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Effects of bromocriptine on human subjects depend on working memory capacity

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PHARMACOLOGICAL manipulation of brain dopamine concentration affects visuospatial working memory in humans and in animals, the latter effects localized to the prefrontal cortex. However, the effects of dopamine agonists on humans are poorly understood. We hypothesized that bromocriptine would have an effect on cognitive functions associated with the prefrontal cortex via its effects on cortical dopamine receptors and on subcortical receptors in areas that project to the neocortex. We found that the effect of bromocriptine on young normal subjects depended on the subjects' working memory capacity. High-capacity subjects performed more poorly on the drug, while low-capacity subjects improved. These results demonstrate an empirical link between a dopamine-mediated working memory system and higher cognitive function in humans.

Key words: Bromocriptine; Dopamine; Prefrontal cortex; Working memory

Introduction

Previous research has shown that bromocriptine, a D2 dopamine receptor agonist, can have a beneficial effect on visuospatial working memory functions in normal human subjects.[1] This form of memory, in which some aspect of a stimulus is maintained over a short interval of time, has also been found to be closely tied to prefrontal cortical function in both lesion and single unit recording studies with monkeys[2] and in neuro-imaging studies with human subjects.[3] In addition, Williams and Goldman-Rakic[4] have demonstrated a direct effect of dopamine antagonists on delay period activity of neurons in monkeys performing working memory tasks.

However, the prefrontal cortex may also serve non-visuospatial working memory functions, and such functions may play a critical role in more complex behavior.[5] Such working memory functions are often assumed to go beyond the passive maintenance of perceptual information, instead serving as a 'workspace' where the more abstract intermediate results of mental computations may be stored.[6,7] These more active working memory functions have also been linked to prefrontal cortex.[8,9] Because of this, it is important to understand the role of dopamine in other types of working memory, and in higher cognitive functions that depend on them. In this study, we examined the effect of bromocriptine on several complex cognitive tasks thought to depend on prefrontal function.

Materials and Methods

The protocol described here was approved by the University of Pennsylvania IRB, and all subjects gave informed consent prior to participation.

We measured the cognitive effects of bromocriptine, a D2 dopamine receptor agonist, in 31 normal human subjects. Each subject was tested twice: once on bromocriptine (2.5 mg orally) and once on a placebo. Order of administration was randomized, and the order of tasks within a session was fixed. The range of peak effectiveness was estimated from previous results[1,10] to occur between 1.5 and 3 h after the tablet was ingested, and cognitive testing was therefore scheduled to occur during this interval.

Because prefrontal function is a complex and poorly understood entity, and no individual TEST is both sensitive to and selective for frontal damage,[11,12] we used a variety of 'frontal' tasks to construct an index of prefrontal function. These tasks included a card sorting task, a task of associative memory, a task of context memory, and the Stroop task of interference, each described briefly here.

The card sorting task was a speeded variant of the Wisconsin Card Sorting task (WCST), in which subjects had to sort a series of cards according to categories that changed whenever the subject achieved eight right in a row. Subjects were given minimal (right/wrong) feedback after each card, but no other information. Successful subjects are able to make use of feedback to alter their sorting strategy

when appropriate. We used computer-based presentation and a 3 s deadline for each trial, to ensure that normal subjects would make errors at the task.

Associative memory was assessed using the fan effect paradigm,[13] in which subjects had to memorize a series of sentences which encoded conflicting information about the associations among various elements (e.g. 'The doctor is in the house' and 'The doctor is in the park'). This task measures susceptibility to interference in memory, as well as the ability to maintain associations under conditions of interference. The ability to associate items in memory has been linked to prefrontal function in a variety of context memory studies.[14] The context memory task was a straightforward task in which subjects were shown two lists of words, and later had to remember on which of the two lists each word had originally appeared.

Subjects were also given a version of the Stroop task, which included two conditions: naming the color of a series of color blocks, and naming the color of a series of conflicting color words (e.g. 'red' printed in blue ink). The difference in time to complete the two tasks was used as a measure of interference.

Subjects were also given two control tasks not hypothesized to depend either on prefrontal function or on working memory/executive functions, in order to rule out general effects of arousal. In a biletter cancellation task, similar to that used by Luciana *et al.*,[1] subjects read through six rows of letters and crossed out all the E^{r}s and C^{r}s. In a recognition memory task, given in conjunction with the context memory task, subjects had to decide whether a presented word had been present in either of the two studied lists.

