Differential Effects of Pergolide and Bromocriptine on Working Memory Performance and Brain Activation after Mild Traumatic Brain Injury (MTBI)

Laura A. Flashman, PhD[1*], Brenna C. McDonald, PsyD[2*], James C. Ford[3], PhD, Rachel M. Kenny[2], MPH, Katharine D. Andrews, PhD[2], Andrew J. Saykin, PsyD[2], Thomas W. McAllister, MD[2]

[1]Wake Forest Medical School and Wake Forest Baptist Medical Center, Winston-Salem, NC

[2]Indiana University School of Medicine, Indianapolis, IN

[3]Geisel School of Medicine at Dartmouth, Hanover, NH and Dartmouth-Hitchcock Medical Center, Lebanon, NH

*Co-first authors

Corresponding Author: Laura A. Flashman, PhD, ABPP, Section Head, Neuropsychology Program, Department of Neurology, Janeway 9th Floor, WFBMC, Medical Center Boulevard, Winston-Salem, NC 27157; e-mail: lflashma@wakehealth.edu; phone: (336) 716-2261; fax: (336) 716-9810

Contact Information:

Brenna C. McDonald, PsyD: Center for Neuroimaging, Department of Radiology and Imaging Sciences, Indiana University School of Medicine, 355 W. 16th St., GH Suite 4100, Indianapolis, IN 46202; e-mail: mcdonalb@iupui.edu; phone: (317) 963-7502; fax: (317) 963-7547

James C. Ford, PhD: Department of Psychiatry, Dartmouth Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03756; e-mail: James.C.Ford@hitchcock.org; phone: (603) 650-5824; fax: (603) 650-0404

Rachel M. Kenny, MPH: Department of Psychiatry, Indiana University School of Medicine, 355 W. 16th St., GH Suite 4800, Indianapolis, IN 46202; e-mail: rackenny@iu.edu; phone: (317) 963-7288; fax: (317) 963-7313

Katharine D. Andrews, PhD: Department of Psychiatry, Indiana University School of Medicine, 355 W. 16th St., GH Suite 4800, Indianapolis, IN 46202; e-mail: kadandre@iupiu.edu; phone: (317) 963-7288; fax: (317) 963-7313

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Andrew J. Saykin, PsyD: Center for Neuroimaging, Department of Radiology and Imaging Sciences, Indiana University School of Medicine, 355 W. 16th St., GH Suite 4100, Indianapolis, IN 46202; e-mail: asaykin@iupui.edu; phone: (317) 963-7501; fax: (317) 963-7547

Thomas W. McAllister, MD: Department of Psychiatry, Indiana University School of Medicine, 355 W. 16th St., GH Suite 4800, Indianapolis, IN 46202; e-mail: twmcalli@iupui.edu; phone: (317) 963-7288; fax: (317) 963-7313

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Abstract

Dopamine D1 and D2 receptors differ with respect to patterns of regional brain distribution and behavioral effects. Preclinical work suggests that D1 agonists enhance working memory, but the absence of selective D1 agonists has constrained using this approach in humans. This study examines working memory performance in mild traumatic brain injury (MTBI) patients when given pergolide, a mixed D1/D2 agonist, compared to bromocriptine, a selective D2 agonist. 15 individuals were studied one month after MTBI and compared to 17 healthy controls. At separate visits participants were administered 1.25mg bromocriptine or 0.05mg pergolide prior to functional MRI using a working memory task (visual-verbal n-back). Results indicated a significant group-by-drug interaction for mean performance across n-back task conditions, where the MTBI group showed better performance on pergolide relative to bromocriptine, while controls showed the opposite pattern. There was also a significant effect of diagnosis, where MTBI patients performed worse than controls, particularly while on bromocriptine, as shown in our prior work. Functional MRI activation during the most challenging task condition (3-back>0-back contrast) showed a significant group-by-drug interaction, with the MTBI group showing increased activation relative to controls in working memory circuitry while on pergolide, including in the left inferior frontal gyrus. Across participants there was a positive correlation between change in activation in this region and change in performance between drug conditions. Results suggest that activation of the D1 receptor may improve working memory performance after MTBI. This has implications for development of pharmacologic strategies to treat cognitive deficits after MTBI.

Keywords: working memory, mild traumatic brain injury, functional MRI, dopamine agonists

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Introduction

Most individuals recover well from mild traumatic brain injury (MTBI), but a subset of patients evidence persistent cognitive impairment, including measurable deficits in speed of information processing, attention, and executive functioning.[1] Executive functioning includes working memory (WM), the ability to retain information and manipulate it while receiving new information.[2, 3] The importance of the prefrontal cortex (PFC) in cognitive functioning, including WM, is well documented.[4, 5] The PFC is exquisitely sensitive to catecholamine levels, which interact with local receptors in an inverted-U dose-response fashion where both excess and insufficient neurotransmitter can impair WM function.[6-9] TBI is thought to generate catecholamine imbalances,[10-12] and dysregulation of PFC circuitry by disruption of catecholamine levels has been a longstanding hypothesis for post-TBI cognitive deficits.[10, 11, 13] While PFC catecholamine pathways can be challenging to explore directly, pharmaceutical agonists may permit differentiation of signaling pathways and allow comparison of differential treatment response in the healthy versus TBI brain. Furthermore, modulation of catecholamine levels in PFC by pharmaceutical agents is a promising but unrefined treatment for post-TBI cognitive sequelae.[14-17]

The PFC contains both D1 and D2 receptors, with D1 being predominant.[18] Current hypotheses suggest D1 receptors mediate neural signaling by limiting response to less preferred stimuli, therefore acting as PFC signaling gates, while D2 receptors increase speed and strength of signal response and are less critical to PFC function than D1 receptors.[7] Bromocriptine is a powerful D2 agonist shown to improve WM performance in both healthy human and animal populations.[19, 20] In our previous work, however, TBI patients showed poorer WM performance when administered bromocriptine relative to placebo, and displayed increased functional MRI (fMRI) activation outside of the task-specific region of interest.[19] This suggests an altered signaling environment in TBI brains,[21] and indicates that bromocriptine may impair the ability to deactivate regions beyond task-related circuitry, potentially requiring compensatory activation to maintain a similar level of WM performance as healthy controls.

