A Mechanistic Account of Striatal Dopamine Function in Cognition: Psychopharmacological Studies with Cabergoline and Haloperidol

Supplemental Material

Michael J. Frank[1*] Randall C. O'Reilly[2]

[1] Dept of Psychology and Program in Neuroscience, University of Arizona

[2] Dept of Psychology and Center for Neuroscience, University of Colorado at Boulder

[*] Corresponding author: mfrank@u.arizona.edu

This supplementary material provides a detailed explication of the procedures and analysis used to determine the basis for the results reported in the main paper.

Methods

Sample

Our sample was 28 healthy participants, 15 females and 13 males, between the ages of eighteen and thirty-five. Mean age was 21. Exclusion criteria included the use of any medications (prescription or non-prescription), illicit drugs, more than 5 cigarettes a day or 4 cups of coffee per week. Participants were recruited with the University of Colorado Paid Subjects website, and were predominantly undergraduate college students.

† This research was supported in part by a General Clinical Research Center Grant from NIH/NCRR (M01RR00051) awarded to the University of Colorado at Boulder. Also supported by ONR grant N00014-03-1-0428 and NIH grant MH069597-01. We thank the staff of the General Clinical Research Center for their assistance, and Karen Richardson for help in administering cognitive tasks to participants. We also thank Kent Hutchison and Tim Curran for helpful discussion.

Justification of Drugs and Dosage Levels

Cabergoline

Although the effects of bromocriptine have been previously studied, there are three reasons for our proposal to instead examine the effects of cabergoline. Cabergoline is a long-lasting D2 agonist used to treat Parkinson's disease, for which it is more effective and better tolerated than bromocriptine in both men and women (Stocchi, Vacca, Berardelli, Onofrj, Manfredi, & Ruggieri, 2003; Corsello, Ubertini, Altomare, Lovicu, Migneco, Rota, & Colosimo, 2003; Biller, Molitch, Vance, Cannistraro, Davis, Simons, Schoenfelder, & Klibanski, 1996; Webster, 1994). Cabergoline also exerts a direct inhibitory effect on the secretion of the hormone prolactin, and as such is used to treat hyperprolactinemia.

1. First and foremost, bromocriptine administration often results in nausea and vomiting - this makes the study uncomfortable for the participant and may lead to confounding results or significant attrition. In contrast, cabergoline has a side effect profile that is considerably milder than bromocriptine. The vast majority of participants that had experienced nausea or other side effects on bromocriptine experienced none on cabergoline, and in those that did the effect was more mild (Colao, Lombardi, & Annunziato, 2000; Biller et al., 1996).
2. Second, the cognitive effects of bromocriptine have been relatively subtle (e.g., Kimberg, D'Esposito & Farah, 1997). This may in part be related to the relatively low affinity (binding strength) of bromocriptine to D2 receptors. In contrast, cabergoline has 7 times affinity for D2 receptor than bromocriptine and also has only very low affinity for D1 (Ichikawa & Kojima, 2001), making it ideal for testing of D2 function.
3. Finally, no known study has examined the cognitive effects of cabergoline and such research may be valuable, independently from testing our specific hypothesis.

As mentioned above, no known studies have tested the effects of cabergoline on cognitive function. Doses of 0.5 - 1.5 mg are typically used to effectively treat hyperprolactinemia, while 7 mg or higher are used to treat Parkinson's disease. We selected a relatively low dose level of 1.25 mg, for several reasons. Although cabergoline is better tolerated than bromocriptine (Biller et al., 1996; Colao et al., 2000), there may be a dose-dependent relationship with respect to nausea which we wanted to circumvent.

