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Pro-dopamine regulation with KB220Z improves working memory in an adult with ADHD-A case report and replication

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Abstract

This case study used a double-blind, placebo controlled, cross-over design, to evaluate the effect of KB220Z, a pro-dopamine regulator, on working memory, neuropsychological and behavioral measures of attention in a 19 year old adult female with Attention Deficit-Hyperactivity Disorder. The participant was tested with eyes closed and with a phonological working memory task. The working memory task required her to remember a random sequence of letters and numbers, and recall them in alphabetical and numerical order. Response measures included the Conner Continuous Performance Test, the Delis-Kaplan Executive Function Inventory, quantitative electroencephalography, and Low-resolution Electromagnetic Tomography. KB220Z, compared to placebo, improved vigilance, response inhibition and verbal fluency functions. Working memory performance substantially improved in response to KB220Z. Quantitative EEG analysis revealed that absolute power in the alpha and theta EEG bands increased during the working memory task, under KB220Z. In addition, Low-resolution Electromagnetic Tomography analysis revealed increases in current source density at 10 Hz in the bilateral dorsal cingulate cortices, bilateral hippocampi and bilateral dorsolateral prefrontal cortices, and increased current source density at 11 Hz in the right hippocampus and right dorsolateral prefrontal cortex, during the working memory task in response to KB220Z. Collectively, these results indicate that pro-dopamine regulation with KB220Z improved working memory and prefrontal, neuropsychological function in conjunction with increased activation of brain regions known to manage executive function, working memory and retrieval of declarative information. These findings replicate and extend our prior case study research with KB220Z and support the value of continued research with this pro-dopamine regulator.

Keywords

attention deficit-hyperactivity disorder; dopamine; kb220z; reward deficiency syndrome; working memory

Abbreviations

QEEG: Quantitative electroencephalography; LORETA: Low-resolution electromagnetic tomography; RDS:

Reward deficiency syndrome; ADHD: Attention deficit-hyperactivity Disorder; WM: Working memory; EC: Eyes closed; DA: Dopamine; D2: Dopamine 2 receptor; SPECT: Single photon emission computerized tomography; MRI: Magnetic resonance imaging; DAT: Dopamine transporter; PET: Positron emission tomography; SUD: Substance use disorder; EEG: Electroencephalogram; Fz: Midline, frontal electrode location; Cz: Midline, central electrode location; Pz: Midline, parietal electrode location; F4 and P4: Right frontal and parietal electrode locations, respectively; BA: Brodmann area; CPT: Conner continuous performance test; WASI-II: Wechsler abbreviated scale of intelligence; IRB: Institutional review board

Introduction

Attention Deficit-Hyperactivity Disorder (ADHD) is a serious neuropsychiatric condition that affects approximately 8.7% of the adolescent population [1] and 4.4% of the adult population [2] in the United States. The world-wide prevalence of ADHD is estimated at 5.29% [3]. The disorder is characterized by impairments in attention, self-regulation (hyperactivity-impulsivity) and executive function [4], as well as problems with Working Memory (WM) [4-6]. These impairments cause significant under achievement in academic, occupational and interpersonal areas of life [7].

Recent research has focused on the contribution of neuroanatomic, neurotransmitter and genetic mechanisms to the pathophysiology of ADHD. Neuroimaging research reveals that ADHD is associated with dysfunction in prefrontal, cingulate and striatal brain regions [8,9]. Bledsoe, Semrud-Clikeman & Pliszka [10] using MRI, reported that ADHD children had reduced right, rostral anterior cingulate cortical thickness, which correlated with parental-teacher reports of the severity of their ADHD symptoms. Thus, children with thinner cortical tissue were rated as having more severe ADHD symptoms. These findings are consistent with Makris et al. [11], who used structural MRI and found cortical thinning in the attention and executive function network of ADHD adults. They noted reduced cortical thickness in the right dorsolateral prefrontal, anterior cingulate and inferior parietal areas.

Dopamine (DA) neurons project from the substantia nigra to the basal ganglia, and support motor function, and they also project from the ventral mesencephalon to the forebrain, and play a vital role in motivation, reward, learning and WM [12]. Synaptic levels of dopamine are influenced by the dopamine transporter (DAT), a protein that removes dopamine from the synapse and absorbs it into the presynaptic neuron. DAT density was 70% greater in adults with ADHD, compared to controls [13], which was consistent with lower post synaptic levels of dopamine in ADHD. Using Single Photon Emission Computerized Tomography (SPECT), with ([Tc-99m] TRODAT-1), a radio-ligand specific for the dopamine transporter, researchers demonstrated that treatment with methylphenidate reduced DAT receptor binding sites which produced clinical improvement in ADHD adults [14]. These researchers also reported increased striatal DAT receptor binding, in adult ADHD, which was reduced by methylphenidate treatment [15]. Volkow, Wang, Fowler, et al. [16], working with Positron Emission Tomography (PET) and [^{11}C] raclopride, a D2 receptor radio-ligand, and normal participants, demonstrated that oral methylphenidate increased extracellular dopamine in the brain. This is significant in light of the ability of methylphenidate to block the dopamine transporter and amplify the effect of dopamine in supporting attention [16]. Notably, Badgaiyan, et al., in a

PET study [17] reported that ADHD adults have reduced tonic (resting) release and increased phasic, task-related release of dopamine in the right caudate nucleus. The increase in phasic DA release may compensate for the reduced tonic baseline, as may be needed, in ADHD. These studies collectively support the role of dopamine dysregulation in the pathophysiology of ADHD.

Dopamine plays a central role in cognitive functions [18] and WM [19] and hippocampal D2 receptor availability correlates positively with memory, executive function and verbal fluency [20]. Aalto, Bruck, Laine, et al. [21] used [^{11}C] FLB457, a high affinity dopamine 2 receptor ligand, in a PET study of vigilance and WM with normal participants. They found that their visual, WM task increased D2 receptor binding in the bilateral, ventrolateral frontal cortex as well as in the left medial temporal cortex, including the amygdala and hippocampus. This result is consistent with Kemppainen, Laine, Kaasinen, et al. [22] who reported reduced hippocampal D2 receptor activity in Alzheimer's Disease patients, which correlated with the patients' reduced memory and naming performance. The consistency in these two studies lies in the relationship between D2 receptor activation and WM performance. Seamans and Yang [23] discuss the complex role of dopamine as a neuromodulator of prefrontal, cognitive function and suggest that dopamine modulates the breadth of information stored in prefrontal, WM networks.

Blum, Cull, Braverman & Comings [24] proposed that ADHD and other impulsive and compulsive disorders, including Substance Use Disorder (SUD), may be subsumed under Reward Deficiency Syndrome (RDS). RDS disorders have a common proposed etiology in reduced sensitivity of the brain's reward circuitry to pleasurable environmental stimulation. Blum attributed RDS to a variant in a gene (A1 allele) that codes the DA D2 receptor. Individuals with the A1 allele have a decreased density of D2 receptors and a relative inability to experience pleasure associated with ordinary stimulation and activities [25]. The relationship between A1 allele of the D2 receptor, RDS and ADHD is summarized in Blum et al. [26]. Individuals with two copies of the A1 allele are at greater risk for alcoholism, SUD and ADHD compared to those with one or no A1 alleles. The occurrence of the A1 allele of the D2 receptor gene correctly classified 77% of alcoholics, while the absence of this allele accurately classified 72% of non-alcoholic research participants [27]. Comings, et al. [28] found that the A1, D2 receptor allele was significantly more prevalent in ADHD (46.2%) as compared to controls (24.5%). This allele was also more prevalent in patients with alcoholism, Tourette's Syndrome and autism. ADHD is clearly a polygenic disorder and has a heritability of .75 [29]. Although no single gene has a large, deterministic role, genes affecting dopamine activity make an important contribution to the expression of ADHD.

Blum, Febo & Badgaiyan [30] have summarized Blum's work, over the last fifty years, in developing a pro-dopamine, nutrigenomic complex (KB220Z), to stabilize the activity of dopamine in RDS. This compound, which includes dopamine precursor amino acids and natural ingredients, was designed to correct the dysregulation of dopamine in the brain's mesolimbic reward system. The goal for this compound is dopamine homeostasis, relieving the cravings associated with addiction and the drive to action associated with impulsive disorders, including ADHD, that are subsumed under RDS. Previously, De France, Hymel, Trachtenberg et al. [31], using normal participants, had demonstrated that an amino acid mixture increased the amplitude of the P300 evoked potential and decreased processing time in spatial

orienting and continuous performance tests. The improvement in function in this early study is similar to that which would be expected from KB220Z with RDS disorders.

Consumption of KB220Z is expected to improve cognitive functions that utilize the D2 receptor. McLaughlin, et al. [32] reported substantial improvements in semantic verbal fluency in an elderly male with mild memory impairment, following consumption of KB220Z. The participant demonstrated an average, baseline Animal Naming score of 14, placing him in the 30th percentile, for his age and gender, for semantic verbal fluency. Following a single, acute dose of KB220Z the patient's verbal fluency score increased to 19 animal names, placing him in the 76%. Following discontinuance of KB220Z, the patient's verbal memory performance decreased to 13 animal names. Notably, with resumption of KB220Z, the patient's verbal fluency score improved to 24 animal names, placing his verbal semantic memory performance in the 98th percentile. These clinical results suggest that activation of the participant's D2 receptors was associated with a dramatic improvement in his semantic verbal fluency.