Pergolide is a mixed D1/D2 agonist. In the absence of selective D1 agonists approved for human use, it offers an opportunity to characterize the role of D1 receptors when contrasted with the effects of a selective D2 agonist. Little research has been done on

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pergolide's effects in TBI patients; however, the high concentration of D1 receptors in the PFC suggests it could be beneficial in improving cognitive deficits after TBI. Pergolide has not previously been systematically studied for effects on cognition after TBI, though several studies have been conducted in healthy controls.[22-27] For example, Muller et al.[22] found that pergolide, but not bromocriptine, facilitated visuospatial WM performance. Kimberg and D'Esposito[23] found improved performance on delayed response tasks after a single dose of pergolide for individuals with higher verbal WM capacity, as well as altered WM-related activation.[24] In contrast, Bartholomeusz et al.[25] found no effect of pergolide or bromocriptine on object WM. In clinical populations, both pergolide and pramipexole (administered for at least one month to separate groups of patients) led to improved WM performance in patients with Parkinson's disease, but only for those with lower WM capacity.[28] Four weeks of pergolide treatment was also associated with improvements in visuospatial WM, executive functioning, and verbal learning and memory in patients with schizotypal personality disorder.[29] In the only study in TBI, McHenry[30] examined the effects of pergolide on language function in a single patient after severe TBI, and found no beneficial effects. Comparing bromocriptine and pergolide effects in individuals with TBI could shed light on the relative role of D1 versus D2 signaling in WM deficits and potential treatment after TBI, and could add further insight into the functioning of D1 and D2 receptors in the PFC. We hypothesized that pergolide would improve WM in TBI patients and show related alterations in brain activation on fMRI.

Materials and Methods

This was a prospective, placebo-controlled, double-blind study of patients with MTBI referred to a Level 1 Trauma Center.

Participants: 15 MTBI patients were studied approximately one month after injury and compared to 17 healthy controls. MTBI diagnosis was established using American Congress of Rehabilitation Medicine criteria.[31] Patients were excluded if they had a history of other neurologic disorders, significant systemic medical illness, or current DSM-IV Axis I diagnosis, based on the Structured Clinical Interview for DSM-IV.[32] Healthy controls were recruited through advertisements and were screened for neurologic, medical, or any past or current psychiatric illness. Written informed consent was obtained, and all study procedures were IRB-approved.

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Study Protocol: We have previously published our findings regarding bromocriptine[19] and guanfacine[33] relative to placebo. Here we compare WM performance and fMRI activation patterns in a subset of participants in[19] who received both bromocriptine and pergolide. In brief, participants were studied on three occasions roughly one week apart as part of a larger study in which each individual received placebo, bromocriptine, and either guanfacine or pergolide in a randomized, counterbalanced order. Order of neuropsychological and fMRI task administration, using alternate forms when available, was also counterbalanced.

Participants had a line for intravenous access placed and had blood samples drawn (baseline and 1, 2, 3, and 4 hours after medication/placebo ingestion) to determine serial serum prolactin levels. Blood was collected in serum separator tubes and immediately sent to the lab. After clotting, samples were centrifuged at 3000 rpm and then immediately frozen and stored at -80^{o}C until ready for assay. The prolactin assay is based on a solid-phase, two-site chemiluminescent immunometric format performed on the Immulite analyzer (Diagnostic Products Corporation, Los Angeles, CA). Dopamine agonists result in decreased release of prolactin, which serves as an indicator of central dopaminergic effect. Participants ingested identical-appearing capsules containing placebo, 1.25mg bromocriptine, or 0.05mg pergolide. Participants and staff were blind to medication condition, and drug and placebo presentation order was counterbalanced. MRI scanning was conducted 2.5-3 hours after drug or placebo ingestion, and neuropsychological testing was conducted after scan completion.

Imaging: All scans were acquired using the same GE Horizon 1.5T LX scanner. A gradient echo, echo-planar sequence was used to provide whole brain coverage: TR=2500ms, TE=40ms, FOV=24cm, NEX=1, 29 5mm thick sagittal slices with no skip, yielding a 64x64 matrix with 3.75mm^2 in-plane resolution. Participants were positioned in the scanner using laser alignment beams, and a non-magnetic deformable foam head holder to stabilize head position. Noise level was attenuated with specialized headphones (Resonance Technology, Van Nuys, CA). Stimuli for the n-back task were programmed in Presentation (Neurobehavioral Systems, Inc., Albany, CA) and presented visually through an MRI compatible goggle system (Resonance Technology, Van Nuys, CA).

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fMRI Task: Participants performed a visual-verbal n-back task presented in a four-condition, blocked design with variable processing load requirements (0-, 1-, 2-, and 3-back conditions). Each n-back condition was presented in 27-second epochs preceded by three seconds of instruction (e.g., "the match is D" or "the match is one back"). Each task condition was presented three times in pseudo-random order (12 epochs total). Participants viewed a string of consonant letters (except L, W, and Y) presented at a rate of one every three seconds. For each stimulus participants used a button press device (Photon Control, Burnaby, BC) to signify whether the current letter was a match (i.e., was the same as the designated target or the letter presented 1, 2, or 3 “back” in the sequence, depending on the condition instructions) or was a non-match. The number of correct and incorrect responses was recorded, along with reaction times. During each epoch there was a possibility of 2 or 3 matches and the number of matches was counterbalanced within and across conditions. In addition, non-target recurrences were presented as foils (e.g., a 2-back match during the 3-back condition). Participants rehearsed a practice version of the task prior to the scan to ensure comprehension of task demands.