Haloperidol

Haloperidol is commonly used as an antipsychotic, and has superior in vivo D2 binding when compared to the other atypical medications (Seeman & Kapur, 2000; Kapur, Remington, Jones, Wilson, DaSilva, Houle, & Zipursky, 1996). Further, while it does have limited affinity for the D1 receptor, it is 25 times more strongly bound to D2 (Bymaster,

Perry, Nelson, Wong, Rasmussen, Moore, & Calligaro, 1999). Animal experiments show that haloperidol increases DA release in the BG but not in PFC; this selective effect is not necessarily observed with other D2 medications (Kuroki, Meltzer, & Ichikawa, 1999). Clinical trials with haloperidol in healthy individuals have demonstrated that haloperidol can be safely used to investigate processes related to dopamine activation (e.g., Malaspina, Colemann, Quitkin, Amador, Kaufmann, Gorman, & Sackeim, 1994; Modell, Mountz, Glaser, & Lee, 1993. Although chronic administration (weeks to months) of haloperidol can induce tardive dyskinesia, this is extremely unlikely to arise from a single low dose (2 mg). Milder side effects may occur, such as sedation, blurred vision, restlessness or mild tremor, but if these do occur they should only be transient.

Previous studies on the effects of haloperidol on cognitive and procedural learning have used 1, 2 and 5 mg (Malaspina et al., 1994; Kumari, Corr, Mulligan, Cotter, Checkley, & Gray, 1997; Peretti, Danion, Kauffmann-Muller, Grangé, Patat, & Rosenzweig, 1997), with significant results found primarily for the 2 and 5 mg groups. Although lower than is typically used to treat schizophrenia, we chose 2 mg as the dose for several reasons. First and foremost, we wish to reduce the possibilities of extra-pyramidal and sedative side effects that are more likely to occur with higher doses. Second, it has been shown that D2 receptors are 50% occupied at an average dose of less than 1 mg (Fitzgerald, Kapur, Remington, Roy, & Zipursky, 2000) (but note that this data is from schizophrenic patients administered haloperidol for at least 10 days prior to measurement of receptor occupancy and that absorption is incomplete on the first dose, motivating us to use more than 1 mg). Although antipsychotic efficacy is typically observed only for occupancies ¿70%, this may be because the threshold for updating or paying attention to information needs to be raised substantially in schizophrenic patients to alleviate delusions/hallucinations. However, to simply detect a difference in threshold induced in healthy individuals, a lower percentage of blocked D2 receptors should be sufficient. Finally, haloperidol also has some affinity for the D1 receptor (albeit 25 times lower than that for D2), which may play more of a role at higher doses. Since we are specifically interested in DA effects in the BG, we would like to reduce the possibility o f the drug exerting its effects on D1 receptors, which (unlike D2) are expressed abundantly in cortex.

Procedures

Procedures were approved by the Scientific Advisory Committee of the University of Colorado Health Sciences Center, and by the University of Colorado Human Research Committee. We used a within-subjects double blind design. Participants reported to the Boulder GCRC for lab tests and a medical exam. A GCRC physician conducted the medical exam, drug test, and reviewed the medical data for each participant. Those who met the study criteria and who received medical approval then proceeded to the pre-experimental session, including the working memory reading span test (Daneman & Carpenter, 1980). They were then scheduled for all three experimental sessions, separated by two weeks.

On the day of the experimental sessions, smoking and drinking alcohol or caffeine was prohibited (enforced via a breathalyzer test). Baseline pre-drug blood samples (5 mL) were drawn and sampled for serum prolactin. Subsequently, participants received a tablet of either 2 mg haloperidol, 1.25 mg cabergoline, or placebo. The assignment of drug type to experimental session number was counterbalanced across participants, as was the order of tasks within a given session. Participants then waited for 2.5 hours to allow the drug to be absorbed (peak plasma levels are reached between 2 and 3 hours for both cabergoline and haloperidol; Persiani, Rocchetti, Pacciarini, Holt, Toon, & Strolin-Benedetti, 1996; Darby, Pasta, Dabiri, & Mosbacher, 1995). During this time, participants watched a video. Pulse rates were also monitored every 15 minutes. The cognitive tests lasted approximately 1.25 hours. Four hours after drug ingestion (approximately 10-15 minutes following test completion) a second blood sample was drawn to measure drug effects on serum prolactin levels. Ratings of subjective arousal, mood, restlessness and other side effects were taken pre and post each experimental session using a visual analog scale.