Steinberg, Blum, McLaughlin, et al. [33] used quantitative EEG analysis (QEEG) and Low-resolution Electromagnetic Tomography (LORETA) to measure the effect of KB220Z on WM and brain electrical activity in an elderly adult with ADHD. The subject had long-standing issues with attention, organization, difficulties with sustained mental effort and procrastination. He was tested during baseline and following consumption of a daily dose (1 ounce) of KB220Z. The tasks included a resting EC condition as well as a WM task. The WM task required the participant to memorize and repeat random sequences of letters and numbers, in ascending order (numbers) and alphabetical order (letters). QEEG for the EC, resting condition, revealed that KB220Z produced an increase in absolute power in theta (4-8 Hz), alpha (8-12 Hz) and beta (12-25 Hz) frequency bands, in frontal (Fz), central (Cz) and parietal (Pz), midline locations. Right hemisphere EEG activity also increased in these bands in frontal (F4) and parietal (P4) locations.

LORETA was also used to study the sources of the EEG signals. LORETA produces measures of current source density, which are estimates of current flow originating from the Brodmann areas of interest. Data are expressed in standard deviation (z score units) that represent current flow for the participant compared to an age and gender matched, normative EEG database. During the WM task we observed that KB220Z increased the z scores for theta (4-7 Hz), low alpha (8-10 Hz) and high alpha (11-13 Hz) current source density in the anterior cingulate, dorsal cingulate and posterior cingulate cortices (Brodmann areas 32, 24 and 31, respectively). Thus, pro-dopamine regulation increased EEG activity in areas of the brain known to support attention and WM [8,9]. With KB220Z, the participant demonstrated an improvement in WM, from 13 to 14 correct letter-number sequences. This improvement in WM is consistent with the KB220Z's effect in activating DA and EEG activity, in the attention and WM areas of the brain. We have confirmed that the participant in Steinberg et al. [33] had the A1 allele of the D2 receptor gene.

In McLaughlin et al. [32] and Steinberg et al. [33], the participants were tested under baseline (no active agent, no placebo) and treatment (KB220Z) conditions, and the participants were aware of which condition was being used on each trial, raising the possibility of expectancy effects. The purpose of the current case report is to replicate these findings [32,33] using a double-blind, placebo-controlled, cross-over

study, which protects the data from experimenter bias. The use of a placebo control allows for assessment of the physiological effects of KB220Z, beyond the impact of the participant's expectations.

Case Presentation

This case study involves a 19 year old, right-handed, female college student, who will be identified with the pseudonym R.B. R.B. reported that she had been experiencing problems with attention and organization since age 5 and had been treated with stimulant medications during her subsequent school years. She had difficulties with sustained attention, which were most notable in school settings when she had long classes. She complained of problems with following through on tasks and needing instructions and prompts to help her complete her work. She also described difficulties with organization and feeling easily overwhelmed by tasks that required sustained mental effort. She claimed that she was easily distracted and forgetful. She described herself as having a tendency to be fidgety and to talk excessively, often intruding into other peoples' conversations. R.B. was not using stimulant medications at the time of the evaluation.

Study Design

The study included two male and four female, adult participants, all of whom had childhood histories of ADHD diagnosis and treatment. Participants were pre-screened to insure that they met the DSM-V criteria for ADHD. Pre-screening measures included administration of the Barkley Adult Attention-Deficit/Hyperactivity Rating Scale as well as the Barkley Deficits in Executive Function Rating Scale. These scales are nationally normed self-reporting instruments for measuring ADHD symptoms and deficits in executive function. All of the participants signed informed consent forms and the study was approved by the Institutional Review Board (IRB) of Curry College. Each participant received $50.00 in compensation at the completion of the study. None of the participants were using medications for ADHD at the time of the study. None of the participants were asked to discontinue any medications to take part in the study. Individuals with a recent history of concussions, or current treatment for depression, anxiety, schizophrenia, bipolar disorder or seizure disorder were excluded from the study.

Each participant was tested twice, (one week apart), once with a placebo (baseline) and once with KB220Z (experimental treatment), a commercially available, pro-dopamine regulator, designed to stabilize and promote the activity of DA D2 receptors. The experimental and placebo conditions were administered in a counter-balanced order, across subjects. The behavioral (Conner Continuous Performance Test), neuropsychological and EEG testing was conducted one hour after the participant consumed KB220Z or the placebo. During administration of the conditions, neither the experimenter nor the participants knew which agent was administered on each trial. One of the experimenters, not involved in the administration of the study or the evaluation of the data, maintained records of which agents were utilized in each session. All participants were debriefed after the conclusion of the study and were informed about which agent had been used during each of their two measurement sessions.

On each testing day the participants first received either the behavioral/EEG protocol or the neuropsychological protocol, administered in a counter-balanced design, within participants. The first

measurement session began with recording the participants' heart rate and blood pressure. A daily dose (2 caplets) of the agent (placebo or KB220Z) was administered, and the participant was allowed to rest for one hour to allow for absorption of the agent. Heart rate and blood pressure measurements were repeated after one hour. At the end of one hour, each participant was administered the Conner Continuous Performance Test (CPT), visual version, to obtain quantitative, objective measures of attention. At the conclusion of the CPT, the participant was fitted with an elastic, electro-cap that provided 19 channels of EEG data (10-20 electrode placements) for amplification by a Deymed Tru-Scan 32 amplifier. Impedance of all electrodes was below 5,000 ohms. Linked ears served as a reference.

During the EEG recording session, four conditions were administered in a Latin Square design, across subjects and research sessions. The conditions included Eyes Closed (EC), eyes open, WM and a default mode network task. Lighting in the room was reduced for all conditions. During eyes open, the participant was asked to maintain fixation on a circle, at eye level, on a viewing screen in front of them. Participants were asked to minimize eye movements and blinks for twenty second intervals, after which the recording was paused for three seconds, while they blinked. The default mode network task requested the participant to avoid thinking and attempt to maintain an "empty mind". The WM task required the participant to remember and repeat random sequences of letters and numbers, in ascending order for the numbers and alphabetical order for the letters. The sequences increased in length and the WM trial was terminated after three consecutive sequences with errors. The EC, eyes open and default mode network tasks each lasted 4.5 minutes. Participants rested for three minutes between tasks. The EEG recording was concurrent with the tasks. EEG records were edited to remove artifacts due to eye movements, muscle activity and sleepiness. The behavioral and EEG protocols required approximately ninety minutes. The present report presents the findings for the EC and the WM conditions, for the placebo and for KB220Z, the active agent.

A trained neuropsychologist administered the Weschsler Abbreviated Scale of Intelligence (WASI-II) on the participants' first day of testing. The Delis-Kaplan Executive Function Inventory was used to assess frontal lobe function after consumption of the placebo and the active agent. The Delis-Kaplan Inventory included the trail-making test with numbers, letters and switching between numbers and letters and the Color-Word Interference (Stroop) Test. The Color-Word Interference test required participants to identify colors, read color names, and identify the color of ink with which a word was printed when the color name conflicted with the color of the ink, e.g., the color name red printed in blue ink (switching from name to ink color). One of the trials in this test also required the participant to ignore the disparity between ink color and color name, and report the color name (inhibit switching). Finally, the Verbal Fluency Test was administered which required the participant to name nouns beginning with a specific letter of the alphabet or belonging to a specific class, e.g., animal names and to switch between methods of classification of the nouns.

The order of administration of the EEG and neuropsychological tests was counter-balanced across participants. The current report presents data on one of the participants, selected from the set of six, because the data is an exemplar of predicted responses to the active agent vs. the placebo on the EEG and

WM measures. Issues related to participant selection will be discussed at the conclusion of the report.

Behavioral and Neuropsychological Test Results

On the Barkley Adult ADHD rating scale R.B. scored in the 97th percentile for severity of inattention problems, the 90th percentile for hyperactivity and the 98th percentile for impulsivity symptoms. The Barkley Deficits in Executive Function Scale revealed self-ratings in the 99th percentile for Self-management to Time, the 94th percentile for Self-organization and Problem Solving, the 96th percentile for Self-restraint, the 97th percentile for Self-motivation and the 91st percentile for Self-regulation of Emotions. These scores, which measure the severity of personal difficulties with the constructs measured by the scales, indicate significant difficulties with executive function. R.B.'s heart rate and blood pressure were within the normal range and showed no significant changes with consumption of KB220Z.

The Conner Continuous Performance Test (CPT) data are presented below. The data are represented as T scores, which have a mean of fifty and a standard deviation of ten. Higher T scores represent poorer performance, relative to the normative group. The neuropsychological data are also presented as T scores, however, for the neuropsychological measures, higher T scores represent better performance.

Table 1: Behavioral and neuropsychological test results (T scores) for the placebo and KB220Z conditions.

