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Amphetamine improves cognitive function in medicated individuals with schizophrenia and in healthy volunteers

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Abstract

Background: Recent research on schizophrenia indicates that cognitive deficits in this illness are important predictors of functional outcome, highlighting the need for treatments that have a positive impact on cognitive function. Here we explore the hypothesis that acute administration of D-amphetamine can improve cognitive function in individuals with schizophrenia who are well-treated with typical antipsychotics, as well as in healthy controls performing under dual task conditions designed to elicit performance deficits analogous to those found in schizophrenia.
Methods: Ten individuals with schizophrenia taking haldol or prolixin and 22 healthy controls performed spatial working memory, language production, and Stroop tasks under both placebo and 0.25 mg/kg of D-amphetamine.
Results: D-Amphetamine improved reactions times on the spatial working memory and Stroop tasks for both individuals with schizophrenia and controls, and improved working memory accuracy in schizophrenia. In addition, D-amphetamine improved language production for both individuals with schizophrenia and controls.
Conclusions: These results provide support for the hypothesis that the adjunctive administration of dopamine agonist can improve cognitive in individuals with schizophrenia taking typical antipsychotics. The results are discussed in terms of their implications for understanding the nature of working memory deficits in schizophrenia, and potential future avenues for cognitive enhancement in this illness.

Keywords: Schizophrenia; Working memory; Amphetamine; Language production; Selective attention

1. Introduction

A growing body of research indicates that cognition in schizophrenia is critically important for functional outcome. For example, the severity of cognitive

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deficits is more predictive of social and vocational outcome in schizophrenia than either positive or negative symptoms (Green, 1996; Harvey et al., 1998; Green et al., 2000; Gold et al., 2002). As has been highlighted by Keefe and Davidson, social and occupational impairments experienced by individuals with schizophrenia lead the largest indirect costs of this illness, both for the individual and for society (Sevy and Davidson, 1995). As such, if we could improve cognition in schizophrenia, and if improved cognition leads to reduced social and occupational dysfunction, such interventions could have a beneficial effect for both individuals with schizophrenia and for society (Davidson and Keefe, 1995).

The growing recognition of the central role of cognition in determining outcome in schizophrenia has lead to a dramatic increase in interest in evaluating whether existing therapies improve cognition, as well on developing new treatments for improving cognition in schizophrenia (Davidson and Keefe, 1995). While there is little evidence that typical antipsychotics improve cognition in schizophrenia (Goldberg and Weinberger, 1996), there is somewhat more evidence that the newer generation of atypical antipsychotics do a better job of improving cognitive function in schizophrenia than the typical antipsychotics (Keefe et al., 1999; Harvey and Keefe, 2001). These are modest effects whose functional significance remains unknown and the interpretation of these effects as specifically related to improved cognitive functioning, rather than an absence of negative side effects in comparison typical agents has also been challenged (Carpenter and Gold, 2002).

Another approach is to examine the use of adjunctive treatments, administered in addition to either typical or atypical antipsychotics, which may specifically target one or more cognitive functions in schizophrenia. For example, one cognitive function that is impaired in schizophrenia is working memory, typically defined as the ability to temporarily maintain and manipulate information (Baddeley, 1986). In part because of the working memory deficits shown by individuals with schizophrenia, there has been interest in agents that influence dopamine function as a potential type of adjunctive treatment for individuals with schizophrenia. This focus on dopamine is driven in large by findings in studies of non-human primates suggesting that optimal dopamine function is critical for working memory performance (Goldman-Rakic et al., 2000). For example, working memory function is impaired in non-human primates following 6-hydroxy-dopamine lesions in PFC (Brozoski et al., 1979), or administration of dopamine antagonists (Sawaguchi and Goldman-Rakic, 1994). In addition, administration of low dose DA agonists can improve working memory in monkeys (Williams and Goldman-Rakic, 1995), especially those with impaired performance (Arnsten et al., 1994; Cai and Arnsten, 1997; Castner et al., 2000).

There is also growing evidence that the administration of dopamine agonists can improve cognition in humans, including working memory. Methylphenidate (Clark et al., 1986; Elliott et al., 1997; Mehta et al., 2000), amphetamine (Mattay et al., 1996; Mattay et al., 2000), bromocriptine (Luciana et al., 1992; Kimberg et al., 1997; Luciana and Collins, 1997; Luciana et al., 1998), and pergolide (Muller et al., 1998; Kimberg and D'Esposito, 2003) have all been shown to improve working memory in healthy human participants. Interestingly, there is also research to suggest that dopamine agonists may be particularly effective for those individuals with the worst performance in the absence of drug (Kimberg et al., 1997; Mattay et al., 2000, 2003; Mehta et al., 2001; Kimberg and D'Esposito, 2003). For example, individuals with the high activity form of the COMT gene (leading to more catabolism of dopamine) have worse working memory performance than individuals with the low activity form of the COMT gene (Egan et al., 2001; Malhotra et al., 2002), and also show the greatest positive benefit of amphetamine (Mattay et al., 2003). Although several of these agents are not selective for dopamine, and it is likely that all of these drugs influence neurotransmitter systems other than the dopamine system, such results are generally consistent with the hypothesis that administration of dopamine agonists can improve working memory. Further, there is evidence that levodopa can improve working memory and related cognitive functions in individuals with impaired dopamine function, such as those with Parkinson's Disease (Cooper et al., 1992; Lange et al., 1995; Kulisevsky et al., 1996, 2000; Cools et al., 2002; Costa et al., 2003).

Interestingly, there is also some evidence that individuals with schizophrenia taking haloperidol