Baseline Working Memory Span

In the pre-screening session, all participants performed the working memory span test (Daneman & Carpenter, 1980). We scored the total number of errors in this test, and then divided the participants in two groups by median split. The median number of errors was 25.

Probabilistic Selection Task Procedures

Participants sit in front of a computer screen in a lighted room and view pairs of visual stimuli that are not easily verbalized (Japanese Hiragana characters, see Figure 4 in main paper). These stimuli are presented in black on a white background, in 72 pt font. They press keys on the left or right side of the keyboard depending on which stimulus they choose to be "correct". Note that the forced-choice nature of the task controls for any differences in overall motor responding. Visual feedback is provided (duration 1.5 seconds) following each choice (the word "Correct!" printed in blue or "Incorrect" printed in red). If no response is made within four seconds, the words "no response detected" are printed in red.

Three different stimulus pairs (AB, CD, EF) are presented in random order. Feedback follows the choice to indicate whether it was correct or incorrect, but this feedback is probabilistic. Choosing stimulus A leads to correct (positive) feedback in 80% of AB trials, whereas choosing stimulus B leads to incorrect (negative) feedback in these trials. CD and EF pairs are less reliable: stimulus C is correct in 70% of CD trials, while E is correct in 60% of EF trials. Over the course of training participants learn to choose stimuli A, C and E more often than B, D, or F.

We enforced a performance criterion (evaluated after each training block of 60 trials) to ensure that all participants were at the same performance level before advancing to test. Because of the different probabilistic structure of each

stimulus pair, we used a different criterion for each (65% A in AB, 60% C in CD, 50% E in EF)[1]. The participant advanced to the test session if all these criteria were met, or after six blocks (360 trials) of training. 5 participants on cabergoline, 4 on haloperidol and 1 on placebo required the full six training blocks before advancing to test. The test session involved presenting the same training pairs in addition to all novel combinations of stimuli, in random sequence. They were instructed (prior to the test phase) to use "gut instinct" if they did not know how to respond to these novel pairs. Each test pair was presented 6 times for a maximum of four seconds duration, and no feedback was provided.

Although there were no differences in the training accuracy among drug conditions, or in the number of trials needed to reach training criteria (see main paper for statistics), we were nevertheless interested in whether overall test performance differed in participants who satisfied training criteria within the first block of training (60 trials) vs. those that required longer. Indeed, those meeting training criteria in the first block performed overall better on test pairs than those who took longer ($F[1,24] = 5.1$, $p = .034$), but this better performance did not interact with positive / negative test condition ($F[1,24] = 0.8$).

Probabilistic Go/NoGo and Reversal Task Procedures

The stimuli employed for this task are colored and textured patterns that are difficult to verbalize (Figure 5 in main paper). As in the selection paradigm, individual patterns that appear in any given session are not reused in other sessions. Each trial begins with a green fixation circle in the center of the screen for 1 second, followed by a stimulus pattern lasting 1 second. For each stimulus, participants press a key on the keyboard or withhold their response. Visual feedback (1 second duration) is provided only after Go responses ("You won a point!" written in blue or "You lost a point" written in red, together with their running "batting average"). If they do not respond within 1 second, feedback written in black letters reads "No points won or lost". Six different patterns (A-F) are presented in random order, associated with reinforcement probabilities of 80%, 70%, 60%, 40%, 30% and 20%. Over time, participants have to learn that three of the stimuli should be associated with a button press (because their corresponding probabilities of reinforcement are greater than 50%), but that responses made to the other three will likely be incorrect.

As in the PS task, we enforced a performance criterion (evaluated after each training block of 60 trials). Participants had to perform at least 70% on stimuli A and F, 60% on B and E and F, and not worse than chance on C and D (which were only 60% reliable). The participant advanced to the test session if all these criteria were met, or after four blocks

[1] In the EF pair, stimulus E is correct 60% of the time, but this is particularly difficult to learn. We therefore used a 50% criterion for this pair simply to ensure that if participants happened to "like" stimulus F at the outset, they nevertheless had to learn that this bias was not going to consistently work.

