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Effects of Dextroamphetamine on Cognitive Performance and Cortical Activation

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Monoaminergic neurotransmitters are known to have modulatory effects on cognition and on neurophysiological function in the cortex. The current study was performed with BOLD fMRI to examine physiological correlates of the effects of dextroamphetamine on working-memory performance in healthy controls. In a group analysis dextroamphetamine increased BOLD signal in the right prefrontal cortex during a task with increasing working-memory load that approached working-memory capacity. However, the effect of dextroamphetamine on performance and on signal change varied across individuals. Dextroamphetamine improved performance only in those subjects who had relatively low working-memory capacity at baseline, whereas in the subjects who had high working-memory capacity at baseline, it worsened performance. In subjects whose performance deteriorated, signal change was greater than that in subjects who had an improvement in performance, and these variations were correlated (Spearman $\rho = 0.89$, $P < 0.02$). These data shed light on the manner in which monoaminergic tone, working memory, and prefrontal function interact and, moreover, demonstrate that even in normal subjects the behavioral and neurophysiologic effects of dextroamphetamine are not homogeneous. These heterogeneic effects of dextroamphetamine may be explained by genetic variations that interact with the effects of dextroamphetamine.

Key Words: **catecholamines; dopamine; dextroamphetamine; BOLD fMRI; cognition; cortical activation; working memory.**

INTRODUCTION

Studies in experimental animals (Foote *et al.*, 1975; Segal and Bloom, 1976; Murphy *et al.*, 1996; Sawaguchi and Goldman-Rakic, 1991; Williams and Goldman-Rakic, 1995; Woodard *et al.*, 1979) and in humans (Weinberger *et al.*, 1988) have implicated monoaminergic neurotransmitters as modulators of neurophysiological function in the cortex. The notion of a signal-to-noise ratio enhancing effect of monoamines on cortical neuronal activity has also been supported by neuroimaging studies that utilized direct receptor agonists (Daniel *et al.*, 1989; Dolan *et al.*, 1995; Friston *et al.*, 1992; Kapur *et al.*, 1994) and indirect monoamine agonists (Daniel *et al.*, 1991; Mattay *et al.*, 1996a). In general, these studies suggest that monoamines tune the response of pyramidal neurons in both a task- and a region-specific manner to optimize task performance. Similar effects have also been considered as aspects of the neurophysiological mechanisms of attention (Driver and Bayliss, 1989; Kastner *et al.*, 1998; Moran and Desimone, 1985; Posner *et al.*, 1980; Treue and Maunsell, 1996).

Consistent with these assumptions, we reported in an earlier study using the PET H_2O^{15} rCBF technique that dextroamphetamine, an indirect monoaminergic agonist, changed rCBF in a task- and in a region-specific manner (Mattay *et al.*, 1996a). In healthy adults performing the Wisconsin Card Sorting Task (WCST) and Ravens Progressive Matrices, dextroamphetamine resulted in a double dissociation in signal change in two specific areas, the inferior frontal gyrus and the hippocampus. During the WCST, dextroamphetamine increased activation in the inferior frontal gyrus but decreased it in the hippocampus, a response pattern seen to a lesser degree with placebo; the opposite pattern was observed during performance of Raven's Progressive Matrices. In general, this study and other neuroimaging studies (Daniel *et al.*, 1991; Dolan *et al.*, 1995; Friston *et al.*, 1992; Kapur *et al.*, 1994) have explored the "where" (i.e., cortical region) and the "when" (i.e., during which task) of the neuromodulatory effects of monoamines, while maintaining the level of difficulty of the experimental task constant. However, the effect of monoamines on the dynamic range of neurophysiological response during tasks with

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varying cognitive demand has not been systematically investigated. It is conceivable that the signal-to-noise enhancing effects of monoamines would affect the dynamic range of the neural responses.

Another issue with the earlier studies is that they relied on group averaging and, thus, may have missed individual heterogeneity of responses to monoamine challenge. For example, monoaminergic drugs have been reported to have individual-specific behavioral effects in healthy subjects. Kimberg *et al.* (1997), in a psychopharmacological study with bromocriptine (a D2-receptor agonist), reported improvement in performance of a visuospatial working-memory task only in subjects with lower working-memory capacity. On the other hand, subjects with high capacity performed more poorly on the drug. They suggested that these population differences (subjects with high vs low working-memory capacity) might be related to different (high vs low) endogenous metabolism of dopamine. It is conceivable that the heterogeneity in this response may arise from genetic variability in either working-memory function or monoaminergic function or both. Recently, it has been reported that genetic variations in the dopamine transporter gene in healthy subjects have quantifiable implications for dopamine transporter availability in the basal ganglia (i.e., phenotypic variation) (Heinz *et al.*, 2000). In the present study, we have explored individual variability in the effects of dextroamphetamine on performance during a working-memory task with increasing load (Callicott *et al.*, 1999) and their neurophysiological correlates using BOLD fMRI.