For replication purposes, a spatial working memory task was included which was similar to that used by Luciana *et al.*,[1] which was adapted from the study conducted by Funahashi *et al.*[19] in monkeys. In this task, subjects had to remember over an interval of 8 s the location of a briefly presented dot, which might appear in any of 16 locations. In order to prevent subjects from using metacognitive strategies, we used a distractor task during the interval, in which subjects had to detect a letter in the center of the screen.

In order to examine the relationship between working memory capacity and complex cognitive behavior related to prefrontal function, testing also included a task of verbal working memory capacity, or reading span.[15] In this task, subjects were required to read a series of sentences, and to remember the last word of each sentence.

Results

Thirty-one subjects were included in most of these analyses (individual subjects were omitted in two instances because they failed to learn how to use the apparatus), and analyses of variance were performed to assess the effect of drug treatment on the various tasks. There was no main effect of bromocriptine on any of the measures ($p > 0.1$ in each case).

Scores on the reading span task, which did not differ significantly either by session or by drug treatment, were used to divide subjects by median split into high-span and low-span groups, so that we could examine the effect of bromocriptine on the two groups separately based on their working memory capacity. In order to rule out regression towards the mean, we used a mean reading span score from both sessions (although the analyses turned out to be insensitive to this, since reading span scores for most subjects were very similar between sessions).

Figure 1 presents the data from the composite index of prefrontal tasks, constructed by normalizing and averaging across key measures from each non-control task. Thus, data from the context, Stroop, card sorting, fan effect and spatial working memory tasks were combined by converting each subject's score for each session to a z-score. The z-scores were all calculated so that lower scores represented better performance (less interference in the case of the Stroop and fan effect tasks), and summed to create a single composite score for each session (two for each subject). A consistent pattern emerged from this analysis: low-span subjects (i.e. lower working memory capacity) performed better on bromocriptine than on the placebo, while high-span subjects performed more poorly on the drug. This interaction between the drug effect and working memory capacity was statistically significant ($p < 0.03$). Note that these results were insensitive to whether we classified subjects using reading span scores from the

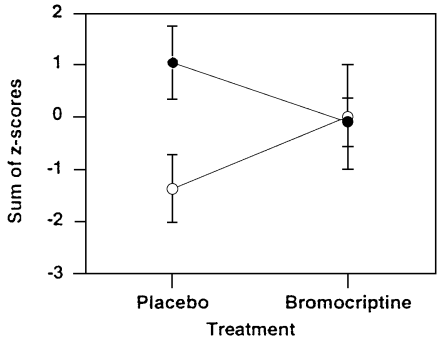

FIG. 1. Composite measure of scores across all tasks (z-scores calculated with higher scores representing poorer performance). The interaction is significant by ANOVA at $p < 0.03$. Unfilled circles = low span. Filled circles = high span.

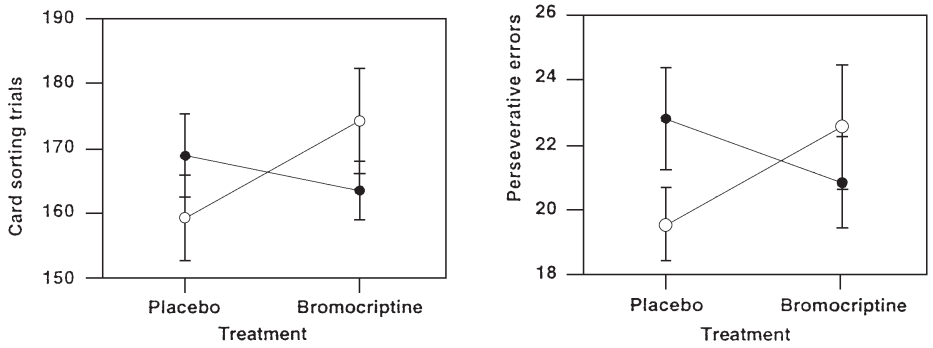

FIG. 2. Results from the card sorting task. Unfilled circles = low span. Filled circles = high span. (**a**) Trials to complete fifteen categories in the card sorting task. Minimum possible score was 120. The treatment by reading span interaction is significant at $p < 0.02$. (**b**) Perseverative errors in the card sorting task. These are errors in which subjects incorrectly continued to use a previously successful strategy even after negative feedback. The treatment by reading span interaction is significant at $p = 0.04$.