(240 trials) of training. The vast majority of participants did not satisfy the criteria before the full four training blocks. Only 14 of 150 subject-sessions did so, 8 on haloperidol, 4 on placebo and 2 on cabergoline.

In the test session, there are 69 trials in which the training patterns A through F are re-presented 6 times each, interleaved with novel combinations of elemental patterns (AC, AD, AE, AF, BD, BE, BF, CD, CE, CF, DF; that is, four overall Go patterns and four overall NoGo patterns) presented 3 times each. In these novel patterns, the left and right halves of the combined pattern each represent one of the training patterns. For example, half of the composite pattern may consist of a familiar pattern that is 80% correct, while the other half consists of one that is 80% incorrect, so that the combined pattern should be equally associated with "Go" and "NoGo". In some cases one of the patterns is more strongly associated (i.e., 80% combined with 60%), but in others the associations are equal (80/80). Each novel test pattern is presented three times, interleaved among elemental training stimuli that are presented six times each.

Reversal

A second training block of 240 trials follows the Go/NoGo test session, in which the probabilities of reinforcement to the different patterns are reversed. Participants have to learn to respond to stimuli that were previously incorrect and stop responding to stimuli that were previously correct.

Working Memory Task Procedures

The working memory segment begins with the standard task with no distractors and an inter-stimulus interval of one second. Each stimulus is presented for 500 ms. There are 50 sequences in the standard task, with 70% A-X target sequences, and 10% each of A-Y, B-X and B-Y.

Next, a longer (3 second) delay period is used during which we present from 0 to 3 distractors sequentially. Each stimulus is presented for 500 ms, and each distractor is presented for 333 ms. The distractors are spaced out evenly throughout the 3 second delay period. When one distractor is presented, there is a 1333 ms delay between the cue and the distractor and between the distractor and the target. For two distractors, the delay between each item is 778 ms. For three distractors, it is 500 ms. Participants have to respond to each distractor with a left button push to ensure that they encode them, but are told to ignore them for the purpose of target detection (Braver, Barch, Keys, Carter, Cohen, Kaye, Janowsky, Taylor, Yesavage, & Mumenthaler, 2001). In the A-X distractor segment, there are 32 trials of which 20 are A-X target sequences, and the remaining 12 are divided equally between A-Y, B-X, and B-Y. This same procedure is followed for the reversal and attentional-shift conditions, for a total of 128 trials in the distractor conditions.

Finally, in the procedural A-X task, different letter stimuli are used (e.g., H,G,Z,P) and participants are instructed to try to figure out what the target sequence is by trial-and-error. They have to respond with a left button push to all

Prolactin Diff (Post - Pre, ng/mL)	Placebo	Cabergoline	Haloperidol
Low Span	-0.4 (0.4)	-8.6 (1.1)	5.92 (3.0)
High Span	-4.2 (1.3)	-10.5 (2.5)	-2.1 (1.0)

Table 1: Drug effects on serum prolactin levels, broken down into participants with low and high working memory span. Prolactin effects were determined by measuring levels after cognitive tasks and subtracting from levels obtained prior to drug administration.

cues, and a right button push to the cue-probe combination that they think is a target. Each stimulus is presented for 500 ms, and the delay between cue and probe is 2 seconds. Feedback follows each probe, either "Correct!" written in blue or "Incorrect" written in red, as in the PS task. There are 24 trials, but in this case the target sequence is equally likely to appear as other sequences (a majority of target sequences would make the learning of targets trivial). This is repeated three times with new target sequences, for a total of 72 trials in the procedural A-X segment.

Data Filtering and Analysis

Filtering

Prior to statistical analysis, we filtered out participants who did not satisfy global performance measures during the test sessions. In the Probabilistic Selection task, we filtered out data from participants who did not perform better than chance (50%) at the most trivial training pair (AB) during test in a given session (Frank, Seeberger, & O'Reilly, 2004). Thus this amounted to six participants on placebo (five low-span), six on haloperidol and two on cabergoline (all low-span), who became globally confused by the test phase; their results in choosing among novel pairs are meaningless. Similarly, in the Go/NoGo task we filtered out participants who did not respond above chance on either of the two most trivial training stimuli (80% Go or 80% NoGo). Using these criteria, two participants on cabergoline and one participant on haloperidol were excluded. For the A-X working memory sessions, we filtered out participants who performed worse than 50% on A-X target sequences, which occur on the majority of trials and are trivial – this amounted to one low-span participant on placebo and three on haloperidol (2 low-span, 1 high-span), who clearly were not paying attention to the task rules.

