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Low-Resolution Electromagnetic Tomography (LORETA) of changed Brain Function Provoked by Pro-Dopamine Regulator (KB220z) in one Adult ADHD case

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Abstract

Attention Deficit-Hyperactivity Disorder (ADHD) often continues into adulthood. Recent neuroimaging studies found lowered baseline dopamine tone in the brains of affected individuals that may place them at risk for Substance Use Disorder (SUD). This is an observational case study of the potential for novel management of Adult ADHD with a non-addictive glutaminergic-dopaminergic optimization complex KB200z. Low-resolution electromagnetic tomography (LORETA) was used to evaluate the effects of KB220z on a 72-year-old male with ADHD, at baseline and one hour following administration. The resultant z-scores, averaged across Eyes Closed, Eyes Open and Working Memory conditions, increased for each frequency band, in the anterior, dorsal and posterior cingulate regions, as well as the right dorsolateral prefrontal cortex during Working Memory, with KB220z. These scores are consistent with other human and animal neuroimaging studies that demonstrated increased connectivity volumes in reward circuitry and may offer a new approach to ADHD treatment. However, larger randomized trials to confirm these results are required.

Keywords

Kb220z; Low-resolution electromagnetic tomography (LORETA); Attention Deficit-Hyperactivity Disorder (ADHD); Cingulate Gyrus; Prefrontal Cortices; Dopamine.

Abbreviations

LORETA: Low-resolution electromagnetic tomography; ADHD: Attention Deficit-Hyperactivity Disorder; ACC: Anterior Cingulate Cortex; rCBF: regional Cerebral Blood Flow; fMRI: functional Magnetic Resonance Imaging; EEG: Electroencephalogram; SUD: Substance Use Disorder; CerDMN: Cerebellar Default Network; PFC-VTA: Prefrontal Cortex- Ventral Tegmental Area; RDS: Reward Deficiency Syndrome; QEEG: quantitative electroencephalography; BOLD: Blood-oxygen-level-dependent; ACG: anterior cingulate gyrus; DCG: dorsal cingulate gyrus; PCG: posterior cingulate gyrus; NMDA: N-Methyl-D-Aspartate; CPT3: Conner Continuous Performance Test; SCT: Sluggish Cognitive Tempo; ROI: Regions of Interest; DAT: dopamine transporter gene; Hz: Hertz; BA: Brodmann Area; DLPFC: dorsolateral prefrontal cortex.

Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is the most common childhood onset psychiatric disorder effecting up to 10% of children and frequently continues into adulthood [1]. Altered neurochemistry in the Anterior Cingulate Cortex (ACC) and right caudate [2] is thought to be an important cause of the behavioral symptoms of ADHD. Lou et al., [3] used SPECT to demonstrate that ADHD children experienced reduced regional Cerebral Blood Flow (rCBF), in the striatum, for tasks involving semantic processing and executive attention. Bush et al., [4] using functional Magnetic Resonance Imaging (fMRI) and a response interference task, found reduced activation of the cognitive division of the ACC in adults with ADHD. Makris et al., [5] used MRI to demonstrate thinning of the cortex in areas concerned with attention and executive functioning in adults with ADHD. The affected areas were in the right hemisphere and included the anterior cingulate, dorsolateral prefrontal and inferior parietal lobule regions. More recently, Bledsoe, Semrud-Clikemak & Pliszka [6] using MRI, reported cortical thinning in the right ACC of children with ADHD. The thinning of the right ACC predicted parent and teacher reports of ADHD symptom severity. Adults with ADHD demonstrate persistent problems with working memory, the ability to maintain and organize information in memory, prior to acting on the information [7]. Electroencephalogram (EEG) research with healthy subjects has demonstrated that successful recollection of words is associated with increased power in the theta band and greater desynchronization in the upper alpha band [8]. Intracranial recordings of cortical and subcortical EEG have also shown that memory for nouns, was predicted by power in the theta frequency band during encoding, for locations in the right temporal and frontal cortex [9]. Theta amplitude increased during a verbal, working memory task, was maintained during a delay period, and decreased at the end of the task, indicating that theta frequency oscillations were correlated with working memory functions [10]. A detailed study of spatial working memory in ADHD children demonstrated that they experienced reduced mid-occipital alpha desynchronization during encoding, which was predictive of memory performance. Both alpha power and mid-frontal theta power were elevated during the maintenance period of the working memory task. The authors concluded that vigilance and encoding difficulties compromise the maintenance of information in working memory for ADHD children [11].

Other areas, especially in the brain reward circuitry, impact behavioral symptoms, especially drug– and non–drug-seeking behaviors [12]. Dopamine neurotransmission has been previously identified as a crucial component of prefrontal cortical function and is impacted by many other primary neurotransmitters, neurogenetics, and epigenetics [13]. Regarding treatment, Yen et al., [14] used a mouse model of ADHD to demonstrate that decreased Glycogen Synthase Kinase 3β (GSK3B) is responsible for the calming effect of amphetamine, initiated through N-Methyl-D-Aspartate (NMDA) receptor signaling effecting the drive for dopamine release in the nucleus accumbens (NAc). It is established that psychostimulant treatment for ADHD is not optimal, and it has been shown in some studies but not all, that psychostimulant treatment increases the risk for co-morbid substance seeking behaviors [15-17]. Both genders with and without comorbidities have higher risk for Substance Use Disorder (SUD) [17] and while debatable, treatment of children with a psychostimulant is not protective against long-term SUD [18].