MATERIALS AND METHODS

Subjects

Ten healthy subjects (8 males and 2 females, mean age 30 years) gave written informed consent and participated in the study, which had the approval of the National Institute of Mental Health Institutional Review Board. The subjects were screened for past and present history of neurological, psychiatric, or substance abuse problems and had no history of other medical problems or medical treatment relevant to cerebral metabolism and blood flow. Subjects were asked to refrain from nicotine and caffeine for at least 4 h and from over-the-counter medications for 24 h before the MRI study.

Data Acquisition

BOLD fMRI data were collected on a standard 1.5-T Signa scanner (Milwaukee, WI) outfitted with a combined RF and gradient insert coil (Medical Advances, Milwaukee, WI) as previously described (gradient echo echo-planar imaging, 44 sagittal (3.75 mm thick) interleaved slices, TE = 60 ms, TR = 4 s, flip angle 90°, FOV 24 cm, matrix 64 × 64) (Mattay *et al.*, 1996b). The fMRI scans were colocalized with high-resolution anatomical scans obtained during the same session for localization.

Cognitive Tasks

BOLD fMRI was conducted while subjects performed three levels of the working memory task—a variation of the *n*-back task specially adapted for an MRI setting as previously described (Callicott *et al.*, 1999). Stimuli were presented via a fiber-optic goggle system (Resonance Technology, Van Nuys, CA), and the responses were recorded via a fiber-optic response box with buttons arranged in the same configuration as the stimuli presented on the screen. *N*-back refers to the number of previous stimuli that the subject had to recall. The stimuli consisted of numbers (1–4) shown in random order and displayed at the points of a diamond-shaped box. Three levels of the task (no-back, 2-back, and 3-back) were presented in 20-s epochs—counterbalanced and interspersed between an "eyes open" rest state—with nine blocks/session (eight epochs/block, i.e., two epochs of rest, no-back, 2-back, and 3-back states in each block). These levels of working-memory load were selected because they approach working-memory capacity in healthy subjects (Callicott *et al.*, 1999). Ninety whole-brain fMRI volumes (time points) were obtained per task condition (5 time-points × 2 task states/epoch × 9 blocks) (see Fig. 1).

Test Conditions and Drug Administration

Subjects were studied in a double-blind crossover design during two fMRI sessions separated by 1 to 2 weeks. All conditions were kept constant for the two visits of each subject. Approximately 120 min before each fMRI session, subjects received an oral dose of either placebo or dextroamphetamine (0.25 mg/kg body weight). Timing of administration of dextroamphetamine was based on pharmacokinetic data indicating that plasma levels of dextroamphetamine administered orally peak 2–3 h after administration of the drug. An amphetamine mood rating scale was administered before and 3 h after administration of the drug (Goldberg *et al.*, 1991). Profile of Mood Scales (POMS) (McNair *et al.*, 1992) and Spielberger anxiety scales (Spielberger, 1983) also were administered after the fMRI scans on each test day. Blood pressure and heart rate were obtained at baseline and every half-hour until the start of the fMRI session (2 h after administration of the drug). These measures were then repeated at the end of the fMRI session. Blood was drawn at the beginning of each fMRI session, and serum dextroamphetamine levels were measured using liquid chromatography (American Medical Laboratories, Chantilly, VA) with a sensitivity of 20 ng/ml. For undetermined reasons, two subjects did not have detectable drug levels and were excluded from further analysis.