Analysis

In order to be consistent across all data analyses, we performed the same statistical test for each analysis. We used SAS v8.0 PROC MIXED to examine both between and within subject differences, using unstructured covariance matrices (which does not make any strong assumptions about the variance and correlation of the data, as do structured

Likert Scale	Placebo	Cabergoline	Haloperidol
Headache	+0.11 (0.1)	+0.46 (0.14)	+0.23 (0.08)
Stomach Ache	0 (0)	+0.04 (0.04)	0 (0)
Nausea	0 (0.05)	-0.04 (0.07)	+0.04 (0.04)
Dizziness	+0.15 (0.11)	+0.25 (0.13)	+0.19 (0.09)
Blurred Vision	+0.11 (0.08)	+0.25 (0.14)	+0.15 (0.1)
Muscle Pain	-0.04 (0.04)	0 (0)	0 (0.06)
Muscle Stiffness	0 (0.05)	+0.13 (0.15)	+0.15 (0.09)
Muscle Twitches	0 (0.05)	0 (0)	+0.15 (0.12)
Good Mood	-0.48 (0.14)	-0.46 (0.18)	-0.38 (0.12)
Bad Mood	+0.19 (0.13)	+0.04 (0.18)	+0.27 (0.2)
Restlessness	+0.59 (0.22)	+0.54 (0.22)	+0.27 (0.17)*
Tenseness	+0.22 (0.11)	0 (0.09)	0.12 (0.16)
Relaxedness	-0.74 (0.17)	-0.67 (0.17)	-0.58 (0.19)
Alertness	-0.07 (0.18)	-0.21 (0.15)	-0.27 (0.18)
Tired/Drowsiness	0.04 (0.18)	0.38 (0.19)	0.54 (0.2)
Clearheadedness	-0.11 (0.2)	-0.29 (0.16)	-0.65 (0.18)
Thought on drug?	2.18 (0.23)	2.42 (0.29)	2.15 (0.23)

Table 2: Subjective rating scale measures. Participants filled out questionnaires before drug ingestion and after completion of cognitive experiments, using a 5-point Likert scale. Values indicate mean (standard error) change scores from baseline (i.e. score post-tablet – score pre-tablet). The only significant within-subject drug difference was that haloperidol resulted in *less* restlessness compared to the placebo condition. In the post-experimentation questionnaire, participants were asked to rate on a 5-point scale whether they thought they were on an active drug during experimentation. * Significant at the .05 level compared to placebo.

covariances). In all analyses we controlled for session number and baseline span group effects, while also testing for interactions between drug and span. In the procedural learning tasks, another factor of positive/negative test condition was added in, along with interactions between this factor and drug and span. In the working memory segments, a distractor factor and its interaction terms (distractor*span, distractor*drug, distractor*span*drug) were included. Where indicated, we tested for specific planned contrasts. In these contrasts, the number of degrees of freedom reflects the entire sample, and not just the participants involved in the particular contrast, because the mixed procedure

WM Ctxt Idx (BX % -AY %,)	Placebo	Cabergoline	Haloperidol
Standard			
Low Span	1.8 (6.8)	29.1 (12.8)	18.0 (10.5)
High Span	6.7 (6.4)	20.0 (6.0)	15.4 (5.6)
Distractors			
Low Span	-3.9 (4.6)	-14.9 (7.8)	-5.7 (7.0)
High Span	-7.9 (2.8)	-8.2 (4.7)	2.6 (9.0)
Learning			
Low Span	-4.2 (2.9)	-1.5 (2.5)	10.6 (3.1)
High Span	2.0 (2.8)	2.6 (3.5)	3.6 (3.7)

Table 3: Working memory (WM) context index in the AX-CPT task under different task and drug conditions, broken down into participants with low and high WM span. Context index represents percent correct responding on AY trials subtracted from percent correct on BX trials, as described in the main paper.

analyzes both between and within effects, and controls for other variables of interest (e.g., session) which apply across all participants. The procedure uses all of the data to provide a more stable estimate of the error term.