Scan Preprocessing: Preprocessing in SPM (Wellcome Department of Cognitive Neurology, University College, London, UK) included spatial realignment using a six parameter model to remove motion-related signal change, normalization into standardized Montreal Neurological Institute atlas space, resampling to $2mm^3$ isotropic voxels, and smoothing to a full width half maximum of 8mm.

Clinical and Neuropsychological Assessment: Participants completed a neuropsychological test battery that assessed level of general intellectual functioning (Wide Range Achievement Test-3 (WRAT-3), Reading subtest;[34] Wechsler Adult Intelligence Scale-III (WAIS-III), Block Design subtest[35]), verbal episodic memory (California Verbal Learning Test (CVLT)[36] or CVLT-II[37]), psychomotor speed (WAIS-III, Digit Symbol-Coding subtest[35]) and WM, executive, and attentional functioning (Trail Making Test, Parts A and B[38] or Delis-Kaplan Executive Function System (D-KEFS), Trail Making Test Conditions 2 and 4;[39] D-KEFS Color-Word Interference Test;[39] Controlled Oral Word Association Test;[40, 41] Paced Auditory Serial Addition Test;[42] Gordon Continuous Performance Test[43]).

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Statistical Analyses: Demographics and Cognitive Measures: Demographic variables were compared with analysis of variance (ANOVA) or chi-square statistics, as appropriate. In-scanner n-back performance and neuropsychological variables were analyzed with repeated measures analysis of covariance (ANCOVA) using maximum likelihood estimation to test effects of drug condition (bromocriptine versus pergolide), diagnosis (MTBI versus control), and their interaction, controlling for order of drug administration, age, and years of education. For the n-back task, performance was calculated as target accuracy adjusted for guessing for each task condition. Additionally, means were calculated across all conditions (mean-back), and across all conditions without 0-back. For neuropsychological test data, raw or standard scores were used as indicated, with the exception of Trail Making. Because the version of the test changed during the study, raw scores for Trails A and B and D-KEFS conditions 2 and 4 were z-transformed using the control group means in the placebo condition, with z-scores utilized for group comparisons.

Serum Prolactin Levels: Repeated measures ANCOVA was also used to assess the effect of bromocriptine and pergolide on serum prolactin levels. A logarithmic transformation was applied to the dependent variables after inspection of initial plots of the data. A random interaction effect was included between individual and treatment period in the crossover design. A fixed effect was included for TBI status and the interaction between TBI status and treatment. All models were fit using Proc Mixed and the heterogenous autoregressive covariance structure in SAS (SAS Institute, Cary, NC).

fMRI Analyses: fMRI analyses included statistical parametric mapping on a voxel-by-voxel basis, using a general linear model approach[44] as implemented in SPM. Smoothed, normalized scans for all individuals were entered into the model, and contrast images comparing pairs of the WM processing load conditions were created for each individual. Given our prior work with this task, analyses focused on the most challenging condition (i.e., 3-back>0-back contrast). These contrast images were then used for the second level multi-subject/between-group random effects analyses. The random effects procedure performs a mixed model analysis to account for both random effects (scan) and fixed effects (task condition).[45]

Random effects analyses were conducted using ANCOVA to construct contrast maps of voxels in which brain activation differed between group and drug condition (full factorial

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model in SPM). Comparisons were conducted within an omnibus group- (two independent levels: MTBI, control) by-drug (two non-independent levels: bromocriptine, pergolide) ANCOVA, covarying for order of drug administration, age, and years of education. The design matrix therefore included both drug conditions for both groups, accounting for the repeated measures nature of the drug factor (i.e., the matrix included four columns, one for each group on each drug). The critical significance threshold (p_{crit}) was set to 0.01, and the main effect of the contrast of interest (i.e., 3-back>0-back; p=0.05) for both groups at both visits was included in the design matrix as an explicit mask (Figure 2A). Given the constraints of the sample size, only clusters of activated voxels with cluster-level $p_{uncorrected}<0.05$ were considered. Effect sizes for significant clusters were calculated using Cohen's D. Two-tailed correlations between brain activation and task performance were performed in SPSS.

Results

Demographics: Sample characteristics are summarized in Table 1. There were no significant group differences for age, sex, or WRAT-3 Reading or WAIS-III Block Design scores (good estimates of premorbid verbal and nonverbal intellectual ability, respectively). Although completed years of education was slightly higher in the control than MTBI group (16.0 versus 14.1 years; p=0.02), this was accounted for by the fact that several MTBI participants were students at the time of study participation and had not attained their final educational achievement; parental education did not differ between groups. MTBI participants entered the protocol a mean of 38.7 ($\pm$14.0) days after injury (range: 19-69). 10 of 15 participants had a definite loss of consciousness with a mean duration of 7.1 ($\pm$13.4) minutes. The MTBI group had a mean Glasgow Coma Scale score of 14.7 ($\pm$0.7) and mean posttraumatic amnesia duration of 8.5 ($\pm$9.9) hours. The protocol was well tolerated by both groups.

Serum Prolactin: Figure 1 shows serum prolactin levels over time for participants while on bromocriptine, pergolide, and placebo. Blunting of serum prolactin levels while on active medication (i.e., bromocriptine and pergolide) started at about 2-2.5 hours after ingestion and lasted for at least 5 hours after ingestion; this encompassed the time when participants were undergoing fMRI and neuropsychological testing and confirmed that there was a central dopaminergic effect when undergoing these procedures. Analyses

showed contrasts of the effects of drug (bromocriptine and pergolide) versus placebo were statistically significant ($p<0.001$) and were not appreciably different between each other ($p=0.11$) or between the TBI and control groups ($p=0.56$).