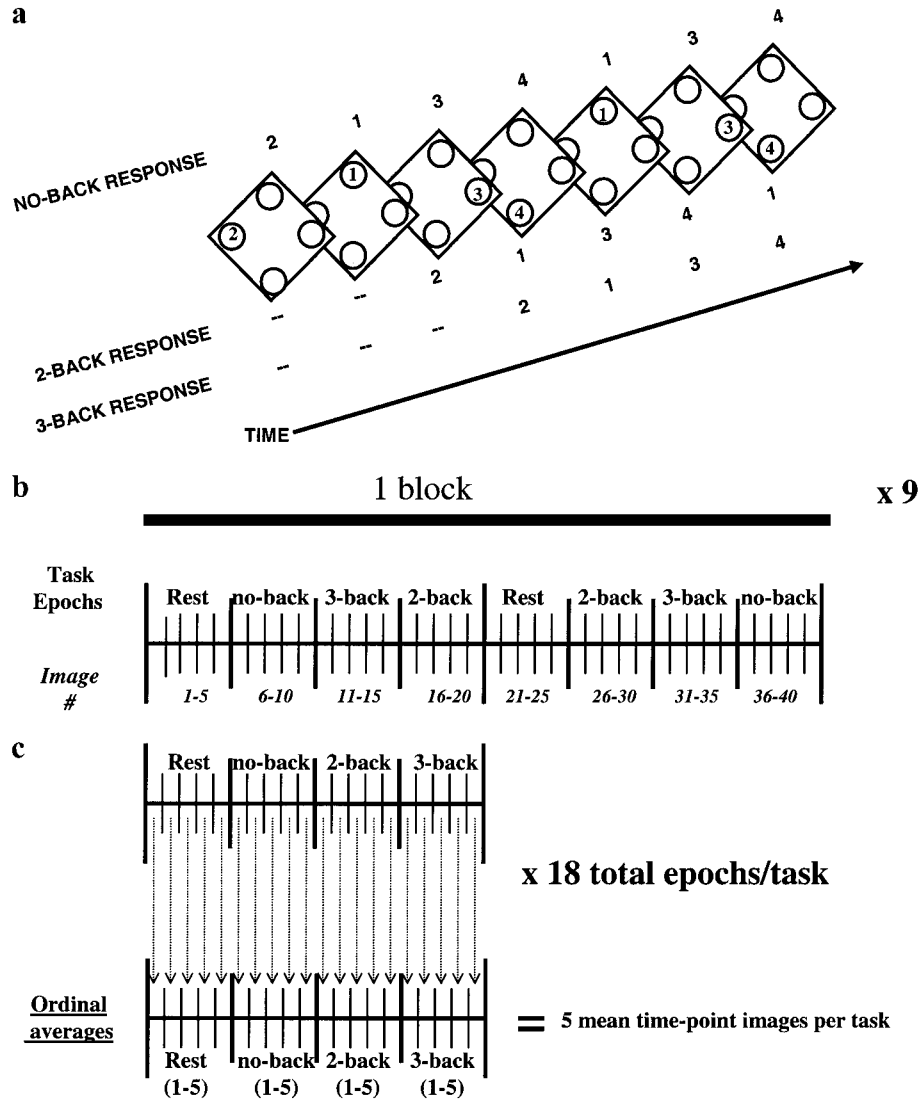

FIG. 1. (a) Rules for the *n*-back working-memory task. (b) Experimental design. No-back, 2-back, and 3-back tasks were presented to the subjects in 20-s epochs, counterbalanced and interspersed between an "eyes open" rest state, with nine blocks per session (8 task epochs/block, i.e., 2 epochs of rest, no-back, 2-back, and 3-back states in each block). (c) Creation of mean time-point pages. Corresponding scans from each of the 18 epochs for each task were averaged to produce five mean time-point images per task, per session, per subject (e.g., mean time-point image 1 was created by averaging the first time-point image from each of the 18 task epochs). To assess the main effect of task load and a task load × time × drug interaction, we used sets of linear contrasts within SPM96. We used five levels for time (mean time-point images 1 through 5), three levels for task load (no-back, 2-back, and 3-back) and two levels for drug state (placebo vs dextroamphetamine). Since we expected a greater signal change during the 3-back task than during the 2-back and no-back tasks, a greater weighting was assigned to the time-point images from the 3-back task than to those from the 2-back task and a greater weighting to the 2-back task than the no-back task. In other words, we tested for a linear regression with working-memory load. Similarly, within each task, to account for the hemodynamic response delay of BOLD signal greater weighting was assigned to the latter time-point images than to the initial time-point images.

Image Processing and Data Analysis

Image reconstruction was performed offline. Following reconstruction of the individual time volumes, each 3D brain volume was registered to the first in the time series using a tricubic-spline interpolation (Ostuni *et al.*, 1997). Data sets were then chosen for their high quality (scan stability) as demonstrated by small motion correction (<2 voxels) and matched voxel variance across the two sessions (Mattay *et al.*, 1996; Weinberger *et al.*, 1996; Callicott *et al.*, 1998). Six subjects met these stringent criteria and were included for further analysis. The individual whole-brain data from these six subjects were then spatially normalized to stereotactic space (Montreal Neurological Institute template) via Automated Image Registration 3.08 (Woods *et al.*, 1998a,b) using

the coregistered anatomical scans and a 30-parameter nonlinear model. Voxel-wise signal intensities were ratio normalized to the whole-brain mean and detrended in a linear fashion with the baseline at each voxel set to 100 (Callicott *et al.*, 1999). The data were then smoothed with a Gaussian filter (8 × 8 × 8 mm) to further control for interindividual variance in sulcal and gyral anatomy.

The time-series data were analyzed as "ordinal averages," analogous to that used in evoked-potential studies, to create mean time-point images (McCarthy *et al.*, 1997). Each 20-s epoch had five 4-s scans. For this analysis, ordered scans from each of the 18 epochs of each task (rest, no-back, 2-back, and 3-back) were labeled 1 to 5, and five mean time-point images per task, per session, were created for each subject (Fig. 1c). We then designed sets of linear contrasts in SPM 96, akin to traditional repeated-measures analysis of variance, to assess the main effect of task load and a task load × time × drug interaction (see Fig. 1 legend for details).

Significant changes in physiological variables (blood pressure and heart rate) and mood scales were assessed using post hoc matched-pair *t* tests. Significant changes in task performance were assessed using a repeated-measures analysis of variance followed by Tukey's Honest Significant Difference post hoc analysis. Additionally, Spearman's correlations were performed between dextroamphetamine-induced percentage BOLD signal change (based on the mean signal intensity value from the fourth and fifth time points, which was the time of maximal signal change) and percentage change in performance relative to placebo.