Behavioral and Neuropsychological Tests	Placebo	KB220Z
Conner Continuous Performance Test (CPT)		
Stimulus detectability (d')	56	54
Omissions errors	51	48
Commission errors	53	53
Perseverations	53	53
Hit Reaction Time (HRT)	53 (421 msc.)	48 (398 msc.)
HRT SD	48	49
Variability	44	47
HRT Block Change	55	57
HRT Inter-stimulus Interval (ISI) Change	69	61
1 second ISI	357 msc.	350 msc.
2 second ISI	407 msc.	388 msc.
4 second ISI	502 msc.	455 msc.
Delis-Kaplan Executive Function Inventory		
Trails-Number	67	60
Trails-Letters	60	60
Trails-Number letter switching	53	60
Trails-Inhibit switching	63	63
Inhibition errors	60	60
Inhibition switching errors	60	60
Color-Word Interference Test		
Color naming	53	57
Color word reading	60	60
Switching to ink color	53	60

Inhibiting switching to ink color	63	63
Inhibition errors	60	60
Inhibition switching errors	60	60
Delis-Kaplan Verbal Fluency Results		
Letter	57	67
Category	60	63
Switching	53	57
Switching accuracy	57	57
Percent set loss errors	53	63
Percent repetition errors	53	44

The CPT data indicate a slight improvement in stimulus detectability and omission scores, as well as a reduction in reaction time in response to the KB220Z. The participant displayed one atypical score, a substantial lengthening of reaction time with longer inter-stimulus intervals, under the placebo condition. The placebo findings suggested a strong indication of problems with vigilance. The KB220Z results showed an improvement in vigilance.

The participant scored in the normal range of intelligence, based on the WASI-II assessment. On the Trail-making Test, she scored at an above average level, on both administrations. However, her performance on the number trail-making sequence (T=60) was lower in response to the active agent compared to T=67 under the placebo.

On the Color-Word Interference Test, the participant was required to identify patches of color, read a list of color names, and identify the color of the ink with which a color name was printed, when the ink color conflicted with the name of the color (color switching); e.g., identifying red ink when the color name is blue. The color switching trial requires the participant to inhibit the over learned response of reading the name of the color in favor of the discrepant color of the ink. Finally, in a separate trial, the participant was asked to ignore the ink and color name discrepancy and read the color name to the examiner (inhibit switching). Under the active agent the participant improved her color identification from T=53 to T=57 and her color switching performance from T=53 to T=60, suggesting improved response inhibition, a prefrontal executive function.

On the DKEFS verbal fluency test, which required the participant to name nouns beginning with a specific letter, the participant improved from T=57 under the placebo to T=67 in response to the active agent. She also showed a slight improvement in naming nouns that belong to a specific category (e.g., animal names) scoring T=60 under the placebo condition and T=63 in response to the active ingredient. When required to switch between letters and categories, as the basis for naming nouns, her performance was consistent at T=57 for the placebo and active agent. She made fewer errors due to losing the "set" of the task under the active ingredient T=63 vs. T=53 under the placebo condition. However, her repetition errors increased under the active agent condition T=44 compared to T=53 for the placebo condition.

The most striking result was obtained during the WM task administered as part of the EEG recording

session. Under the placebo condition the participant was able to remember and correctly arrange 10 letter-number sequences. However, in response to KB220Z, the active agent, she was able to recall and arrange 14 random sequences of letters and numbers.

EEG and LORETA findings

Surface EEG recordings were obtained from the 19 standard electrode locations of the International 10-20 placement system. The WM condition was conducted with the participant's eyes closed.

Table 2: Quantitative EEG (QEEG) results (z scores) for midline, left and right hemispheres, for EC and WM tasks, under placebo and active agents.

Placebo						KB220Z					
EC Placebo	Delta	Theta	Alpha	Beta	Hi Beta	EC KB220Z	Delta	Theta	Alpha	Beta	Hi Beta
Midline	1-4Hz	4-8Hz	8-12Hz	12-25Hz	25-30Hz	Midline	1-4Hz	4-8Hz	8-12Hz	12-25Hz	25-30Hz
Fz, Cz, Pz						Fz, Cz, Pz					
Average	-0.82	-0.60	-0.50	-0.79	-0.60	Average	-1.56	-1.12	-0.14	-0.59	-0.62
Left Hemi						Left Hemi					
FP1, FP3, C3, P3, 01, F7, T3, T5						FP1, FP3, C3, P3, 01, F7, T3, T5					
Average	-0.64	-0.46	-0.24	-0.60	-0.66	Average	-1.16	-0.81	0.01	-.033	-0.50
Right Hemi						Right Hemi					
FP2, F4, C4, P4, 02, F8, T4, T6						FP2, F4, C4, P4, 02, F8, T4, T6					
Average	-0.87	-0.88	-0.66	-0.97	-0.79	Average	-1.39	-1.14	-0.09	-0.53	-0.69
Grand						Grand					
Average						Average					
19 Channels	-0.77	-0.66	-0.46	-0.78	-0.71	19 Channels	-1.32	-0.99	-0.06	-0.45	-0.60
WM	Delta	Theta	Alpha	Beta	Hi Beta	WM	Delta	Theta	Alpha	Beta	Hi Beta
Placebo	1-4Hz	4-8Hz	8-12Hz	12-25Hz	25-30Hz	KB220Z	1-4Hz	4-8Hz	8-12Hz	12-25Hz	25-30Hz
Midline						Midline					
Fz, Cz, Pz						Fz, Cz, Pz					
Average	-0.59	-0.85	-1.72	-0.68	0.18	Average	-1.01	-0.86	0.23	-0.61	-0.41
Left Hemi						Left Hemi					
FP1, FP3, C3, P3, 01, F7, T3, T5						FP1, FP3, C3, P3, 01, F7, T3, T5					
Average	0.01	-0.57	-1.49	-0.06	-0.49	Average	-0.48	-0.24	0.36	-0.19	-0.17
Right Hemi						Right Hemi					
FP2, F4, C4, P4, O2, F8, T4, T6						FP2, F4, C4, P4, O2, F8, T4, T6					
Average	0.05	-0.76	-1.65	-0.75	0.37	Average	-0.85	-0.67	0.33	-0.42	-0.36
Grand						Grand					
Average						Average					
19 Channels	-0.07	-0.70	-1.59	-0.45	0.39	19 Channels	-0.72	-0.52	0.33	-0.36	-0.29

Table 2 presents the average, surface quantitative EEG (QEEG) findings for the EC and WM conditions in response to the placebo and the active agent. The data are absolute EEG power in each of the frequency bands. EEG power is presented as z scores (standard deviation units) which indicate the participant's EEG power relative to the EEG records in a normative, age and gender matched database.

The data in the top half of Table 2 compares the effect of KB220Z with placebo (EC for both conditions) on absolute EEG power in the various frequency bands. The grand average represents the average for the 19 electrode locations for the EC conditions. A comparison of the grand average of the 19 electrode positions for the active agent and the placebo indicates that KB220Z is associated with a decrease in delta and theta activity, and an increase in alpha, beta and high beta activity. Increased activity is noted by less negative z scores and decreased activity is noted by more negative z scores. This finding is also evident at the level of midline, left and right hemisphere EEG averages. The only discrepant finding is a slight decrease in absolute power in the high beta (25-30 Hz) frequency range, for the midline placements (Fz, Cz and Pz).

Table 3: Quantitative EEG (QEEG) analysis of changes in absolute power (z scores) for midline, left and right hemisphere electrode locations, for the EC and WM conditions, under placebo and KB220Z.

EC PLacebo	Theta	Alpha		Theta	Alpha	EC KB220Z	Theta	Alpha		Theta	Alpha
Midline						Midline					
Fz	-.55	-.47				Fz	-.99	-.14			
Cz	-.55	-.56				Cz	-1.15	-.15			
Pz	-.69	-.46				Pz	-1.21	-.14			
Average	-.60	-.50				Average	-1.12	-.14			
Left Hemi			Right Hemi			Left Hemi			Right Hemi		
FP1	-.44	-.49	FP2	-.58	-.67	FP1	-.13	-.10	FP2	-.26	-.15
F3	-.43	-.41	F4	-.65	-.57	F3	-.83	-.02	F4	-1.10	-.18
C3	-.41	-.38	C4	-.90	-.78	C3	-.92	-.05	C4	-1.43	-.29
P3	-.48	-.32	P4	-.98	-.64	P3	-1.14	-.15	P4	-1.42	-.19
O1	-.44	.07	O2	-.66	-.22	O1	-.84	.23	O2	-.87	.26
F7	-.67	-.52	F8	-.84	-.68	F7	-.75	-.06	F8	-1.02	-.19
T3	-.40	-.06	T4	-1.17	-.88	T3	-.92	.13	T4	-1.65	-.07
T5	-.37	.19	T6	-1.28	-.80	T5	-.91	.11	T6	-1.33	.10
Average	-.46	-.24		-.88	-.66	Average	-.81	.01		-1.14	-.09
WM Placebo	Theta	Alpha		Theta	Alpha	WM KB220Z	Theta	Alpha		Theta	Alpha
Midline						Midline					
Fz	-.67	-1.54				Fz	-.93	.35			
Cz	-.81	-1.78				Cz	-.88	.27			
Pz	-1.08	-1.84				Pz	-.78	.07			