Drug Effects on Physiological Measures

Drug Effects on Serum Prolactin Secretion

Prolactin levels were obtained before drug ingestion and four hours later, after cognitive tests. See Table 1 for drug effects on prolactin levels.

Drug Effects on Pulse Rate

There was a main effect of drug on pulse rate ($F[2,27] = 4.9$, $p = .015$). Planned contrasts revealed that cabergoline increased pulse rate relative to placebo ($F[1,27] = 9.5$, $p = .0046$), while haloperidol had no significant effect on pulse rate ($F[1,27] = 1.2$, n.s.). The slightly but significantly increased pulse rates by cabergoline are similar to cardiovascular effects caused by other D2 agonists (Quinn, Illas, Lhermitte, & Agid, 1981).

Attentional-Shift Accuracy (%)	Placebo	Cabergoline	Haloperidol
Attend New			
Low Span	96.9 (2.1)	97.0 (2.0)	92.8 (3.3)
High Span	89.8 (2.8)	82.6 (4.8)	89.3 (4.1)
Ignore Old			
Low Span	92.3 (2.0)	92.4 (2.0)	84.1 (3.4)
High Span	91.5 (2.0)	89. (2.4)	87.6 (2.4)

Table 4: Attentional-shifting accuracy in the AX-CPT task under different task and drug conditions, broken down into participants with low and high WM span. Attend New refers to performance in trials when only the newly task-relevant information was present, whereas Ignore Old refers to performance in trials that included previously task-relevant distractors.

Drug Effects on Subjective Rating Scales

The mean change scores for the subjective rating scales are shown in Table 2. There were no significant reported side physical effects between drug conditions, although there was a trend for cabergoline to be associated with increased likelihood of developing a headache ($p = 0.06$). For mental side effects, all drugs were associated with decreases in good mood, but there were no differences between either of the active drugs and placebo. The only significant within-subject difference was that haloperidol was associated with *less* restlessness compared with placebo ($p = 0.025$). There were trends for haloperidol to be associated with less clearheadedness ($p = .06$) and more drowsiness ($p = 0.16$) compared with placebo. None of these effects were confounding with interpretation of the results reported in the main paper, which involved both enhancements and impairments depending on task condition.

Additional Data

Tables 3 and 4 present additional raw data for working memory and attentional results that were only presented relative to placebo in the main paper.

References

Biller, B. M., Molitch, M. E., Vance, M. L., Cannistraro, K. B., Davis, K. R., Simons, J., Schoenfelder, J. R., & Klibanski, A. (1996). Treatment of prolactin-secreting macroadenomas with the once-weekly dopamine agonist cabergoline. *Journal of Clinical Endicronology & Metabolism*, *81*, 2338–43.

Braver, T. S., Barch, D. M., Keys, B. A., Carter, C. S., Cohen, J. D., Kaye, J. A., Janowsky, J. S., Taylor, S. F., Yesavage, J. A., & Mumenthaler, M. S. (2001). Context processing in older adults: Evidence for a theory relating cognitive control to neurobiology in healthy aging. *Journal of Experimental Psychology General*, *130*, 746–763.

Bymaster, F., Perry, K. W., Nelson, D. L., Wong, D. T., Rasmussen, K., Moore, N. A., & Calligaro, D. O. (1999). Olanzapine: a basic science update. *British Journal of Psychiatry Supplement*, *37*, 36–40.

Colao, A., Lombardi, G., & Annunziato, L. (2000). Cabergoline. *Expert Opinion on Pharmacotherapy*, *1*, 555–74.