RESULTS

Clinical Variables

Dextroamphetamine caused a significant increase in mean systolic blood pressure (from 102 to 119 mm Hg; $P < 0.01$) and pulse rate (mean pulse 63 to 69/min; $P < 0.05$). On the Amphetamine Mood Rating Scale, subjects reported feeling significantly more focused while on dextroamphetamine (mean score: placebo, −4.66; dextroamphetamine, 10.8; $P < 0.03$). Though not statistically significant, POMS rating revealed that, in general, subjects reported feeling less confused (mean score: placebo, 4.33; dextroamphetamine, 2.5; $P = 0.1$) on dextroamphetamine. There were no significant differences in the Spielberger Anxiety Rating Scales. Serum dextroamphetamine levels ~2 h after drug administration ranged from 36 to 45 ng/ml (mean 41.13 ng/ml).

Brain Activation Patterns

There was a main effect of load on both days that mapped to very similar locales (Figs. 2a and 2b). The spatial distribution of the load effects included prefrontal cortex (BA 9–10/44–46), pericingulate region covering the medial frontal gyrus, supplementary motor area (medial BA 6) and anterior cingulate (BA 24, 32), and parietal cortex (BA 7, 39–40), consistent with earlier studies using this task (Callicott *et al.*, 1999). A load × time × drug interaction was found only in right BA 9 (*x*, *y*, and *z* coordinates = 26, 31, 36; *Z* score = 5.57, $P < 0.002$ corrected at the voxel level) (Fig. 3a). Plots of the normalized signal intensity from this region reveal that while the initial time points show residual effects of signal change from the preceding events, consistent with the BOLD signal delay (Buckner *et al.*, 1998), time points 3 through 5 reflect clear signal intensity differences across the three tasks. Dextroamphetamine, compared with placebo, produced a greater stepwise increase in BOLD signal intensity in both the 2-back and the 3-back tasks relative to the no-back task. The increase in signal also was greater in the 3-back condition than during the 2-back condition. Interestingly, there was a decrease in signal during no-back. The plot also suggests that the signal changes tend to peak sooner on dextroamphetamine (Fig. 3b). However, three-way interactions are difficult to interpret, and the basis of this effect is not clear from our data. Nevertheless, we cannot rule out the possibility that the hemodynamic delay associated with the BOLD response is affected by dextroamphetamine.

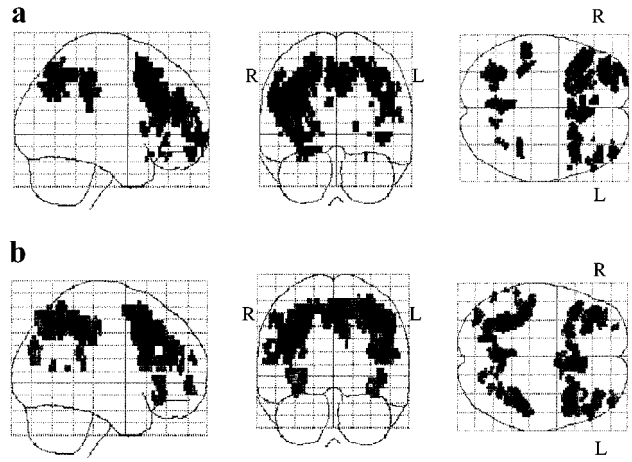

FIG. 2. Group activation maps from SPM96 showing regions with a significant response to changing working-memory load presented in the sagittal, coronal, and transverse "look-through" views (*Z* score > 4.2). (a) Placebo and (b) dextroamphetamine. Data were maintained in radiological convention (R = L). On both days, the *n*-back task evoked a dispersed cortical network inclusive of bilateral prefrontal cortices, parietal cortices, and anterior and posterior cingulate cortices.

Task Performance

There was a main effect of task load on performance (F (2,14) = 8.88, $P < 0.003$). On both days