Average	-.85	-1.72				Average	-.86	.23			
Left Hemi			Right Hemi			Left Hemi			Right Hemi		
FP1	.20	-1.15	FP2	.13	-1.29	FP1	.61	.42	FP2	.31	.46
F3	-.50	-1.48	F4	-.63	-1.58	F3	-.71	.43	F4	-.77	.34
C3	-.68	-1.68	C4	-1.15	-1.88	C3	-.69	.33	C4	-1.10	.07
P3	-.88	-1.72	P4	-1.34	-1.97	P3	-.85	.11	P4	-1.01	.03
O1	-.87	-1.80	O2	-1.08	-1.91	O1	-.45	.44	O2	-.29	.59
F7	-.41	-1.36	F8	-.06	-1.31	F7	-.11	.32	F8	-.50	.38
T3	-.69	-1.32	T4	-1.27	-1.99	T3	-.77	.43	T4	-1.37	.29
T5	-.72	-1.39	T6	-1.65	-2.08	T5	-.67	.36	T6	-.62	.49
Average	-.57	-1.49		-.88	-1.75	Average	-.24	.36		-.67	.33

The bottom half of table 2 presents the data for the WM conditions, in response to placebo and KB220Z. The grand average reveals that power was reduced in the delta and high beta frequency bands and increased in the theta and alpha and beta bands in response to KB220Z for the WM task. This trend was also evident at the regional level with the exception of midline theta power, which decreased very slightly under KB220Z and beta power, which also decreased slightly in the left hemisphere under KB220Z. Thus, the general impact of pro-dopamine regulation under conditions of increased WM demand was to increase power in the 4-25 Hz frequency range, while decreasing power in the very low (delta) and hi beta (25-30 Hz) frequency ranges.

Table 3 presents a more detailed summary of quantitative EEG findings for changes in theta and alpha activity for the EC and WM conditions under placebo and KB220Z. We present these data because theta and alpha activity have been important in studies of WM [6, 34-36].

Comparing the WM task under placebo, with EC under placebo reveals that during the WM task almost all of the electrode locations show reduced theta and alpha electrical activity. This effect is clear in the differences between the midline placements as well as the left and right hemisphere averages. The only exceptions to this pattern were found in FP1, FP2, F7 & F8, which had increased their theta activity in response to the WM task. FP1 and FP2 lie over the most anterior portion of the prefrontal cortex (BA 10, frontopolar), and are involved in executive control over multiple cognitive tasks [37]. In addition, F7 lies over the inferior frontal gyrus (BA 45/47) which includes Broca's area and F8 lies over the middle, frontal gyrus (BA45/47) [38]. Thus, one would expect activation in these regions in response to a WM task that involves letters and numbers.

In contrast, the WM task under KB220Z, as compared to EC under KB220Z, produced increased theta and alpha electrical activity in the midline locations and all of the locations in the left and right hemisphere. Thus, KB220Z, a pro-dopamine regulator, in conjunction with a WM task that engages DA activity, produces a dissociation in EEG activation, as compared to the WM task with the placebo.

Table 4 presents a Low-resolution electromagnetic (LORETA) analysis of current source density measurements (represented as z scores relative to a normative database) for the midline and bilateral frontal areas that comprise the anterior attention network and are involved in WM functions. The areas in this analysis (left and right hemisphere) are Brodmann areas 8 (frontal eye fields), 9 (superior frontal), 10 (frontopolar), 24 (dorsal cingulate cortex), 28 (hippocampus), 32 (anterior cingulate cortex) & 46 (dorsolateral prefrontal cortex). The LORETA data, averaged across the noted areas, indicates that KB220Z, compared to placebo increased current source density (less negative z scores) averaged across EC and WM conditions in the theta, lo alpha, and hi alpha frequency bands across a broad range of frontal and midline cortical regions. This effect was most notable under the WM condition, where KB220Z increased electrical activity in the three frequency bands.

Table 4: Average LORETA Z score values for left and right attention areas for EC and WM conditions under placebo and KB220Z.

		Placebo					KB220Z		
	Theta	Lo Alpha	Hi Alpha	Average		Theta	Lo Alpha	Hi Alpha	Average
	4-7 Hz	8-10 Hz	11-13 Hz			4-7 Hz	8-10 Hz	11-13 Hz	
EC	-0.93	-1.03	-0.33	-0.76	EC	-0.97	-0.70	-0.03	-0.57
WM	-0.58	-1.41	-0.97	-0.99	WM	-0.45	-0.20	-0.06	-0.24
Average	-0.76	-1.22	-0.65	-0.88	Average	-0.71	-0.45	-0.05	-0.40

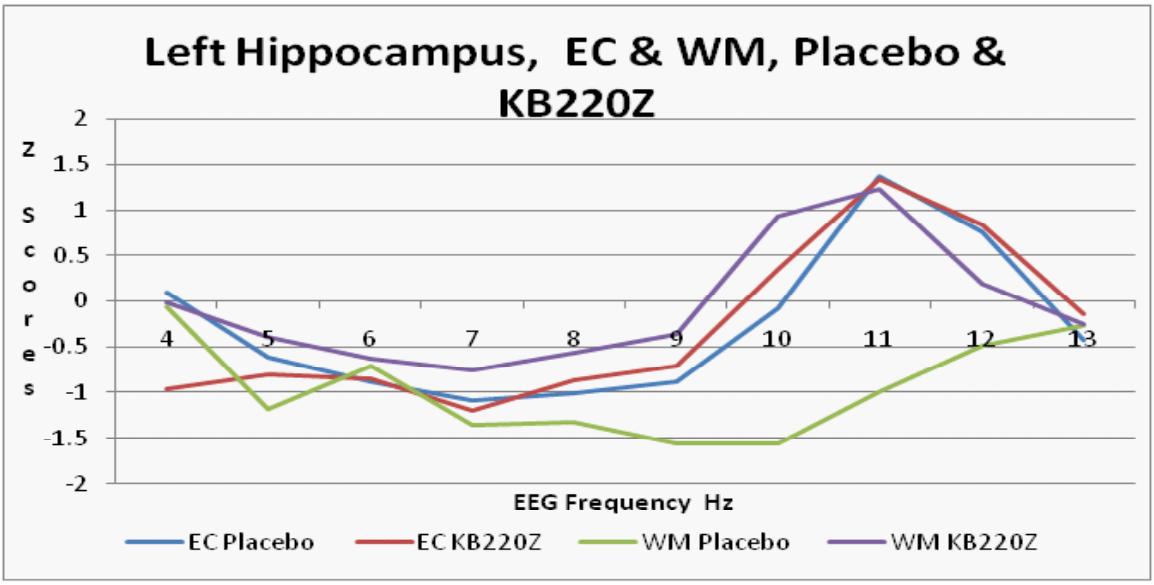

Figure 1: LORETA current source density values (z scores) for the left hippocampus, by frequency, for the EC and Letter-Number Sequencing task, under placebo and active agent conditions.

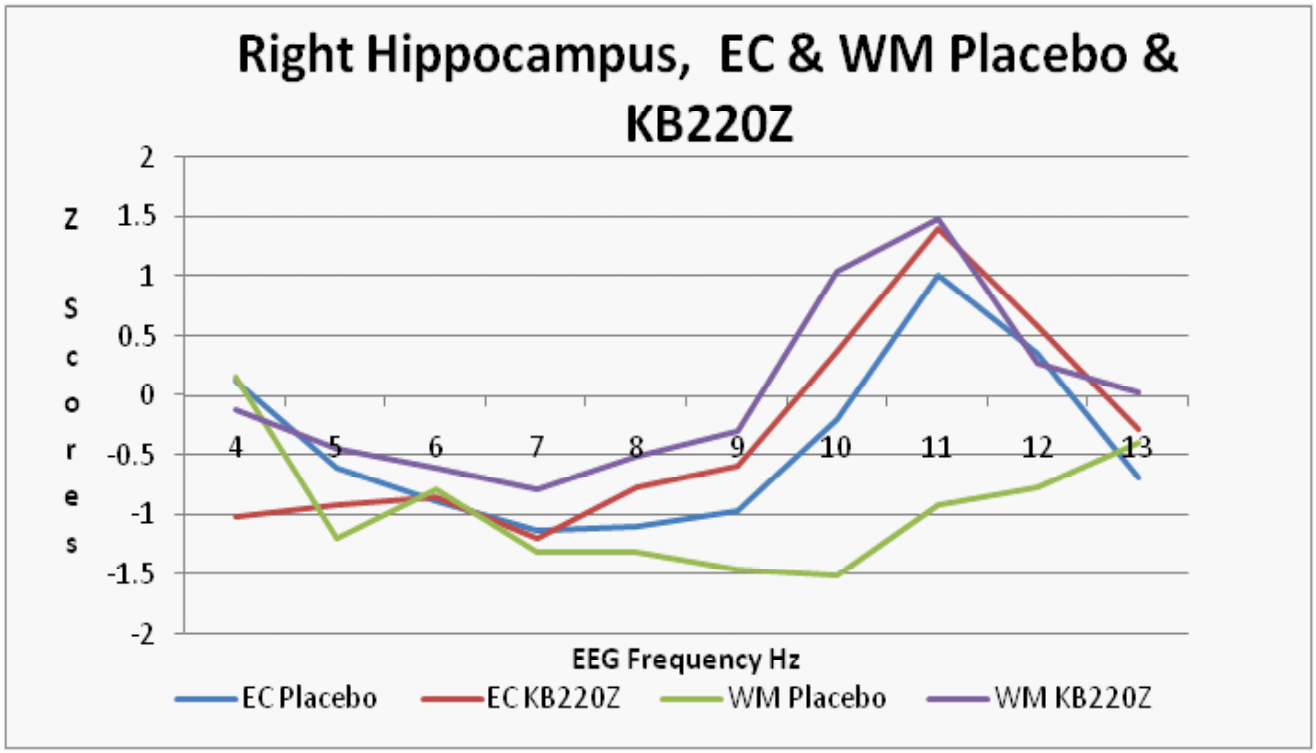

Figure 2: LORETA current source density values (z scores) for the right hippocampus for Eyes Closed and Letter-Number sequencing conditions, by frequency for the placebo and active agent conditions.

