placebo, or between 10 mg and 15 mg *d*-amphetamine (Gabbay et al., 2010).

While there have been few studies conducted to investigate the effects of amphetamines on ERP components, a number of single dose studies have also been conducted using methylphenidate (MPH), which is similarly a reuptake inhibitor of both noradrenalin and dopamine. In healthy individuals acute MPH administration has been found to have a large positive effect on memory performance, while effects are lacking in other cognitive domains (Repantis et al., 2010). With regard to the electrophysiological effects of MPH, Brumaghim et al. (1987, study 2) provided evidence to suggest that P300 latency was reduced following MPH administration in normal adults. Similarly, Cooper et al. (2005) reported a linear dose-related reduction in P300 latency with increasing MPH dosage (5 mg, 15 mg or 45 mg). In contrast, both Naylor et al. (1985) and Fitzpatrick et al. (1988) reported that MPH had no effect on P300 latency, although reaction time was found to improve.

Some authors have interpreted improvements in reaction time in the absence of effects on P300 latency as evidence that stimulant drugs act on processes involved in response selection rather than improving working memory (Callaway, 1983, 1984; Naylor et al., 1985). However, the reason for the discrepancy in electrophysiological sequelae may also be attributable to differences in the drugs administered; with many of the negative results reported relating to MPH rather than amphetamine. Both MPH and *d*-amphetamine cause an increase extracellular dopamine in the cortex and striatum. However, *d*-amphetamine is found to be slightly more potent than MPH, with the average therapeutic dose of MPH found to be roughly twice that of *d*-amphetamine (Solanto, 2000). The mechanisms of action by which these compounds increase dopamine are also different; MPH increases synaptic dopamine via blockade of its reuptake while *d*-amphetamine increases the active discharge of vesicular dopamine into extracellular space, some of which is passively diffused into the synapse. While synaptic levels of dopamine are comparable for the two compounds, extracellular levels of dopamine are around four times higher with *d*-amphetamine in comparison to MPH (Schiffer et al., 2006). Due to differences in mechanism of action and potency it is foreseeable that these two compounds may have differential effects on ERP components.

In relation to the effects of amphetamines on the earlier N200 component of the ERP there is less research than on the P300 component in healthy adult samples. For the majority of studies in which the acute effects of stimulants on the P300 are examined, data on the earlier wave forms (i.e. N200) are not reported. In the drug preference study of Gabbay et al. (2010), no effects of *d*-amphetamine were reported in relation to N200 amplitude or latency, when comparing placebo with 10 mg and 15 mg doses. The limited research that has examined the effects of stimulants, predominantly MPH, on the N200 component, has involved ADHD patients. Although these studies have generally reported the N200 component to be insensitive to MPH in ADHD patients (Halliday et al., 1983; Jonkman et al., 1999; Taylor et al., 1993; Winsberg et al., 1997) there have been some studies that have reported stimulant-induced modulations to the N200 waveform (Ozdag et al., 2004; Verbaten et al., 1994).

Verbaten et al. (1994) noted an increase in N200 amplitude following a 10 mg dose of MPH in children with ADHD. In contrast, Ozdag et al. (2004) demonstrated that MPH normalised several ERP indices in children with ADHD (but not N200 amplitude), suggesting that while MPH may improve working memory it has less influence on stimulus evaluation processes (Ozdag et al., 2004). However, considering the inherent differences in brain function associated with ADHD, it is difficult to extrapolate from these studies as to the acute effects of stimulants on electrophysiological parameters in the normal population.

Another important research question that has yet to be adequately addressed in previous ERP studies of amphetamines is the differential effects of *d*-amphetamine in comparison to methamphetamine. Methamphetamine is considered to be a