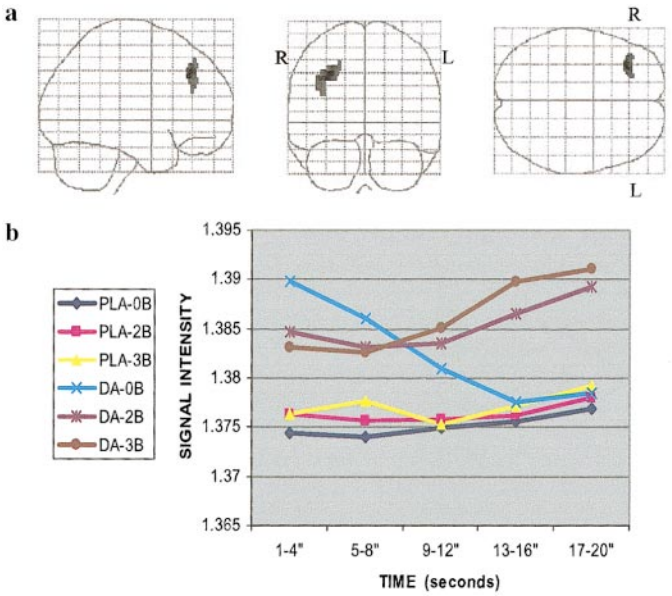

FIG. 3. (a) Group activation map showing a significant drug × load × time interaction in the right prefrontal cortex (BA 9) (Z score > 4.2). (b) Signal intensity plots from a voxel in the right prefrontal cortex showing a drug × load × time interaction (Z score = 5.57). x axis, time; y axis, normalized signal intensity (PLA, placebo; DA, dextroamphetamine). Due to the inherent delay in the decay of BOLD signal back to baseline following a stimulus, the initial time points (0–8 s) in the epoch show residual effects of signal change from preceding events.

performance accuracy during 2-back and 3-back decreased relative to the no-back. (mean performance (% correct) ± standard deviation—Placebo day: no-back = 97.3 ± 4.8, 2-back = 94.1 ± 3.8, 3-back = 94.4 ± 4.6. Dextroamphetamine day: no-back = 96.7 ± 6.4, 2-back = 93.4 ± 5.5, 3-back = 93.2 ± 6.3). While as a group, the subjects showed no significant difference in performance of 2-back and 3-back tasks across drug conditions, dextroamphetamine had individual-specific effects on performance. Dextroamphetamine improved performance during 3-back only in those subjects (N = 3) that had relatively low working memory capacity at baseline (mean performance—placebo day = 91.1, dextroamphetamine day = 97). In the subjects (N = 3) that had high working-memory capacity at baseline, performance deteriorated on dextroamphetamine (mean performance—placebo day = 97.7, dextroamphetamine day = 87.6). This dissociation was seen only during the more difficult 3-back task (Fig. 4).

Relationship between Task Performance and Brain Activation

Interestingly, on dextroamphetamine, a dissociation was also seen in the relationship between task performance and brain activation. During 3-back, in right BA 9 (the area that showed a significant drug × time × load interaction), there was a significant inverse relationship between dextroamphetamine-induced effect on the magnitude of signal change and performance change ($\rho = -0.89$, $P < 0.02$); smaller signal changes were associated with improved performance while larger signal changes were associated with deterioration in performance (Fig. 5). Similar correlations were not found during the 2-back task.

DISCUSSION

The results of our study support the notion that dextroamphetamine causes cognitively and regionally specific signal augmentation, as evidenced by the greater increase in cortical signal in the prefrontal cortex (BA 9) on dextroamphetamine during the working-memory conditions (2-back and 3-back) and a decrease in signal during the nonmemory condition (no-back) (Fig. 3b). However, this overall group effect was dominated at the highest load by the response of a subset of subjects which obscured more subtle neurophysiological and behavioral phenomena. It may be speculated that the significantly greater signal noted during the working-memory tasks in the PFC on dextroamphetamine is due to increased dopamine D-1 receptor stimulation. The same mechanism might explain the decrease associated with the no-memory matching task (no-back), as both responses reflect task-specific "tuning" of BA 9 neuronal activity.

The role of dopamine in prefrontal cortical function, especially working memory, has been well established (Sawaguchi and Goldman-Rakic, 1991; Murphy *et al.*, 1996). Additionally, electrophysiological studies of prefrontal cortex pyramidal cells in animals indicate that dopamine agonists "sharpen" NMDA-mediated and other depolarizing synaptic signals arriving on apical dendrites by attenuating high-threshold calcium spikes that amplify signals propagated along the dendrite (Seamans *et al.*, 1997; Yang and Seamans, 1996).

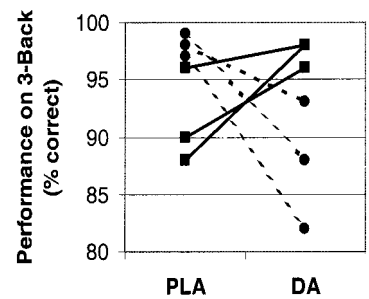

FIG. 4. Differential effect of dextroamphetamine on performance (% correct) of the more difficult 3-back task. In the high performers (dashed lines), i.e., the subjects with relatively higher working-memory capacity on placebo, dextroamphetamine worsened their performance. Conversely, in the lower performers (solid lines), i.e., the subjects with relatively lower working-memory capacity on placebo, dextroamphetamine improved their performance.