Corsello, S. M., Ubertini, G., Altomare, M., Lovicu, R. M., Migneco, M. G., Rota, C. A., & Colosimo, C. (2003). Giant prolactinomas in men: efficacy of cabergoline treatment. *Clinical Endocrinology*, *58*, 662–70.

Daneman, M., & Carpenter, P. A. (1980). Individual differences in working memory and reading. *Journal of Verbal Learning and Verbal Behavior*, *19*, 450–466.

Darby, J. K., Pasta, D. J., Dabiri, L., & Mosbacher, D. (1995). Haloperidol dose and blood level variability: toxicity and interindividual variability in the nonresponder patient in the clinical practice setting. *Journal of Clinical Psychopharmacology*, *15*, 334–40.

Fitzgerald, P. B., Kapur, S., Remington, G., Roy, P., & Zipursky, R. B. (2000). Predicting haloperidol occupancy of central dopamine D_2 receptors from plasma levels. *Psychopharmacology*, *149*, 1–5.

Frank, M. J., Seeberger, L. C., & O'Reilly, R. C. (2004). By carrot or by stick: Cognitive reinforcement learning in Parkinsonism. *Science*, *306*, 1940–3.

Ichikawa, K., & Kojima, M. (2001). Pharmacological effects of cabergoline against parkinsonism. *Nippon Yakurigaku Zasshi*, *117*, 395–400.

Kapur, S., Remington, G., Jones, C., Wilson, A., DaSilva, J., Houle, S., & Zipursky, R. B. (1996). High levels of dopamine D_2 receptor occupancy with low-dose haloperidol treatment: a PET study. *American Journal of Psychiatry*, *153*, 948–950.

Kumari, V., Corr, P. J., Mulligan, O. F., Cotter, P. A., Checkley, S. A., & Gray, J. A. (1997). Effects of acute administration of *d*-amphetamine and haloperidol on procedural learning in man. *Psychopharmacology*, *129*, 271–76.

Kuroki, T., Meltzer, H. Y., & Ichikawa, J. (1999). Effects of antipsychotic drugs on extracellular dopamine levels in rat medial prefrontal cortex and nucleus accumbens. *J Pharmacol Exp Ther*, *288*(2), 774–781.

Malaspina, D., Colemann, E. A., Quitkin, M., Amador, X. F., Kaufmann, C. A., Gorman, J. M., & Sackeim, H. A. (1994). Effects of pharmacologic catecholamine manipulation on smooth pursuit eye movements in normals. *Schizophrenia Research*, *13*, 151–9.

Modell, J. G., Mountz, J. M., Glaser, F. B., & Lee, J. Y. (1993). Effect on haloperidol on measures of craving and impaired control in alcoholic subjects. *Alcohol Clinical and Experimental Research*, *17*, 234–40.

Peretti, C. S., Danion, J. M., Kauffmann-Muller, F., Grangé, D., Patat, A., & Rosenzweig, P. (1997). Effects of haloperidol and amisulpiride on motor and cognitive skill learning in healthy volunteers. *Psychopharmacology*, *131*, 329–38.

Persiani, S., Rocchetti, M., Pacciarini, M. A., Holt, B., Toon, S., & Strolin-Benedetti, M. (1996). The effect of food on cabergoline pharmacokinetics and tolerability in healthy volunteers. *Biopharmaceutics and Drug Disposition*, *17*, 443–55.

Quinn, N., Illas, A., Lhermitte, F., & Agid, Y. (1981). Bromocriptine in Parkinson's disease: a study of cardiovascular effects. *Journal of Neurology, Neurosurgery and Psychiatry*, *44*, 426–9.

Seeman, P., & Kapur, S. (2000). Schizophrenia: More dopamine, more D2 receptors. *Proceedings of the National Academy of Sciences*, *97*, 7673.

Stocchi, F., Vacca, L., Berardelli, A., Onofrj, M., Manfredi, M., & Ruggieri, S. (2003). Dual dopamine agonist treatment in Parkinson's disease. *Journal of Neurology*, *250*, 822–826.

Webster, J. e. a. (1994). Comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. *New England Journal of Medicine*, *31*, 904–909.