Neuropsychological Measures: In general, both groups performed comparably whether they were taking pergolide or bromocriptine, with no significant effects of diagnosis or drug across tasks, with one exception. For the Trail Making Test, Trial 2/Trails A condition, there was a main effect of drug, with both the MTBI and healthy control groups performing better when on pergolide than when on bromocriptine ($p=0.03$; Table 2).

In-scanner WM Performance: Similar to the neuropsychological measures, there were generally no significant within-group differences for pergolide relative to bromocriptine, with the exception of the 0-back condition, where the MTBI group showed better performance on pergolide than bromocriptine ($p=0.04$; Table 2). Between-group comparisons showed that when on bromocriptine the MTBI group showed significantly poorer performance than controls for 0-back, 3-back, mean-back, and mean-back excluding 0-back (all $p<0.05$). There was a significant main effect of group for mean-back score, with controls performing better than those with MTBI ($p=0.03$). There were significant interaction effects for 0-back, 3-back, and mean-back scores, wherein the MTBI group performed better when taking pergolide than bromocriptine, while controls showed the opposite pattern. That is, while the MTBI group consistently performed worse than the control group across n-back conditions, pergolide was associated with better n-back performance for the MTBI group relative to bromocriptine, whereas controls performed less well on pergolide relative to bromocriptine.

fMRI Results: Both groups showed the expected pattern of robust bilateral frontoparietal activation during WM processing while performing the 3-back task regardless of drug condition. A significant group-by-drug interaction was found, wherein the MTBI group showed increased activation relative to healthy controls in WM circuitry including bilateral frontal and parietal regions while on pergolide relative to bromocriptine (Figure 2B, Table 3). There were no regions in which controls showed significantly increased activation relative to the MTBI group on pergolide relative to bromocriptine. Review of effect sizes for significant clusters showed nearly all were medium to large effect sizes

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(Cohen's D generally 0.7 to 1.1; Table 3), although it should be noted that confidence intervals are relatively wide given the modest sample size.

Examination of the clusters found to be significant in this interaction showed that across all participants there was a positive correlation between change in activation in the left inferior frontal gyrus (Brodmann Area 46) cluster and change in performance between drug conditions (r=0.43, p=0.01; Figure 2C), such that increased 3-back performance on pergolide relative to bromocriptine was associated with increased left inferior frontal gyrus activation.

Discussion

The results of this study provide additional evidence of differential alterations in dopaminergic systems that impact WM performance and brain activation one month after MTBI. Because D1 and D2 receptors differ with respect to patterns of regional brain distribution and effect, we compared two pharmacological agents with different dopamine profiles. We have previously shown that MTBI patients showed poorer WM performance on bromocriptine, a selective D2 agonist, relative to placebo. In addition, healthy controls showed greater activation in frontoparietal WM circuitry relative to MTBI patients on bromocriptine, while patients showed greater activation outside WM circuitry.[19] The literature suggests that D1 stimulation enhances WM, and that D1 receptors may play a more important role in WM than D2 receptors.[46] Furthermore, there is relatively greater D1 than D2 receptor density in the PFC, a region critical to effective WM functioning. In the current study we therefore examined the same participants to compare performance and brain activation after administration of pergolide relative to bromocriptine. We hypothesized that pergolide, a mixed D1/D2 agonist, would improve WM in MTBI patients, presumably mediated by stimulation of D1 receptors.

Our findings support this hypothesis. We saw significant interactions on several measures of n-back performance (0-back, 3-back, and mean-back), in which participants with MTBI showed relatively better performance on pergolide relative to bromocriptine, and healthy control participants showed the opposite. This pattern was seen in the context of poorer performance for MTBI patients relative to controls in general across conditions of the n-back task, differences which reached statistical significance when on bromocriptine.

Examination of fMRI data further supported the behavioral findings, showing a significant

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group-by-drug interaction during the most challenging task condition (3-back>0-back contrast), in which the MTBI group showed increased activation in frontoparietal WM circuitry regions relative to controls when on pergolide relative to bromocriptine. Across participants there was a significant correlation between a cluster of activation in the left inferior frontal gyrus and 3-back task performance, such that greater activation on pergolide relative to bromocriptine correlated with improved task performance. In contrast, the two groups performed similarly on clinical neuropsychological measures, regardless of whether they were given pergolide or bromocriptine.

The current results extend our understanding of the mechanism of cognitive complaints and dysfunction after MTBI by suggesting that WM difficulties after MTBI may be related to D1 receptor functioning. MTBI patients showed improved WM functioning and concomitant increases in activation of frontoparietal brain circuitry on pergolide, a mixed D1/D2 receptor agonist, relative to bromocriptine, a selective D2 receptor agonist, suggesting an important role for D1 receptors in improving performance after MTBI. Of particular interest is that an overall n-back performance indicator, the mean-back accuracy score, showed a significant (p=0.02) drug-by-diagnosis interaction. Examination of this interaction revealed better performance for the MTBI group on pergolide relative to bromocriptine, while healthy controls showed the opposite pattern. This builds upon our prior finding that MTBI patients showed poorer mean-back performance on bromocriptine relative to placebo, while controls showed stable to slightly improved performance.[19] Examination of the differences observed in activation of brain regions within WM circuitry on these two agents is informative. Our earlier work suggested that bromocriptine facilitated selective recruitment of task-related processing resources in the healthy brain but not in the brains of individuals after MTBI. Across both groups improved task performance correlated with increased activation in the right middle frontal gyrus (Brodmann Area 9).[19] In the current study treatment with pergolide resulted in increased activation in task-related neural circuitry during WM processing in MTBI patients relative to controls, including in the left inferior frontal gyrus (Brodmann Area 46). Again, activation correlated with task performance across both groups. This is particularly compelling as there is higher D1 receptor density in Brodmann Area 46 than in other frontal cortical regions,[47, 48] providing a potential biological basis for the observed effect.