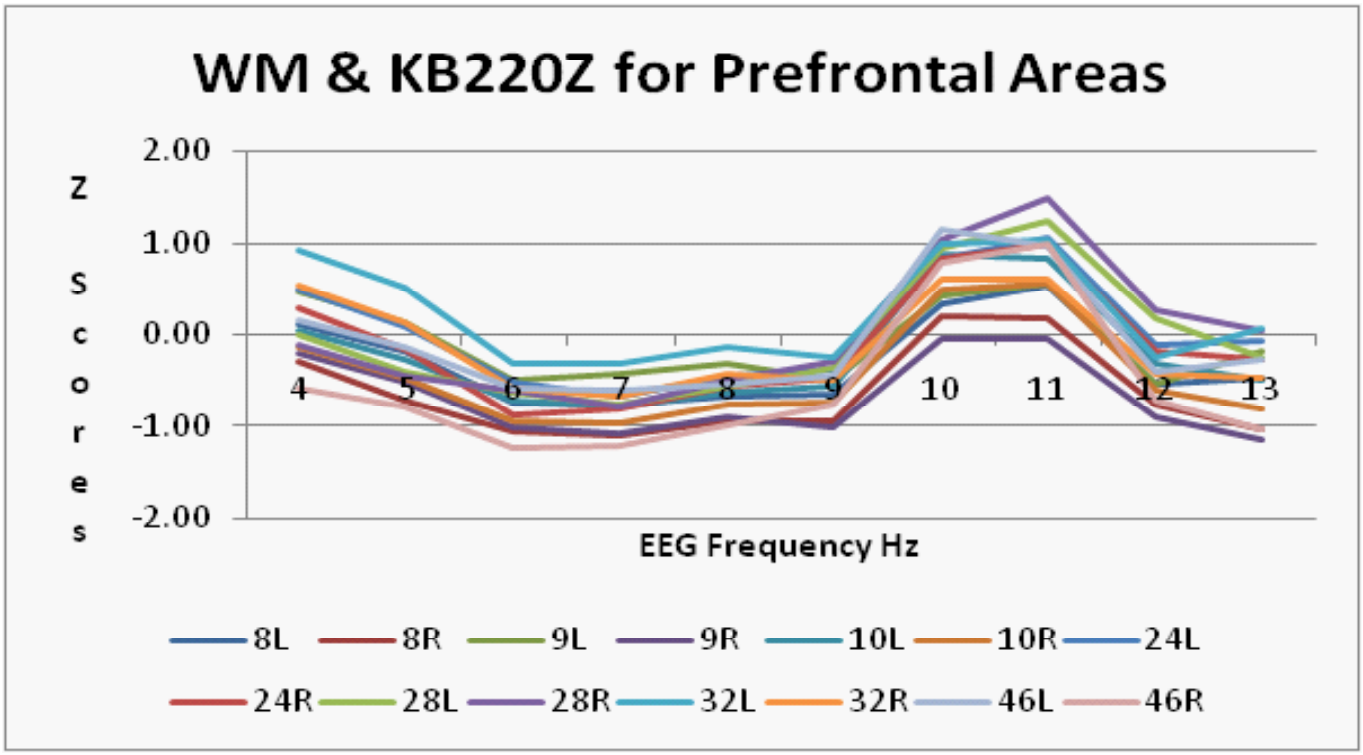

Figure 3: LORETA current source density measurements for each prefrontal area by EEG frequency for the WM task under KB220Z.

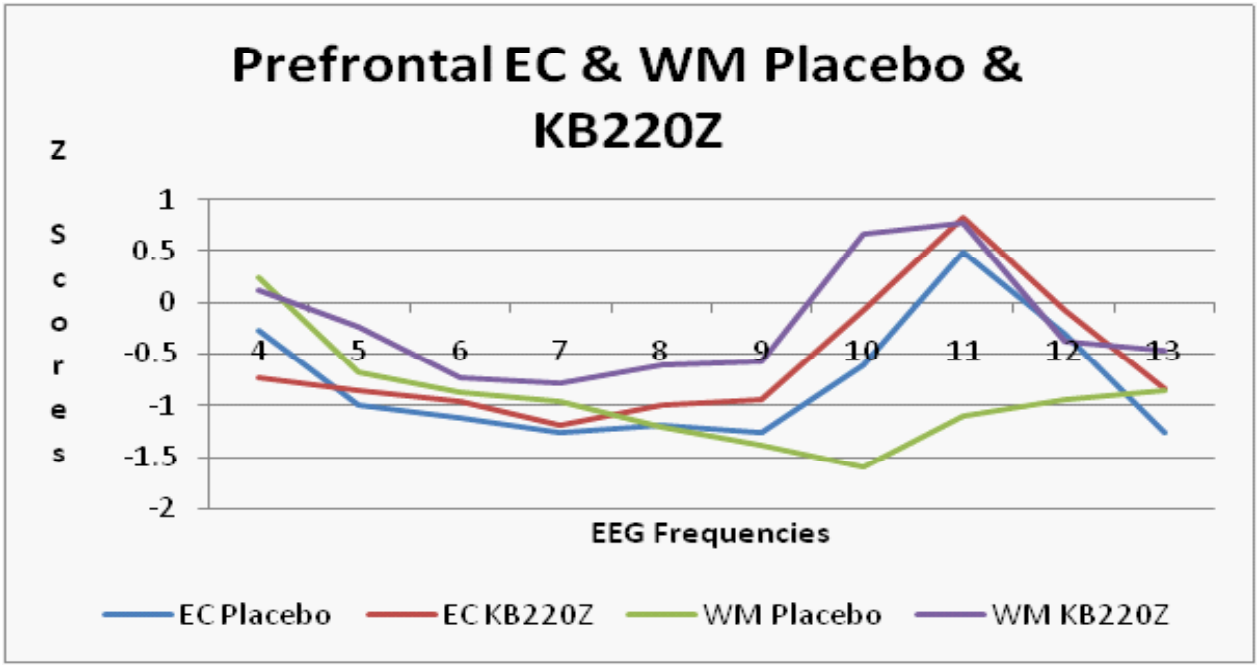

Figure 4: LORETA current source density values (z scores) for prefrontal areas, by frequency, for EC and Letter-Number Sequencing task under placebo and active agent conditions.

Figures 1 and 2 present LORETA current source density values (z scores) for the left and right hippocampi, respectively, for the EC and WM under the placebo and KB220Z as a function of EEG frequency. The data for left and right hippocampi are very similar. From 5-9 Hz, all conditions show reduced current source density. However, both EC conditions and the WM task under the active agent show peaks of activity at 11Hz. The WM condition produced the greatest difference between KB220Z and placebo at 10-11 Hz. These findings were fundamentally the same for the left and right hippocampi. The peak electrical activity at 11 Hz in the hippocampus for the WM condition under KB220Z is meaningful, given the known role of the hippocampus in memory [20,21]. In this regard, it is noteworthy that R.B. showed a dramatic improvement in WM performance from 10 letter-number sequences under the placebo, to 14 letter number sequences under KB220Z.

Figure 3 presents LORETA current source density values (z scores) for the bilateral prefrontal Brodmann areas 8 (frontal eye fields), 9 (superior frontal), 10 (frontopolar), 24 (dorsal cingulate cortex), 28 (hippocampus), 32 (anterior cingulate cortex) and 46 (dorsolateral prefrontal cortex). Data are presented for the 4-13 Hz frequency range for the WM task under the active agent.

Figure 3 indicates that the prefrontal areas responded in a similar fashion to the demands of the letter-number sequencing task, under the impact of the active agent. The left anterior cingulate (BA 32) and superior frontal regions (BA 8), and left hippocampus showed elevated activity at 4Hz and these values declined from 5-9 Hz with all values peaking at 10-11 Hz. Thus, the administration of a pro-dopamine regulator had a widespread, activating effect on the prefrontal cortex during performance of a demanding WM task. Given the similarity of response of the prefrontal areas to KB220Z for the WM task, we present average data for the above areas across all four conditions in Fig. 4.