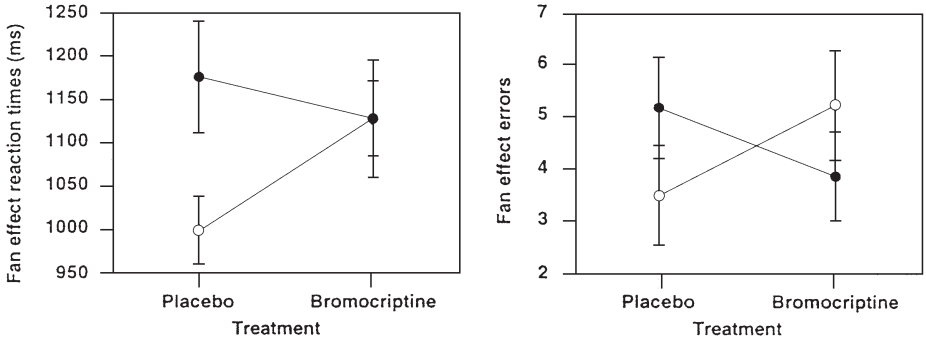

FIG. 3. Results from the fan effect task. (**a**) Reaction times in the fan effect recognition text. The treatment × reading span interaction is significant at $p < 0.05$. ○ = low span. ● = high span. (**b**) Errors in the fan effect recognition task (out of 256 trials). The treatment × reading span interaction is significant at $p < 0.05$.

drug session or the placebo session. This rules out an interpretation of these results as regression towards the mean.

In order to understand these results further, we also examined all of the tasks individually, including the control tasks. Figures 2 and 3 illustrate the pattern with the WCST and the fan effect. On both tasks, off the drug, not surprisingly, low-span subjects performed non-significantly more poorly than high-span subjects. On the drug, however, this pattern was actually reversed, and low-span subjects performed better than high-span subjects. This effect was due both to poorer performance by the high-span subjects and better performance by the low-span subjects. On the WCST, the treatment by span interaction was significant in both cases ($p < 0.02$ for trials, $p = 0.04$ for perseverative errors). A similar trend was observed for non-perseverative errors ($p < 0.07$). On the fan effect, the dependent measures of interest were taken from a recognition task: the reaction times to correct 'yes' responses, and the number of errors were both assessed, collapsed across fan levels (making the task essentially a simple test of associative memory). Drug treatment and reading span interacted in predicting both reaction time ($p < 0.05$) and errors ($p < 0.05$). The fact that both measures show the same pattern is important, because it demonstrates that the interaction is not an artifact of a speed–accuracy trade off.

In three other tasks (context memory, Stroop interference, spatial working memory), the patterns (reading span by treatment effect) were similar, but not at the level of statistical significance ($p = 0.16$, $p > 0.5$, and $p > 0.5$, respectively). Importantly, the control tasks (letter cancellation and recognition memory) showed no significant interactions ($p > 0.2$ in both cases), and the non-significant interactions were numerically in the opposite direction. Finally, there was no significant main effect of bromocriptine on reading span itself ($p > 0.4$), nor was the effect of bromocriptine on reading span different for low-span or high-span subjects.

Discussion

The pattern that emerges from these data is that the effect of bromocriptine on performance was most often worse for subjects with greater working

memory capacities. Not surprisingly, high-span subjects performed consistently better than low-span subjects when on the placebo. However, in many cases bromocriptine served to reduce or eliminate those differences. High-span subjects suffered (cognitively) on bromocriptine, while low-span subjects were helped by it. This surprising result is a concrete demonstration of the relationship between dopamine and the more active form of working memory implicated in complex cognitive tasks (especially 'frontal' tasks). These results may also suggest that the tasks may differ in their sensitivity to the administration of bromocriptine, as not all of the experimental tasks yielded significant interactions when taken individually. It is certainly also possible that not all of these tasks are strongly dependent on dopamine-dependent processes. As well, the use of a verbal working memory capacity task (as contrasted with spatial) to subdivide subjects may have weakened the results in the case of those tasks less susceptible to verbal mediation. For example, the reading span task did not significantly predict the effect of drug treatment for the spatial working memory task considered alone. The spatial working memory task was probably the least susceptible among the tasks used in the present study to verbal mediation. Given that the correlation between visuospatial and verbal working memory capacities is small, it is unlikely that the reading span task adequately divided the subjects into high and low spatial working memory capacity groups. However, since we did not include an independent measure of visuospatial working memory capacity, we cannot test this directly. By contrast, the two control tasks offered no such suggestive effects. The corresponding interaction did not reach statistical significance, and in both cases was in the opposite direction. This rules out a simple explanation of general arousal effects.