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While MTBI patients showed improved WM performance on pergolide relative to bromocriptine, healthy controls showed the opposite pattern. This may reflect the inverted-U dose-response effects noted for dopamine levels in prior work, where there has been found to be an optimal level of dopaminergic tone that promotes WM functioning, with both lower or higher levels resulting in lower functioning.[6-9] In our cohort, controls may already have been functioning at an optimal baseline level in terms of D1 activity, such that administration of pergolide resulted in overall poorer performance relative to bromocriptine, whereas for MTBI patients, this medication could have helped to correct injury-related abnormalities in dopaminergic system functioning. Prior work has emphasized the particular sensitivity of the PFC to the dopaminergic environment, and the importance of considering not only an individual's baseline level of dopaminergic functioning, but also the type of cognitive task being conducted.[9] These complexities may explain the differential responses to varying pharmacological agents we observed in healthy and injured brains. In future work it will be informative to examine proxies of brain dopamine levels, for example using [^{11}C]raclopride or [^{18}F]fallypride PET, to better understand relationships between dopaminergic system functioning, cognitive performance, and brain activation.

One possible mechanism that may account for enhanced performance on the n-back task in MTBI patients on pergolide may have to do with the role of dopamine in the improvement of neuronal signal-to-noise ratio (SNR). Dopamine is crucial in optimizing SNR of local cortical microcircuits in visual cortical networks,[49, 50] principally due to D1- and D2-receptor-mediated effects on pyramidal and local circuit neurons, which mediate neuronal excitability and recurrent inhibition. Abnormal dopamine activity (i.e., increased dopamine receptor availability due to decreased levels of dopamine) has also been shown to be related to poorer WM performance in patients with schizophrenia.[51] Yousif et al.[52] found that use of pergolide, but not cabergoline (a D2 agonist), maintained visual perceptual performance despite a TMS-induced reduction in SNR, in a dose-dependent manner. Together, these studies suggest that decreases in the ratio of D1/D2 signaling might be improved with medications such as antipsychotics, which target D2 receptors, or D1/D2 receptor agonists such as pergolide, by increasing cortical SNR and positively impacting visual perceptual performance. These findings, together with the documented

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effects of dopamine on brain plasticity and learning, offer promise that medications such as pergolide could help improve rehabilitation efforts in individuals with TBI.

The current findings also offer potential new insights into our prior work with other pharmacological agents. In a separate group of patients studied using the same design as in the current work we reported that a single administration of 2.0mg of guanfacine, an α-2 adrenergic receptor agonist, resulted in improved WM performance in MTBI patients but not controls, with concomitant increased activation in WM circuitry. As noted above for D1 receptors, α-2 adrenergic receptors also have particularly high density in Brodmann Area 46.[47, 48] We also examined the utility of cognitive-behavioral therapy in combination with methylphenidate, a norepinephrine and dopamine reuptake inhibitor, to treat cognitive concerns after TBI. We found post-treatment improvements in aspects of attention, episodic and working memory, and executive functioning,[53] again with increased activation in WM circuitry,[54] including in left Brodmann Area 10 and right Brodmann Area 45, the latter of which also shows relatively higher α-2 adrenergic receptor density. Taken together, these findings offer support for the hypothesis that alterations in dopaminergic and adrenergic system functioning can underlie cognitive problems after MTBI, and suggest that pharmacologic agents targeting dopamine D1 and/or α-2 adrenergic receptors may be more beneficial than those targeting dopamine D2 receptors.

There are important limitations to consider when interpreting the current findings. This cohort had overall mild injury severity; these results therefore may not apply to those with moderate to severe injuries. We also intentionally excluded MTBI participants with significant medical and psychiatric disorders; therefore these results may not generalize to all individuals with MTBI. Further research in more heterogeneous cohorts with other comorbid conditions will be important to confirm these findings. Medication was administered as a single fixed dose, which may not be representative of the results of ongoing treatment, so direct clinical recommendations cannot be made as a result of this study. We detected differences in WM performance on the challenging n-back task, but not on other neuropsychological measures. This may indicate the need for more sensitive cognitive tasks to detect differences between MTBI patients and controls and/or changes over time in this population. Finally, this was a small cohort, not fully powered for multiple

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comparison correlation; however, the moderate to large effect sizes that we observed for neuroimaging suggest that these findings may be clinically relevant. Further research in larger cohorts will be important to replicate these findings and explore additional research questions. For example, the current study cannot address differential effects of D1 and D2 receptors forming heteromers with distinct signaling characteristics as compared to their constituent receptors.[55]

Overall, the current results are most consistent with the conclusion that MTBI is associated with alterations in dopaminergic function that impact WM-related function and brain activation one month after MTBI, and that dopamine receptors differ with respect to effect of activity on cognition shortly after MTBI. Specifically, it appears that D1 stimulation can enhance WM performance in the first 4-6 weeks after injury, despite our previous findings that a selective D2 agonist did not improve cognitive function. This finding may argue for renewed interest in identification of a selective D1 agonist for human use, such as the agent (PF-3628) recently characterized by Wang et al.,[56] which showed evidence for an excitatory effect on WM-related dorsolateral prefrontal neuronal firing in primates, in an inverted-U dose-response fashion. Further exploration of other cognitive abilities, including episodic memory, will help clarify the role of various dopaminergic agents on other brain systems and circuits. In addition, future work should examine the effects that different dosing strategies, severity of injury, and the injury to treatment interval have on cognitive and brain outcomes. Finally, the literature also suggests a role of genotype on dopaminergic system functioning, cognitive outcome, and brain activation after TBI.[13, 57-61] Interactions between genotype and dopaminergic system functioning (e.g., dopamine genetic risk score) should therefore also be further explored with regard to pharmacological treatment of cognitive symptoms after TBI.