Figure 4 presents average data (z scores) for current source density across all of the measured areas

of the prefrontal cortex by experimental condition and EEG frequency. For the EC conditions (placebo and active) KB220Z produced slightly greater electrical activity from 5-13 Hz with z score values peaking at 11 Hz. The WM task produced dramatic increases in current source density under KB220Z compared to the placebo. The greatest differences between the active and placebo conditions for WM were seen at 10-11 Hz.

Figure 4 reveals that R.B., an adult college student with ADHD, had below average (z scores less than zero) current source density in frontal and midline structures, from 5-9 Hz, across all four conditions. Notably, her z score values were generally highest for the 4-10 Hz frequency range for the WM condition under the active ingredient as compared to the placebo. At 11 Hz, the values for EC with KB220Z and WM with KB220Z were identical. As a general summary, between 4 – 13 Hz for the WM condition the z scores values were greater for KB220Z than for the placebo. In a similar manner, from 5-13 Hz under the EC conditions z score values were greater under KB220Z than under the placebo.

We evaluated quantitative differences in the response of the EEG to the placebo and KB220Z conditions for the WM task with a Factor Analysis of the EEG data. The 28 brain regions (14 regions across two tasks) were considered replications of subjects, and the frequencies 4 Hz, 6Hz, 7 Hz, 8 Hz, 12 Hz, and 13 Hz were treated as dependent variables. The 5 Hz, 9 Hz, 10 Hz and 11 Hz frequencies were not included in the factor analysis because they had high correlations with other EEG frequency variables which were included. The Principal Components factor analysis used Varimax rotation to produce two rotated factors with eigenvalues greater than one. The EEG data entries for the analysis were the z scores for each frequency and Brodmann area under the placebo and KB220Z conditions. The conditions were coded as 1 for placebo and 2 for KB220Z. Table 5 presents the rotated factor loadings for each factor and EEG frequency. Factor 1 had an eigenvalue of 4.469 and accounted for 63.84% of the variance in the correlations among the z scores for the different frequencies. Factor 2 had an eigenvalue of 1.503 and accounted for 21.47% of the variance in the correlations.

Table 5. Rotated factor loadings for Factors 1 and 2, by EEG frequency and experimental condition.

	4 Hz	6 Hz	7 Hz	8 Hz	12 Hz	13 Hz	Condition
Factor 1	-.097	.518	.387	.875**	.868**	.718**	.925**
Factor 2	.942**	.794**	.800**	.380	.307	.485	-.144

The pattern of factor loadings clearly indicates that Factor 1 represents alpha activity since the loadings for 8 Hz, 12 Hz and 13 Hz are all high and statistically significant. Notably, the experimental condition variable coded 2 for administration of KB220Z loads .925 on Factor 1, indicating a very powerful association between the effect of KB220Z and the EEG values in the alpha frequency range across the prefrontal brain areas represented in the study. Factor 2, in contrast, has the highest loadings on EEG frequencies at 4Hz, 6 Hz and 7 Hz identifying the function of this factor as EEG activity in the theta frequency range (**p<.01).

As a further test of differences in the EEG caused by the administration of KB220Z, we conducted a Discriminant Analysis using brain regions as replications of subjects and the EEG frequencies at 10 Hz and

11 Hz as variables to predict which brain areas responded to the placebo or KB220Z. The Discriminant Analysis produced a Wilks Lambda of .036, which was statistically significant at the .001 level. The discriminant function had an eigenvalue of 26.615 which accounted for 100% of the variance in the data. The canonical correlation between the 10Hz and 11 Hz EEG activity and the classification variable (placebo response or KB220Z response) was .982. Finally, the discriminant function correctly classified all of the 14 brain regions for the placebo condition and all of the 14 brain regions for the KB220Z condition. The classification produced an X^2 of 28, d.f.=1, p<.001.

We then examined differences between the z scores($(z_{diff}=z_1-z_2)/sqrt(2)$), [39] by frequency and brain region, for the WM task under the KB220Z and the placebo conditions. Our goal was to determine which brain regions and EEG frequencies showed statistically significant increases in electrical activity under the KB220Z condition. We found statistically significant increases in EEG activity (p<.05), at 10Hz for the left dorsal cingulate cortex, Z=1.65, the right dorsal cingulate cortex, Z=1.70, the left hippocampus, Z=1.76, the right hippocampus, Z=1.80 and the left and right dorsolateral prefrontal cortices, Z=1.89 and Z=1.85, respectively. In addition, we found statistically significant increases in electrical activity at 11 Hz in the right hippocampus (Z=1.69) and the right dorsolateral prefrontal cortex (Z=1.78). The differences in z scores between EC with KB220Z and EC with placebo, by frequency and brain region, were not statistically significant. These results collectively demonstrate that KB220Z had an activating effect on EEG activity in the alpha frequency range, with statistically significant elevations in the dorsal cingulate, hippocampal and dorsolateral prefrontal regions at 10 Hz, and the right hippocampus and dorsolateral prefrontal regions at 11 Hz.

Discussion & Conclusions

KB220Z is a compound comprised of amino acids and natural ingredients designed by Blum (29) to enhance and stabilize the activity of DA in the brain's reward cascade and prefrontal areas. The current case study demonstrates a dramatic improvement in WM performance for an adult college student, with ADHD, following consumption of a daily dose of KB220Z. The results of the factor analysis indicate that the prefrontal areas under study demonstrated notable EEG responses in the alpha frequency range to the administration of KB220Z. These results were supported by the discriminant analysis which correctly classified all brain regions as responding to either the placebo or the KB220Z treatment. Finally, we observed substantial, statistically significant increases (p<.05) in electrical activity at 10 Hz in the left and right hippocampi, left and right dorsal cingulate cortices, and left and right dorsolateral prefrontal cortices for our WM task under KB220Z compared to placebo. The increase in hippocampal activity is meaningful in light of the contribution of hippocampal D2 receptors to WM [21], and the Takashi et al. [20] report of a positive correlation between hippocampal D2 receptor binding with immediate auditory verbal learning, as well as with immediate and delayed visual spatial memory and phonemic verbal fluency. Our findings are also interesting in light of Kemppainen, et al. [22] who reported that hippocampal D2 receptor binding potential was reduced in Alzheimer's patients and the reduced availability of hippocampal D2 receptors correlated with decreases in verbal memory as measured by the Wechsler Memory Scale-Revised. Thus, increases in hippocampal D2 receptor activity are associated with increased WM performance and decreased D2

receptor activity are associated with poorer WM performance. R.B.'s dramatic improvement in WM under KB220Z is consistent with our prior report [32] of increased semantic verbal fluency in an elderly man with mild memory impairment and replicates our finding of improved WM in an elderly male with ADHD following consumption of KB220Z [33]. This latter finding is meaningful in light of our determination that the participant had the A1 allele of the D2 receptor gene, which has the effect of decreasing the density of D2 receptors. Thus, the likely impact of KB220Z for this individual was to increase dopamine D2 receptor binding with a consequent improvement in WM.

R.B.'s improved verbal fluency performance in response to KB220Z replicates the McLaughlin, et al. report [32] of increased verbal fluency induced by KB220Z in an elderly male with mild memory impairment. R.B.'s improved maintenance of the "set" of the task under KB220Z is also indicative of improved executive control, a prefrontal neuropsychological function.

Table 2 presents the results of Quantitative EEG (QEEG) findings for absolute power in midline, left-hemisphere and right-hemisphere locations for the delta (0-4Hz), theta (4-7 Hz), low alpha (8-10 Hz), high alpha (11-13Hz), beta (12-25 Hz) and high beta (35-30Hz) frequency bands.

Looking at the grand averages for the EC placebo and EC KB220Z data, the active agent reduced power in the delta and theta bands, and increased power in the alpha, beta and high beta frequency bands. For the WM task the active agent reduced delta and high beta band power and increased theta, alpha and beta power. The two consistent findings are increased power in the alpha and beta bands as a result of KB220Z under EC and working WM demand conditions.

The activating effect of KB220Z is also evident in the LORETA z scores data (Table 4) from areas of the brain concerned with attention and executive function. The data reflect increased, bilateral activation of the frontal eye fields (BA 8), superior frontal cortex (BA 9), frontopolar regions (BA 10), hippocampus (BA 28), anterior cingulate (BA 32) and dorsal cingulate cortices (BA 24), and the dorsolateral prefrontal cortex (BA 46).

Activation of these prefrontal areas, which are involved in attention and executive control, was associated with an improvement in stimulus discrimination and a reduction in omission errors on the Conner CPT, a shortening of Hit Reaction Time, and an improvement in vigilance performance. Improved response inhibition was seen on the switching task (naming ink color not color names) of the Color Word Interference Test. Verbal fluency also improved for naming nouns beginning with letters and belonging to categories and switching between letters and categories. The participant did have more word repetition errors under the active agent. It is not clear why this occurred but the increased repetition errors may be related to the faster reaction time the participant demonstrated on the Conner CPT in response to KB220Z. These collective effects are evidence of improved attention and self-regulation in association with pro-dopamine regulation.