The interaction that we observed is especially interesting in light of the recent report by Williams and Goldman-Rakic,[4] in which they describe dose-dependent effects of a D1 dopamine receptor antagonist in monkeys. They reported that low doses of the drug enhanced delay period activity of mnemonic neurons, while higher doses inhibited firing for all units, including those showing delay period activity. There are certainly substantial differences between the two results. Our study used a fixed dose and two human subject groups receiving a D2 agonist, while Williams and Goldman-Rakic varied the dosage of a Dl antagonist in monkeys. However, both findings suggest that there is an optimal level of dopamine for working memory and the cognitive processes that depend on it, and that at higher level of dopamine and/or working memory capacity, additional dopamine impairs rather than facilitates performance.

We failed to replicate the results of Luciana *et al.*[1] in the spatial working memory task. While there were some differences between the two tasks (most notably our use of a distractor to prevent subjects from fixating on imperfections in the screen), we feel that this apparent conflict can be resolved simply, given our other findings. Our results suggest that the main effect of bromocriptine should depend on the normal working memory capacity of the subjects. It is possible than the subjects used by Luciana *et al.* simply had lower average visual working memory capacities than our subjects, and were therefore more likely to benefit from the drug treatment. This is suggested by the fact that half of their subjects in fact did not improve on the drug, but showed slightly poorer performance.

The lack of any direct effects of bromocriptine on reading span can be explained simply in terms of the working memory processes involved in the different tasks. The reading span task is a measure of verbal working memory capacity, not of working memory maintenance, or of active working memory processes. A survey of relevant data from prefrontal dysfunction suggests that the prefrontal cortex is preferentially responsible for maintenance, as indexed by delayed-response type tasks,[16] and not for capacity, as indexed by measures of working memory span.[17] And theoretical accounts suggest involvement of the prefrontal cortex in the use of active working memory processes to guide behavior,[5] not in working memory capacity. The more complex tasks used in this study probably do not depend on a simple subset of working memory function, but probably require both capacity and maintenance of representations, and other aspects of working memory function. It is not surprising, therefore, that a measure of capacity should predict the effects of a manipulation that directly affects only the other aspects of working memory function. However, a manipulation of prefrontal function would still be expected to affect only maintenance and other active working memory functions, and not capacity.

The remainder of this discussion considers a high-level working memory account of the interaction that we found. Note, however, that the strong implication of these data, that of a relationship between dopamine and working memory functions, does not depend on this more speculative account. We hope here to provide an intuitive causal link to explain this relationship. The account described here therefore relies on the hypothesized effect of bromocriptine on cognitive resources, and on how behavior depends on these resources. In addition, we depend on the work of Servan-Schreiber *et al.*[18] in modeling the response characteristics of systems of dopaminergic neurons.

It is possible to interpret these results in terms of the effect of bromocriptine on working memory within the response discrimination framework proposed by Kimberg and Farah.[5] Within this framework, we can characterize each task as a signal detection problem: the subject must decide between two or more competing responses, given some stimulus. Each response has a level of activation, and choosing correctly entails discriminating between these levels of activation. The sigmoid activation function[18] can be used to describe the mapping of input activation levels onto responses. In the middle range of this function, where the slope is greatest, it will be most effective in discriminating among inputs: small differences in activation will map onto a clear discrimination between responses. Towards the left or the right, however, where the slope is much smaller, small differences in input activation will make virtually no difference in the response.

If lower verbal working memory capacity entails maintaining the activation of representations at generally lower levels of activation, then the input activation to such a system might be at generally lower levels (i.e. toward the left of the sigmoid activation function). In such a case, the presence of additional activation would have the effect of shifting the levels of the input slightly to the right, into the more sensitive region of the function, magnifying differences between input levels and allowing the system to make finer discriminations. Conversely, if higher working memory capacity entails generally higher levels of activation, boosting these levels will result in reduced sensitivity to differences among inputs. While such a model is only a first approximation of what would happen in a more complex system, this example shows one mechanism by which such an interaction might be obtained.

Conclusion

A measure of verbal working memory capacity predicted the effects of a dopamine agonist on performance at an aggregate measure of tasks supposed to depend on prefrontal function (but not on control tasks). These results suggest a close connection between dopamine-mediated prefrontal function and working memory capacity. While previous studies have demonstrated a role of dopamine in maintenance aspects of working memory function, this is the first concrete demonstration of direct effects of dopaminergic agents on higher cognitive function in human subjects.

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