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Author Disclosure Statement

Laura A. Flashman, PhD: No competing financial interests exist.

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Table 1. Sample Characteristics

	Control (N=17)	MTBI (N=15)	p
Age	33.6 ± 10.6	27.4 ± 10.7	0.11
Education	16.0 ± 2.4	14.1 ± 2.0	0.02
WRAT-3 Reading Standard Score	110.2 ± 8.2	105.8 ± 10.9[a]	0.20
WAIS-III Block Design Scaled Score	12.5 ± 2.8	12.7 ± 3.3	0.81
Maternal Education (years)	13.8 ± 2.3	13.9 ± 2.5	0.96
Paternal Education (years)	15.5 ± 2.9	13.9 ± 2.6	0.12
Sex			0.29
Male	7 (41.2%)	9 (60.0%)	
Female	10 (58.8%)	6 (40.0%)	

Values are Mean ± SD

[a]N=14, one participant did not have a WRAT-3 Reading Score

WRAT=Wide Range Achievement Test, WAIS=Wechsler Adult Intelligence Scale

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Table 2. Neuropsychological Performance Bromocriptine vs. Pergolide

		Control (N=17)			MTBI (N=15)			Control vs. MTBI p-value		Overall p-value		
Score	N	Bromocriptine Unadjusted Mean±SE	Pergolide Unadjusted Mean±SE	p	Bromocriptine Unadjusted Mean±SE	Pergolide Unadjusted Mean±SE	p	Bromo-criptine	Pergolide	Dx	Drug	Interaction
WAIS-III Digit Symbol-Coding, Scaled Score	63	13.4 ± 0.67	12.5 ± 0.72	0.27	12.8 ± 0.85	12.3 ± 0.79	0.62	0.81	0.66	0.73	0.29	0.68
CVLT												
Total Trials 1-5	64	57.2 ± 2.1	56.9 ± 2.7	0.94	55.0 ± 1.8	53.8 ± 1.7	0.73	0.98	0.77	0.86	0.85	0.75
Short Delay Free Recall	64	13.1 ± 0.59	11.9 ± 0.74	0.18	12.5 ± 0.53	12.5 ± 0.69	0.54	0.57	0.05	0.15	0.64	0.15
Long Delay Free Recall	64	13.5 ± 0.68	12.6 ± 0.75	0.22	12.3 ± 0.66	12.8 ± 0.74	0.27	0.85	0.24	0.59	0.97	0.09
Trail Making Test (z-score)												
Trial 2/Trails A	63	0.15 ± 0.22	0.31 ± 0.16	0.09	0.04 ± 0.19	0.19 ± 0.13	0.13	1.00	0.94	0.97	**0.03**	0.95
Trial 4/Trails B	62	0.42 ± 0.10	0.36 ± 0.07	0.83	0.20 ± 0.13	0.01 ± 0.13	0.47	0.22	0.05	0.07	0.72	0.48
D-KEFS Color-Word Interference Test												
Word Reading (secs)	63	20.2 ± 0.67	19.4 ± 0.58	0.24	21.9 ± 0.84	21.1 ± 0.9	0.41	0.26	0.20	0.19	0.18	0.84
Color Naming (secs)	63	24.8 ± 0.74	25.5 ± 0.48	0.78	26.9 ± 1.3	27.4 ± 1.2	0.91	0.20	0.23	0.19	0.80	0.91
Interference (secs)	63	44.9 ± 1.5	47.1 ± 1.7	0.32	45.4 ± 2.6	48.7 ± 2.8	0.09	0.88	0.59	0.72	0.07	0.54
Switching (secs)	63	48.6 ± 2.0	51.3 ± 3.6	0.74	55.9 ± 4.8	50.8 ± 2.9	0.15	0.59	0.73	0.92	0.41	0.17

		Control (N=17)			MTBI (N=15)			Control vs. MTBI p-value		Overall p-value		
Score	N	Bromocriptine Unadjusted Mean±SE	Pergolide Unadjusted Mean±SE	p	Bromocriptine Unadjusted Mean±SE	Pergolide Unadjusted Mean±SE	p	Bromo-criptine	Pergolide	Dx	Drug	Interaction
COWAT (raw)	63	45.2 ± 1.8	45.4 ± 2.3	0.28	42.2 ± 2.9	41.1 ± 2.3	0.70	0.44	0.27	0.32	0.33	0.63
PASAT (raw score/60)												
Trial A	53	53.3 ± 2.1	47.8 ± 2.6	0.12	46.4 ± 3.3	46.2 ± 4.1	0.40	0.16	0.79	0.38	0.71	0.09
Trial B	51	49.9 ± 2.5	43.9 ± 2.9	0.27	40.8 ± 3.4	41.8 ± 4.2	0.49	0.09	0.33	0.17	0.85	0.20
Trial C	52	41.1 ± 2.6	37.1 ± 2.8	0.88	34.9 ± 3.6	38.3 ± 4.6	0.21	0.22	0.52	0.33	0.31	0.37
Trial D	50	27.9 ± 2.5	26.0 ± 2.3	0.79	26.0 ± 3.2	26.7 ± 3.3	0.61	0.56	0.69	0.60	0.59	0.82
CPT												
Simple Reaction Time, # Correct	64	29.8 ± 0.14	29.9 ± 0.06	0.35	29.3 ± 0.21	29.2 ± 0.30	0.77	0.52	0.08	0.14	0.68	0.37
Simple Reaction Time, Reaction Time	64	289 ± 17.6	295 ± 14.9	0.73	278 ± 11.8	281 ± 10.6	0.90	0.98	0.92	0.96	0.76	0.88
Vigilance, # Correct	63	29.7 ± 0.19	29.8 ± 0.14	0.57	29.9 ± 0.09	29.7 ± 0.13	0.62	0.52	0.83	0.80	0.98	0.43
Vigilance, Reaction Time	64	355 ± 21.5	371 ± 17.3	0.35	351 ± 15.9	350 ± 15.5	0.54	0.56	0.89	0.81	0.85	0.25
Distractibility, # Correct	63	28.5 ± 0.58	28.0 ± 0.81	0.84	28.5 ± 0.53	26.9 ± 1.1	0.21	0.97	0.42	0.65	0.32	0.41
Distractibility, Reaction	63	374 ± 22.3	413 ± 20.9	0.27	381 ± 14.6	398 ± 21.5	0.88	0.43	0.93	0.64	0.53	0.36
N-Back												