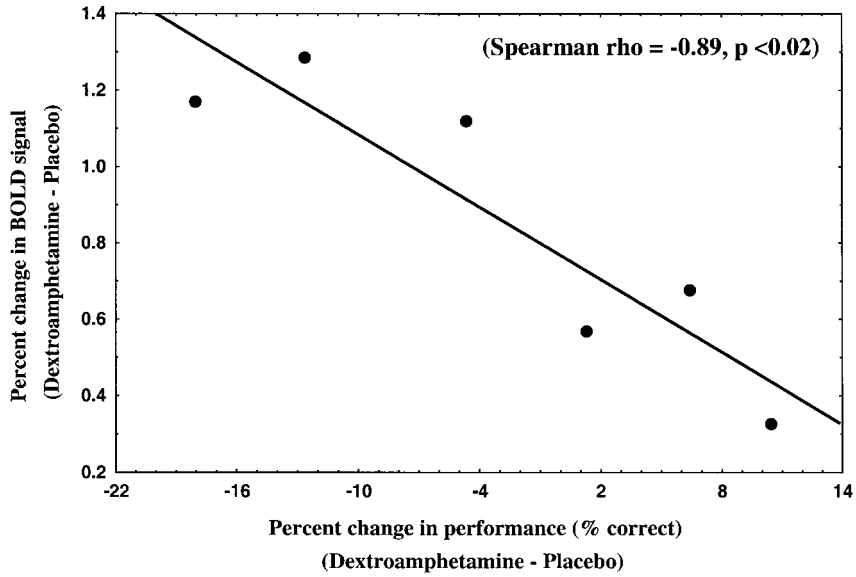

FIG. 5. Relationship between dextroamphetamine-induced change (from placebo) in performance and change in BOLD signal during the 3-back task in right BA 9 (the area that showed a significant drug × load × time interaction). *x* axis, percentage change in performance; *y* axis, percentage change in BOLD signal. Subjects with smaller dextroamphetamine-induced increases in BOLD signal (relative to placebo) showed an improvement in performance while the converse was seen in subjects with large increases in BOLD signal.

Recently, Chen *et al.* (1997) demonstrated the utility of BOLD fMRI in the examination of the effects of neurotransmitter stimulation. Using PET receptor imaging, microdialysis, and fMRI they demonstrated an increase in BOLD signal following stimulation with two dopaminergic ligands (dextroamphetamine and the dopamine transporter antagonist 2B-carbomethoxy-3B(-4-fluorophenyl) tropane) in regions of the brain with high dopamine receptor density. Our finding of increased signal on dextroamphetamine during the working-memory task is consistent with these earlier studies.

Further, our results show that the effect of dextroamphetamine at both the behavioral and the neurophysiological levels was heterogeneous (Figs. 4 and 5). Subjects who had relatively higher working-memory capacity at baseline (on placebo) showed a greater signal increase in prefrontal cortex (BA9) and a deterioration in performance compared with those who had relatively lower working-memory capacity at baseline and improved in performance. These behavioral findings are consistent with those of Kimberg *et al.* (1997) described above. These results are also broadly consistent with those of Fleming *et al.* (1995), who found that in healthy individuals dextroamphetamine improved or deteriorated performance on various tasks depending on their score on a novelty-seeking personality scale, a potential measure of dopaminergic tone. It is possible that these various individual differences in the effects of dextroamphetamine on prefrontal cortical activation and working-memory performance might be related to individual differences in dopamine function.

While the results of this study should be viewed with caution and any conclusions tentative because of the small sample size, it is tempting to speculate about a few implications. Several lines of evidence suggest an inverted "U"-shaped relationship between dopamine activity and working memory whereby excessive as well as insufficient D1 receptor stimulation impairs PFC cognitive function (Arnsten, 1994, 1997, 1998; Murphy *et al.*, 1996; Verma and Moghaddam, 1996; Williams and Goldman-Rakic, 1995). This phenomenon is further supported by electrophysiological evidence that suboptimal levels of D1 receptor stimulation result in unfocused signals, whereas optimal levels of D1 receptor stimulation focus signals and thus promote signal transfer from dendrite to soma (Zhart *et al.*, 1997; Arnsten, 1998). However, with excessive levels of D1 receptor stimulation, signals are oversharpened and do not reach the soma because of abolition of high-threshold calcium spikes. In our study, it is possible that in subjects with a relatively higher working-memory capacity, dextroamphetamine raised their dopaminergic tone beyond the optimal range of the inverted-U dose–response curve and had a deleterious effect on their performance, specifically on a task approaching their working-memory capacity. Conversely, in subjects with lower working-memory capacity, dextroamphetamine may have raised their monoaminergic tone from the insufficient range to the optimal range of the inverted-U dose–response curve and had a beneficial effect on their performance. One intriguing possibility for future study is that these population differences may be due to allelic variation of dopamine

system genes (e.g., catechol-*O*-methyl-transferase, dopamine transporter, dopamine receptors). This notion is supported by the recent findings of Winsberg and Comings (1999) who attributed variability in dopamine transmission genes to explain the subject-dependent variability in clinical response to methylphenidate in ADHD.

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REFERENCES

Arnsten, A. F. 1994. Dopamine D1 receptor mechanisms in the cognitive performance of young adult and aged monkeys. *Psychopharmacology* **116:** 143–151.

Arnsten, A. F. 1997. Catecholamine regulation of the prefrontal cortex. *J. Psychopharmcol.* **11:** 151–162.

Arnsten, A. F. 1998. Catecholamine modulation of prefrontal cortical cognitive function. *Trends Cognit. Sci.* **2:** 436–444.