Figures 1-4 indicate that electrical activity peaked at 10-11 Hz, for the WM task under KB220Z, compared to the placebo. The greatest difference between the active agent and the placebo occurred in

this frequency range. This effect was statistically significant at 10 Hz, bilaterally in the hippocampus, the dorsal cingulate and the dorsolateral prefrontal areas, as well as at 11 Hz in the right hippocampus and right dorsolateral prefrontal cortex. Increases in electrical activity with KB220Z during the WM task were generally seen across the left and right prefrontal cortex but with the exception of the areas noted above, they were not statistically significant. A strong placebo effect was also seen in the comparison of KB220Z with EC compared to the placebo with EC. However, the WM task with KB220Z was more activating than WM with the placebo, in the 10-11 Hz frequency range. This may have been due to an interaction between WM eliciting DA activation and KB220Z supporting enhanced DA activity. Thus, under conditions of high WM demand, the active agent was far more effective than placebo in influencing the EEG.

Activation of DA across the brain reward circuitry has been demonstrated by Febo et al. [40] with fMRI in naïve rodents. Their study revealed significantly increased resting state functional connectivity with KB220Z compared to placebo. The areas affected include the nucleus accumbens, anterior cingulate gyrus, anterior thalamic nuclei, hippocampus, prelimbic and infralimbic loci. Significant functional connectivity, increased brain connectivity volume recruitment (potential neuroplasticity), and dopaminergic functionality were found across the brain reward circuitry. Increases in functional connectivity were specific to these regions and were not broadly distributed across the brain.

Prefrontal regions, including the anterior and dorsal cingulate cortices, are involved in emotional and cognitive decision making [41], recall of experiences and reinstatement of drug seeking behavior [42]. The Febo, et al. [40] finding of KB220Z induced dopamine activation across the brain reward system, as well as our finding of significant increases in DA D2 activation across hippocampal, dorsolateral and dorsal cingulate, prefrontal areas, may provide a partial explanation for drug relapse prevention as observed in a number of long-term studies using KB220 variants [43-45].

It is noteworthy that Blum, et al [46] reported on using KB220Z to overcome QEEG abnormalities and reward gene deficits during protracted abstinence in male psychostimulant and poly-drug abusers. They found positive outcomes using QEEG imaging in a randomized, triple-blind, placebo-controlled, crossover study involving oral KB220. Their results showed an increase of parietal alpha and low beta EEG activity. Significant differences were found between the placebo and KB220Z conditions and these differences consistently occurred after weeks 1 and 2 in the frontal regions ($p=.03$). The authors were the first researchers to show involvement of the prefrontal cortex in the QEEG response to a natural, putative D2 agonist, in substance use disorder individuals with the DA D2 A1 allele. Significant QEEG differences were found between those who received 1 dose of placebo compared with those who were administered KB220Z. This agent induced positive regulation of the dysregulated brain electrical activity in these SUD individuals. The results are indicative of a state change from low amplitude or low power in the brain to a more regulated state by increasing an average of 6.169 microvolts^2 across the prefrontal cortical region. Blum, et al. [46] also found that while 50% of the subjects carried the DRD2 A1 allele, 100% carried ≥ 1 risk allele. Specifically, based on the proposed addiction risk score [46] for these 14 subjects, 72% had moderate-to-severe addiction risk. Similar findings were obtained by repeating the experiment in 3 additional currently abstinent poly-drug abusers carrying the DRD2 A1 allele.

DA release in the ventral striatum is responsive to placebo effects and reflects the expectation of reward [47,48]. In addition, DA release responds to the unpredictability of rewards and decreases when expected rewards do not occur [49]. Thus, DA responds when rewards are greater than expected and decreases when rewards are less than expected [50]. WM is an area of difficulty for individuals with ADHD [4,5]. The enhancement of DA activity with KB220Z in the WM task may have facilitated R.B.'s performance and expectations for task success, further amplifying the EEG difference between the WM task under KB220Z vs. the placebo condition. Although speculative, this hypothesis is consistent with the difficult nature of the task and the reaction of DA to expectations for success or failure.

An important question concerns the mechanisms that are responsible for the improvement in WM and the increase in alpha power in response to pro-dopamine regulation. Dopaminergic neurons originate in the substantia nigra and project to the caudate nucleus and the putamen, forming the nigrostriatal system that contributes to movement control. The mesolimbic DA pathway originates in the ventral tegmentum and projects to the nucleus accumbens and prefrontal cortex. This latter pathway is part of the brain's reward system and plays a vital role in attention, learning, motivation and the expectation of reward [12].

The role of DA in cognitive activity [18] and executive function is well established [51]. Seamans & Yang [23] have detailed the neuromodulatory effects of DA on prefrontal cortical function. Aalto et al. [21] employed [^{11}C] FLB457, a high affinity D2 receptor-ligand to show that a verbal WM task increased D2 receptor binding in the bilateral, ventrolateral frontal cortex and left medial temporal cortex (amygdala and hippocampus). These authors concluded that frontotemporal, dopaminergic activity is involved in human WM. Takahashi et al. [20] subsequently demonstrated that [^{11}C] FLB457 binding potential in the hippocampus correlated positively with memory function, executive function and verbal fluency, underscoring the important role of hippocampal D2 receptor activity in these neuropsychological functions. Thus, the putative enhancement of D2 activity with KB220Z may increase the electrical activity of areas demonstrated to be involved in WM.

Alpha EEG activity is produced by cortico-thalamic circuits that include the nucleus reticularis of the thalamus [52]. This circuit is modulated by dorsal striatal efferents to the globus pallidus, which exert inhibitory influence on the thalamus. Di Michelle, Prichep, John & Chabot [52] have proposed that, in ADHD, activation of inhibitory D2 receptors in the striatum might reduce the inhibitory globus pallidus output to the thalamus, with this disinhibition of the thalamus leading to increased thalamic excitation, and enhanced, prefrontal alpha activity.

We have observed widespread, increases in prefrontal alpha frequency activity (10-11 Hz) in response to KB220Z, a putative D2 receptor agonist. This elevation in 10-11 Hz activity was pronounced in the left and right hippocampus (Brodmann area 28) as revealed by LORETA current source density analysis. In addition, surface EEG analysis (Table 3) revealed substantial increases in alpha activity, in response to KB220Z, in midline and widespread bilateral cortical regions. Finally, increases in 10-11 Hz activity (Table 4) were observed in frontopolar (BA 10), frontal eye fields (BA 8), superior frontal (BA 9), dorsolateral prefrontal (BA 46), anterior cingulate (BA 32), and dorsal cingulate (BA 24) regions. This elevation in

alpha band EEG activity coincided with increased D2 receptor activation by KB220Z and an increase in the participants WM performance from 10 – 14 letter number sequences.

An elegant study by Lenartowicz, et al. [6] examined EEG correlates of the vigilance, encoding and maintenance components of a spatial WM task in children with ADHD compared to children with typical development. Their data revealed reduced mid-frontal, event-related potentials in response to a task-related alerting cue in the ADHD children which indicated a deficit in vigilance. In addition, they found reduced mid-occipital, event-related desynchronization in the alpha band during encoding which predicted reduced memory performance. This effect was primarily seen under conditions of low task difficulty which also suggested problems with vigilance. Theta and alpha power increased during the maintenance interval of the WM task and the researchers suggested that the increase in power reflected compensation for impaired encoding and maintenance of information. Lenartowicz, et al. [6] concluded that deficits in vigilance, encoding and maintenance are factors in reduced visual-spatial WM in ADHD children.

The current study employed a difficult letter-number sequencing task to assess auditory WM. Increasing WM load is associated with increases in alpha band power in central and posterior locations, during the retention interval [53]. Khader, Jost, Ranganath & Rosler [54], using a spatial WM task, reported increased alpha (occipital-parietal) and theta power (mid-frontal) for correctly remembered stimuli. Their data demonstrated that these EEG frequencies were associated with successful long-term memory encoding. Klimesch [55] has proposed that synchronous alpha band activity inhibits the processing of task irrelevant stimuli, facilitating access to stored, task-relevant information. Finally, alpha power has been demonstrated to increase with information load and reflect active maintenance and updating of memory content [56].

A comparison of WM under KB220Z and EC under KB220Z (Table 3) reveals increases in midline theta power for surface EEG recordings at Fz, Cz & Pz electrode locations. In addition, theta activity increased in all other regions for the WM task under KB220Z. In contrast, under the placebo conditions, the increased information load of the WM task led to a reduction in theta activity in all regions except FP1, FP2, F7 & F8. It is worth noting that FP1 and FP2, (BA 10, anterior frontal pole) support executive control over multiple mental tasks [37]. Furthermore, electrode locations F7 (inferior frontal gyrus, Broca's area) and F8 (middle frontal gyrus) include BA 45 (ventrolateral cortex) demonstrated by Aalto et al. [21] to be activated by WM demands. Thus, the increase in theta activity in FP1, FP2, F7 & F8, for the WM task under placebo likely reflects the engagement of these areas in WM processing. The increase in midline theta activity, for the WM task under KB220Z is consistent with an increase in vigilance under increased information processing load. This interpretation is supported by improvements in stimulus detectability, omission errors, hit reaction time and changes in reaction time with increasing inter-stimulus intervals, as revealed by the Conner CPT scores under KB220Z administration.