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		Control (N=17)			MTBI (N=15)			Control vs. MTBI p-value		Overall p-value		
Score	N	Bromocriptine Unadjusted Mean±SE	Pergolide Unadjusted Mean±SE	p	Bromocriptine Unadjusted Mean±SE	Pergolide Unadjusted Mean±SE	p	Bromo-criptine	Pergolide	Dx	Drug	Interaction
Corrected 0-Back	64	97.5 ± 1.4	91.8 ± 3.1	0.30	83.1 ± 4.5	91.1 ± 3.0	**0.04**	**0.01**	0.72	0.15	0.44	**0.02**
Corrected 1-Back	64	93.5 ± 2.0	95.2 ± 1.7	0.54	89.4 ± 3.8	88.5 ± 2.9	0.88	0.43	0.16	0.19	0.77	0.57
Corrected 2-Back	64	89.7 ± 3.0	87.7 ± 3.1	0.63	73.9 ± 5.9	80.0 ± 5.6	0.16	0.09	0.62	0.22	0.50	0.16
Corrected 3-Back	64	80.5 ± 4.2	69.6 ± 3.0	0.09	62.5 ± 6.7	66.7 ± 3.5	0.31	**0.02**	0.74	0.11	0.68	**<0.05**
Mean-Back	64	90.3 ± 1.4	86.1 ± 1.7	0.17	77.2 ± 3.5	81.6 ± 2.3	0.05	**<0.01**	0.48	**0.03**	0.63	**0.02**
Mean-Back without 0-Back	64	87.9 ± 1.8	84.2 ± 1.8	0.25	75.3 ± 4.4	78.4 ± 3.2	0.18	**0.02**	0.40	0.08	0.85	0.07

WAIS=Wechsler Adult Intelligence Scale, CVLT=California Verbal Learning Test, D-KEFS=Delis-Kaplan Executive Function System, COWAT=Controlled Oral Word Association Test, PASAT=Paced Auditory Serial Addition Test, CPT=Continuous Performance Test

Table 3. Regional Task-Related Activation Changes 3-Back>0-Back Bromocriptine vs. Pergolide

MNI coordinates	Cluster extent (k)	Cluster-level	Cluster-level	T	Region description (for cluster peak)	Effect size Cohen's D (confidence interval)
Increased Activation in MTBI Relative to HC on Pergolide Relative to Bromocriptine						
-20 -18 10	243	0.52	<0.01	4.68	Left Thalamus	0.81 (0.067, 1.556)
38 -50 -44	455	0.06	0.001	4.39	Right Cerebellum	1.07 (0.303, 1.833)
-40 40 4	530	0.03	<0.001	4.08	Left Inferior Frontal Gyrus BA 46	1.04 (0.279, 1.804)
50 -46 42	126	0.98	<0.05	3.92	Right Inferior Parietal Lobule BA 40	0.66 (-0.075, 1.394)
40 44 0	162	0.90	0.03	3.89	Right Inferior Frontal Gyrus BA 46	0.81 (0.064, 1.552)
24 -6 44	144	0.95	0.04	3.87	Right Middle Frontal Gyrus BA 6	0.74 (0.003, 1.483)
-16 -72 42	502	0.04	<0.001	3.61	Left Precuneus BA7	0.76 (0.019, 1.502)
22 58 40	300	0.31	<0.01	3.42	Right Superior Frontal Gyrus BA 9	0.86 (0.111, 1.607)
-34 0 34	164	0.89	0.03	3.38	Left Precentral Gyrus BA 6	0.36 (-0.363, 1.08)
24 16 14	311	0.27	<0.01	3.26	Right Claustrum	0.76 (0.022, 1.505)
Increased Activation in HC Relative to MTBI on Pergolide Relative to Bromocriptine						
No significant clusters						