Buckner, R. L., Koutsaal, W., Schacter, D. L., Dale, A. M., Rotte, M., and Rosen, B. R. 1998. Functional-anatomic study of episodic retrieval. II. Selective averaging of event-related fMRI trials to test the retrieval success hypothesis. *NeuroImage* **7:** 163–175.

Callicott, J. H., Mattay, V. S., Bertolino, A., Finn, K., Coppola, R., Frank, J. A., Goldberg, T. E., and Weinberger, D. R. 1999. Physiological characteristics of capacity constraints in working memory as revealed by functional MRI. *Cereb. Cortex* **9:** 20–26.

Callicott, J. H., Ramsey, N. F., Tallent, K., Bertolino, A., Knable, M. B., Coppola, R., Goldberg, T. E., van Gelderen, P., Mattay, V. S., Frank, J. A., Moonen, C. T. W., and Weinberger, D. R. 1998. Functional magnetic resonance imaging brain mapping in psychiatry: Methodological issues illustrated in a study of working memory in schizophrenia. *Neuropsychopharmacology* **18:** 186–196.

Chen, Y. C. I., Galpern, W. R., Brownell, A.-L., Matthews, R. T., Bogdanov, M., Isacson, O., Keltner, J. R., Beal, M. F., Rosen, B. R., and Jenkins, B. G. 1997. Detection of dopaminergic neurotransmitter activity using pharmacologic MRI: Correlation with PET, microdialysis, and behavioral data. *Magn. Reson. Med.* **38:** 389–398.

Daniel, D. G., Berman, K. F., and Weinberger, D. R. 1989. The effect of apomorphine on regional cerebral blood flow in schizophrenia. *J. Neuropsychiatry Clin. Neurosci.* **1:** 377–384.

Daniel, D. G., Weinberger, D. R., Jones, D. W., Zigun, J. R., Coppola, R., Handel, S., Bigelow, L. B., Goldberg, T. E., Berman, K. F., and Kleinman, J. E. 1991. The effect of amphetamine on regional cerebral blood flow during cognitive activation in schizophrenia. *J. Neurosci.* **11:** 1907–1917.

Dolan, R. J., Fletcher, P., Frith, C. D., Friston, K. J., Frackowiak, R. S. J., and Grasby, P. M. 1995. Dopaminergic modulation of impaired cognitive activation in the anterior cingulate cortex in schizophrenia. *Nature* **378:** 180–182.

Driver, J., and Bayliss, G. C. 1989. Movement and visual attention: The spotlight metaphor breaks down. *J. Exp. Psychol.* **15:** 448.

Fleming, K., Bigelow, L. B., Weinberger, D. R., and Goldberg, T. E. 1995. Neurophysiological effects of amphetamine may correlate with personality characteristics. *Psychopharmacol. Bull.* **31:** 357–362.

Foote, S. L., Freedman, R., and Oliver, P. A. 1975. Effects of putative neurotransmitters on neuronal activity in monkey auditory cortex. *Brain Res.* **86:** 229–242.

Friston, K. J., Grasby, P. M., Bench, C. J., Frith, C. D., Cowen, P. J., Liddle, P. F., Frackowiak, R. S. J., and Dolan, R. J. 1992. Measuring the neuromodulatory effects of drugs in man with positron emission tomography. *Neurosci. Lett.* **141:** 106–110.

Friston, K. J., Holmes, A. P., Worsley, K. J., Poline, J. B., Frith, C. D., and Frackowiak, R. S. J. 1995. Statistical parametric mapping in functional imaging: A general approach. *Hum. Brain Mapp.* **2:** 189–210.

Goldberg, T. E., Bigelow, L. B., Kleinman, J. E., Daniel, D. G., and Weinberger, D. R. 1991. Effects of coadministration of amphetamine and haloperidol on the affect, motor behavior, and cognition of patients with schizophrenia. *Am. J. Psychiatry* **148:** 78–84.

Heinz, A., Goldman, D., Jones, D. W., Palmour, R., Hommer, D., Gorey, J. G., Lee, K. S., Linnoila, M., and Weinberger, D. R. (2000). Striatal dopamine transporter availability and genotype in abstinent alcohol-dependent patients and control subjects. *Neuropsychopharmacology* **22:** 133–139.

Kapur, S., Meyer, J., Houle, S., and Brown, G. M. 1994. Modulation of cortical neuronal activity by a serotonergic agent: A PET study in humans. *Brain Res.* **646:** 292–294.

Kastner, S., Weerd, P. D., Desimone, R., and Ungerleider, L. G. 1998. Mechanisms of directed attention in the human extrastriate cortex as revealed by functional MRI. *Science* **282:** 108–111.

Kimberg, D. Y., D'Esposito, M., and Farah, M. J. 1997. Effects of bromocriptine on human subjects depend on working memory capacity. *NeuroReport* **8:** 3581–3585.

Mattay, V. S., Berman, K. F., Ostrem, J. L., Esposito, G., Horn, J. D. V., Bigelow, L. B., and Weiberger, D. R. 1996a. Dextroamphetamine enhances "neural network-specific" physiological signals: A positron-emission tomography rCBF study. *J. Neurosci.* **16:** 4816–4822.