In contrast, under the placebo condition, increased WM demand decreased alpha power at midline locations (Fz , Cz & Pz) as well as all other bilateral regions. However, alpha power in all 19 electrode locations increased in response to the WM task under KB220Z. These findings suggest that KB220Z is reversing

the reduction in theta and alpha power seen in the placebo condition under the WM task. The consequent increase in midline theta with KB220Z may be facilitating increased vigilance and maintenance of information in WM, consistent with the findings of Lenartowicz, et al. [6]. Our finding of increased WM performance in association with increased midline theta and occipital alpha power is also consistent with the results of Jensen, et al [53] and Khader, et al. [54]. The increase in alpha power at 10-11 Hz that we have observed throughout widespread areas of the prefrontal cortex is also in accord with increased access to stored information as proposed by Klimesch [55] and the Manza et al. [56] finding that alpha power regulates access to information during WM updating. We note, however, that Klimesch [55] speaks of alpha activity facilitating access to stored semantic information whereas the present study deals with sequencing, memory and retrieval of letters and numbers.

The finding of increased bilateral electrical activity, at 10 Hz, in the dorsal cingulate cortex, the hippocampus and the dorsolateral cortex is meaningful in light of the roles of the dorsal cingulate in cognitive processing [41], monitoring and making adjustments for changes in cognitive demands and behavioral adaptation [57]. Moreover, the activation of the hippocampi and dorsolateral prefrontal areas by the WM task under KB220Z, with a large increase in WM performance, is consistent with interactions between the hippocampi and dorsolateral prefrontal areas during memory retrieval [58,59]. We suggest that KB220Z may be facilitating WM performance by activating brain regions that monitor and adjust for cognitive demand and support the encoding and retrieval of declarative information.

In summary, we replicated our earlier findings [33] of increased theta and alpha power, in frontal and attention network regions, resulting from administration of a pro-dopamine regulator, KB220Z. In addition, our current finding of improvement in WM with KB220Z is also in agreement with our earlier report [32] of dramatic improvements in verbal fluency in an elderly male with mild memory impairment, following ingestion of KB220Z. Increased WM performance and hippocampal D2 activation from KB220Z is particularly relevant in light of Kemppainen et al. [22] finding of decreased hippocampal D2 receptors in Alzheimer's Disease, which correlated with reduced memory performance. Also relevant is the Takahashi, et al. [20] finding that hippocampal D2 receptor binding correlates with memory performance and modulates prefrontal executive functions. Figure 3 demonstrates that of all the areas measured, the left and right hippocampi (BA 28) exhibited the largest electrical response at 11 Hz to KB220Z. The current study adds a robust demonstration of enhanced, prefrontal and hippocampal alpha activity to our understanding of the potential neurophysiological bases for the memory improvement.

With respect to potential mechanisms that might account for the behavioral and cognitive changes we have seen with KB220Z, diMichelle, et al. [52] suggest that activation of D2 receptors in the striatum may disinhibit thalamo-cortical activity. This putative disinhibition of thalamic activity may contribute to the widespread increase in alpha activity observed in prefrontal cortical locations in response to a putative, pro-dopamine agonist. This increase in alpha activity at 10-11 Hz was especially evident during the WM task, which engages dopaminergic activity. The increase in hippocampal alpha activity may have improved encoding of the letter number sequences. Enhanced vigilance associated with increased, mid-frontal theta, and enhanced access to stored information associated with increased prefrontal alpha activity may have

contributed to increased WM performance. Increased activation of hippocampal D2 receptors modulates prefrontal executive function [60] and this, too, may have contributed to improved WM and neuropsychological performance in response to KB220Z. Finally, the increase in 10 Hz electrical activity, with KB220Z during WM, in the bilateral dorsal cingulate, bilateral hippocampi and bilateral dorsolateral prefrontal cortex may indicate enhanced activation of a network of brain regions that supports the operation of WM, retrieval of declarative information and the management of cognitive demands.

Strengths & Limitations of the Study

Our data indicate that pro-dopamine regulation has improved WM and prefrontal neuropsychological function in an adult with ADHD. The study employed a double-blind, placebo-controlled, cross-over design.This design strengthens the study by protecting the data from biases due to the experimenter or participant's knowledge of the conditions of the study. The use of a placebo condition allows for an accurate assessment of the pharmacological effects of KB220Z beyond the influence of participant expectations. This study replicates our prior case studies that reported changes in prefrontal EEG and LORETA activity in the attention network with KB220Z (33) in an elderly male with ADHD, as well as improvements in verbal fluency in an elderly male with mild memory impairment [32]. The current case study provides modest generalization from the prior cases by demonstrating similar effects with a young, college-age woman with ADHD.

A limitation of the current study is that it is a single case report, selected from a larger set of six participants. We cannot confirm, at this time, why this particular participant was an exemplar of a strong, positive response to KB220Z. We believe that she had the A1 allele of the D2 receptor gene which leads to a significant reduction in the density of D2 receptors and is the basis for RDS. Evidence for this proposition that reduced D2 receptors are relevant to the effects we observed is the high impulsivity score the participant achieved (98% severity) on the Barkley Adult ADHD Rating Scale and the high score she produced on the Self-Restraint scale (96%) of the Barkley Deficit in Executive Functioning Scale.

Impulsivity is a signature characteristic of ADHD and RDS. Cools, Sheridan, Jacobs and D'Esposito [61] used fMRI with a delayed, matching to sample, visual spatial WM task, to study the fronto-striatal effects of bromocriptine, a D2 agonist, in participants with high vs. low impulsivity. Bromocriptine modulated striatal activity concurrently with flexible updating of WM and also modulated lateral prefrontal activity during a resistance to distraction component of the task. These effects only occurred for the high impulsivity participants and not the low impulsivity participants, which implicated reduced D2 receptor function as a moderating variable. Thus, high impulsivity and low D2 receptor activity may predict a positive response of WM to DA agonists [61]. The central role of D2 receptor function in RDS and its many subordinate conditions, e.g., ADHD, SUD, impulsive and compulsive behavior disorders [24], etc., argues for genetic testing for the A1 allele of the D2 receptor gene in the treatment of these disorders [62]. However, genetic testing for this gene variant [62] was not feasible in this study because we could not obtain approval for this request from the IRB. The idea that carriers of the DRD2 A1 allele fare much better with the KB220Z agent has been previously supported by Lawford, et al. [63] and Blum, et al [64]. In fact, we observed an improvement in

WM [33] in a participant with the A1 allele of the D2 receptor, following consumption of KB220Z.

The participants in this study were all adult college students, with a history of ADHD, but no current usage of medications for ADHD. A substantial percentage of children with ADHD will continue to be symptomatic into adulthood [7,65]. The developmental trajectory for ADHD reveals that the hyperactivity component of the disorder tends to improve with age but the inattention problems are likely to persist. The selection of adult, successful, non-medicated college students for our study suggests that we may not have included participants sufficiently symptomatic to reveal the full beneficial effects of KB220Z on DA function. A post-experiment review of the data for the five participants who were not included in this report indicated that one did not present symptoms sufficient to sustain a current ADHD diagnosis. In addition, two other participants produced EEG data that did not discriminate among the experimental conditions. Finally, two additional participants had EEG records with mixed effects, that is, electrical activation that was greater for the placebo condition (in theta and/or alpha frequency ranges) than the active treatment conditions (KB220Z). The issue of symptom severity and participant selection is important. Noble et al. [25], in their early research on genetic typing of individuals with alcoholism employed severe alcoholics to observe the behavioral expression of the A1 DR2 genotype. They found a positive relationship between the occurrence of the A1 allele of the D2 receptor gene and the presence of alcoholism, underscoring the importance of the severity of alcoholism as a marker for the presence of the A1 allele. These ambiguities may be resolved with improved, pre-experimental screening of participants. However, future studies will also benefit from genetic testing for at least the A1 allele [62], a gene variant that codes for the D2 receptor and contributes to RDS and ADHD. With due regard for the difficulties noted above, the participant in this case study demonstrates the value of pro-dopamine regulation for improvements in the behavioral, neuropsychological and electrophysiological correlates of ADHD and the need for additional follow-up research.

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Conflicts of Interest

KB holds patents and technological proprietary information assigned or licensed to Genus Health, LLC. KB owns stock in both Geneus Health LLC and Restoregen LLC through their company Igene, LLC. Drs. Steinberg, Modestino, Thanos and Blum are on the Scientific Advisory Board of Geneus Health.

Author Contribution

The draft was developed by BS and then edited by KB. EC conducted the neuropsychological assessments. All authors reviewed and made comments and approved the manuscript. EJM, along with BS carried out the hands-on experimental work. BS and KB developed the experimental design. The study was approved by the Curry College IRB.

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