Figure Legends

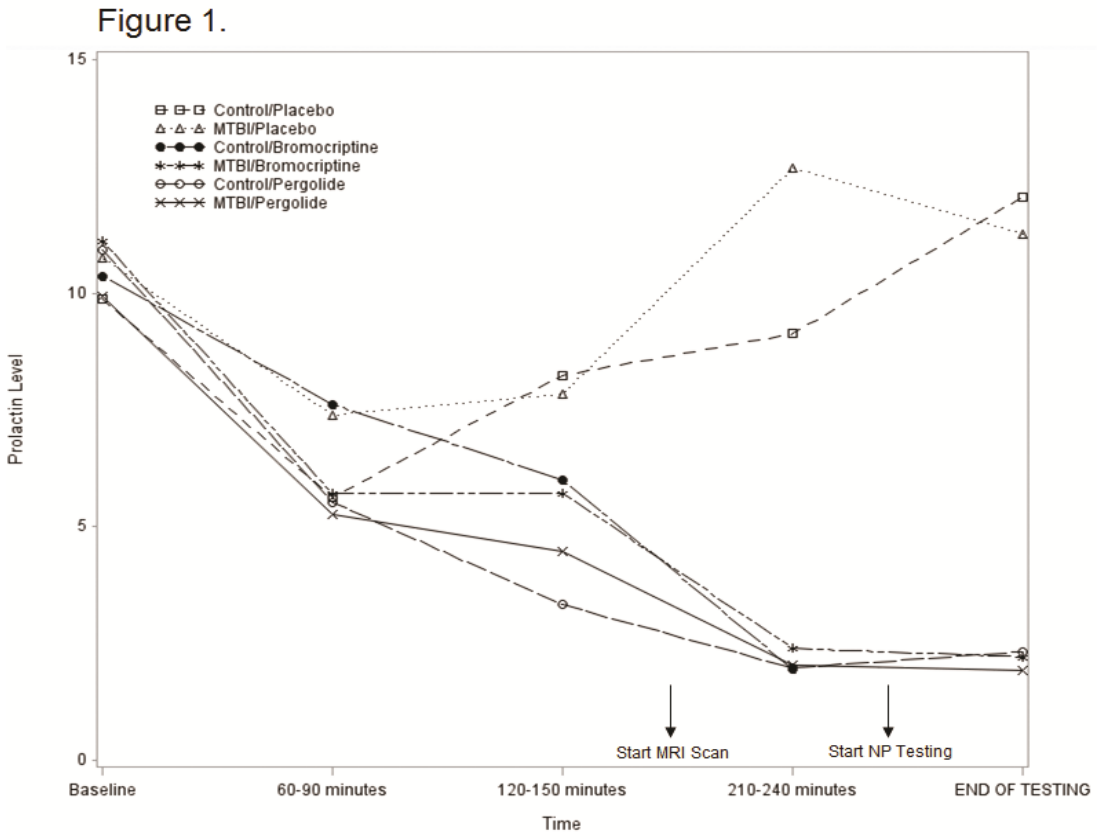

Figure 1. Prolactin time trends by drug condition (placebo, bromocriptine, pergolide) and participant group (Mild Traumatic Brain Injury = MTBI, Healthy Control = Control). The targeted times for beginning MRI and neuropsychological (NP) testing are noted. Prolactin suppression is evident during the scan and cognitive assessment time periods for both bromocriptine and pergolide relative to placebo, but does not differ by drug or group (see text for statistics).

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Figure 2.

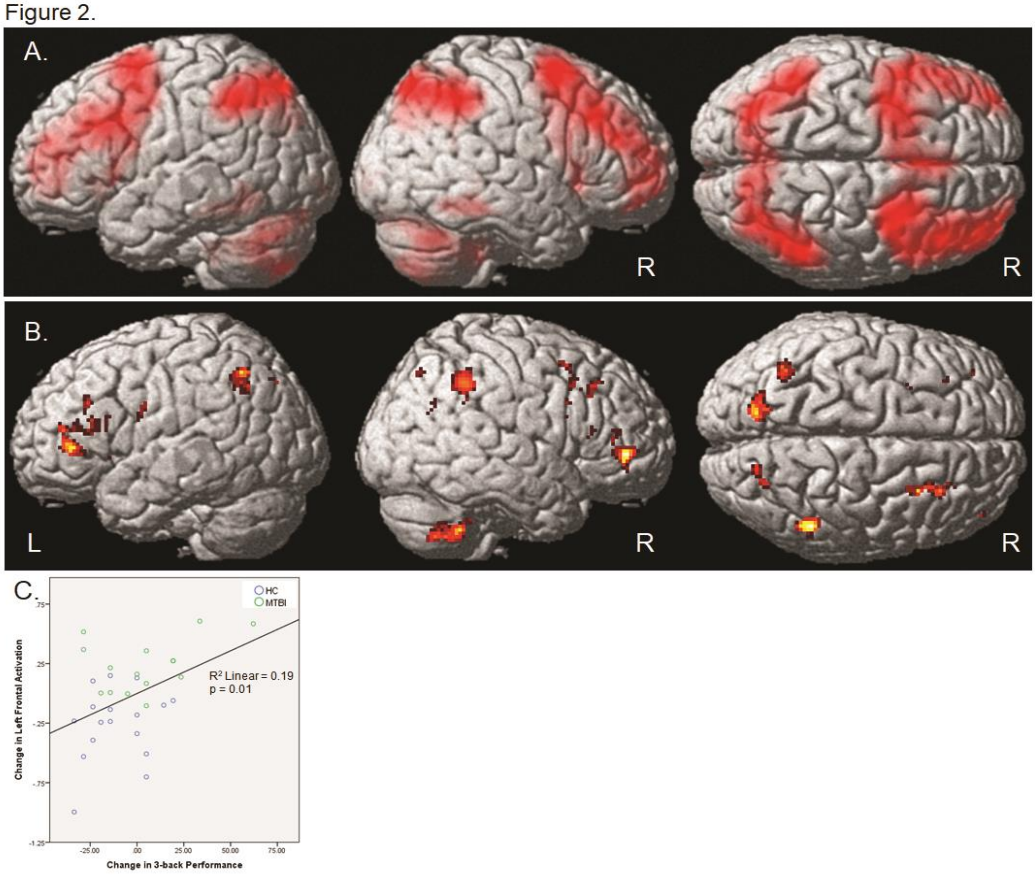

Figure 2. A. Average activation during the visual-verbal n-back task for both groups for both study visits (3-back>0-back contrast, p = 0.05), used as an explicit mask for statistical analyses. B. Increased activation in working memory circuitry during the visual-verbal n-back task (3-back>0-back contrast) for mild traumatic brain injury relative to healthy control group on pergolide relative to bromocriptine (p_{crit} = .01, cluster-level $p_{uncorrected}$ < 0.05). C. Correlation of change in left inferior frontal gyrus activation with change in 3-back performance across all participants.