Mattay, V. S., Frank, J. A., Santha, A. K. S., Pekar, J. J., Duyn, J. H., McLaughlin, A. C., and Weinberger. D. R. 1996b. Whole-brain functional mapping with isotropic MR imaging. *Radiology* **201:** 399–404.

McCarthy, G., Luby, M., Gore, J., and Goldman-Rakic, P. 1997. Infrequent events transiently activate human prefrontal and parietal cortex as measured by functional MRI. *J. Neurophysiology* **77:** 1630–1634.

McNair, D., Lorr, M., and Droppleman, L. 1992. *Profile of Mood States.* Educational and Industrial Testing Service, San Diego.

Moran, J., and Desimone, R. 1985. Selective attention gates visual processing in the extrastriate cortex. *Science* **229:** 782.

Murphy, B. L., Arnsten, A. F. T., Goldman-Rakic, P. S., and Roth, R. H. 1996. Increased dopamine turnover in the prefrontal cortex impairs spatial working memory performance in rats and monkeys. *Proc. Natl. Acad. Sci. USA* **93:** 1325–1329.

Ostuni, J., Santha, A., Mattay, V., Weinberger, D., Levin, R., and Frank, J. 1997. Analysis of interpolation effects in the reslicing of functional MR images. *J. Comput. Assisted Tomogr.* **21:** 803–810.

Posner, M. I., Snyder, C. R. R., and Davidson, B. J. 1980. Attention and the detection of signals. *J. Exp. Psychol.* **109:** 160–174.

Sawaguchi, T., and Goldman-Rakic, P. S. 1991. D1 dopamine receptors in pre-frontal cortex: Involvement in working memory. *Science* **251:** 947–950.

Seamans, J., Gorelova, N., and Yang, C. 1997. Contributions of voltage gated Ca^{2+} channels in the proximal versus distal dendrites to synaptic integration in prefrontal cortical neurons. *J. Neurosci.* **17:** 5936–5948.

Segal, M., and Bloom, F. E. 1976. The action of norepinephrine in the rat hippocampus. III. Hippocampal cellular responses to locus coeruleus stimulation in the awake rat. *Brain Res.* **107:** 499–511.

Spielberger, C. 1983. *Manual for the State-Trait Anxiety.* Consulting Psychologists Press, Paolo, CA.

Treue, S., and Maunsell, J. H. R. 1996. Attentional modulation of visual motion processing in cortical areas MT and MST. *Nature* **382:** 539.

Verma, A., and Moghaddam, B. 1996. NMDA receptor antagonists impair prefrontal cortex function as assessed via spatial delayed alteration performance in rats: Modulation by dopamine. *J. Neurosci.* **16:** 373–379.

Weinberger, D. R., Berman, K. F., and Illowsky, B. 1988. Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia. III. A new cohort and evidence for a monoaminergic mechanism. *Arch. Gen. Psychiatry* **45:** 609–615.

Weinberger, D. R., Mattay, V., Callicott, J., Kotrla, K., Santha, A., Gelderen, P. v., Duyn, J., Moonen, C., and Frank, J. 1996. FMRI application in schizophrenia research. *NeuroImage* **4:** S118–S126.

Williams, G. V., and Goldman-Rakic, P. S. 1995. Modulation of memory fields by dopamine D1 receptors in prefrontal cortex. *Nature* **376:** 572–550.

Winsberg, B. G., and Comings, D. E. 1999. Association of the dopamine transporter gene (DAT1) with poor methylphenidate response. *J. Am. Acad. Child Adolesc. Psychiatry* **38:** 1474–1477.

Woodard, D., Moises, H., Waterhouse, B., Hoffer, B., and Freedman, R. 1979. Modulatory actions of norepinephrine in the central nervous system. *Fed. Proc.* **38:** 2109–2116.

Woods, R. P., Grafton, S. T., Holmes, C. J., Cherry, S. R., and Mazziotta, J. C. 1998a. Automated image registration. II. Intersubject validation of linear and nonlinear models. *J. Comput. Assisted Tomogr.* **22:** 153–165.

Woods, R. P., Grafton, S. T., Watson, J. D. G., Sicotte, N. L., and Mazziotta, J. C. 1998b. Automated image registration. I. General methods and intrasubject, intramodality validation. *J. Comput. Assisted Tomogr.* **22:** 139–152.

Yang, C. R., and Seamans, J. K. 1996. Dopamine D1 receptor actions in layers V–VI rat prefrontal cortex neurons *in vitro:* Modulation of dendritic–somatic signal integration. *J. Neurosci.* **16:** 1922–1935.

Zhart, J., Taylor, J. R., Matthew, R. G., and Arnsten, A. F. T. 1997. Supranormal stimulation of D1 dopamine receptors in the rodent prefrontal cortex impairs spatial working memory performance. *J. Neurosci.* **17:** 8528–8535.