It is noteworthy, Kucyi et al., [19] found novel evidence of impaired Cerebellar Default Network

(CerDMN) linked to cortical networks in ADHD and highlights a role of cerebro-cerebellar interactions in cognitive function. The Kucyi et al., [19] data provides support for the potential targeting of CerDMN areas for therapeutic interventions in ADHD.

Neuroscientists are challenged to find better treatments for ADHD a known subset of Reward Deficiency Syndrome (RDS) having genetic and epigenetic antecedents to "hypodopaminergic trait / state" [20]. The development of the glutaminergic-dopaminergic optimization complex (KB220z) has taken decades of research. The benefit from treatment with KB220z has been characterized, in over 25 clinical trials including recent neuroimaging studies for many RDS behaviors including addiction. The quantitative electroencephalography (QEEG) and fMRI neuroimaging studies have shown substantial clinical utility with observed Blood-oxygen-level-dependent (BOLD) activation of Prefrontal Cortex-Ventral Tegmental Area (PFC-VTA) dopaminergic neurons leading to both enhanced resting state functional connectivity and volume in abstinent psychostimulant and heroin addicts [21-22].

To further determine the neuropharmacological effects of KB220z we decided to test the acute effect on brain function in an ADHD case by utilizing Low-Resolution Electromagnetic Tomography (LORETA) [23-24].

Case Presentation

This case study involved a 72-year-old male physician, diagnosed with ADHD, Inattention-type. SK has been highly functional but had a number of organizational and attentional problems. He had never been treated with amphetamine.

SK denies any history of restlessness in grade school, where he excelled, but reports he was a "class clown," who in both grade school and high school, would often blurt out answers as well as jokes in class. He reports that he was inclined to look out the window or watch the clock frequently during both grade school and high school.

SK remembers a tendency to tense his triceps and gastrocnemius muscles in grade school and currently notes an inclination to rub his thumb and first digit together (all motor tics). He denies any past or current tendencies to whistle, hum, sing, talk to himself under his breath, clear his throat or his nose repeatedly, or engage in coprolalia, palilalia or echolalia.

Medical History: The patient denies any major medical problems, such as hyperlipidemia, hypertension or coronary artery disease. He underwent surgery for a deviated nasal septum, when in high school. He reports a history of "dry eyes" and Chronic Pelvic Pain Syndrome (CPPS). Current medications include Hytrin 1-2 mg q d, p r n for CPPS.

Psychiatric History: SK underwent psychoanalysis for three years as a young adult. There was no (available) diagnosis of ADD or ADHD during the period when he attended grade school or high school.

Family RDS History: Both parents are deceased. SK, an only child, remembers his father as having one symptom (vocal tic), consistent with Tourette's syndrome (daily whistling). His father also had gambling and smoking addictions (2+ PPD). His mother had a period of alcohol dependence for eight years. His maternal grandfather and paternal grandmother suffered from alcoholism.

Personal RDS History: There is no history of addictive behavior or substance dependence. The

patient, consistent with his above ADD-type symptoms, reports a pronounced tendency to procrastinate and be disorganized.

A trial of Synaptamine (30ml per day) produced an increase in organizational ability with decreased procrastination; both noted the first day of its ingestion. Also, he was able to engage in the sustained reading of ordinarily uninteresting material, such as finishing an entire article in the Wall Street Journal on economics.

Mental status exam: The subject was oriented in all three spheres. His exam was unremarkable for significant mood, sensory/perceptual changes or thought disorder. Concentration was somewhat impaired, but there is no evidence of short-term memory impairment. Sleep and appetite are normal. There is no history of nightmares or lucid dreams.

ADHD Testing

SK's educational background includes completion of doctoral degrees in professional and academic areas of study. He presented with concerns relating to attention and organization and requested an evaluation for potential Attention Deficit Hyperactivity Disorder (ADHD).

On the day of LORETA testing, SK had a number of Pre-tests. He was evaluated with the Barkley Adult ADHD Rating Scale, the Barkley Deficits in Executive Functioning Scale, the Conner Continuous Performance Test (CPT3), as well as a clinical interview. Given SK's exceptional educational achievements his I.Q. was not tested but was estimated to be in the superior range.

SK described difficulties with sustained attention, problems following through on tasks, personal and professional disorganization, avoidance of activities requiring sustained mental effort and challenges with distraction. These difficulties have been long-standing concerns that occur in a variety of settings and affect his personal, social and occupational functions. His self-report of inattention symptoms on the Barkley Adult ADHD Rating scale places him in the 99th percentile for severity, relative to the normative group. Also, his total score for ADHD symptoms (including hyperactivity and impulsivity) placed him in the 95th percentile. These collective current symptoms are consistent with the DSM-5 criteria for Attention Deficit Hyperactivity Disorder, Inattention type. However, we have not been able to obtain sufficient evidence of a childhood onset of these symptoms. Accordingly, our diagnosis for SK is Other Specified Attention-Deficit Hyperactivity Disorder (insufficient childhood symptoms). Moffitt, et al, [25] reported on a forty year, longitudinal study of 1,037 individuals (born in 1972-1973) in Dunedin, New Zealand. They found a 6% childhood prevalence of ADHD, as well as an adult ADHD prevalence of 3%. The most interesting finding of the study was that the child and adult ADHD groups showed almost no overlap in their clinical characteristics, and 90% of the adult diagnosed cases had no childhood history of ADHD symptoms and no childhood neuropsychological deficits. The authors suggested that adult-onset ADHD may have a different etiology from childhood ADHD and this difference may require reconsideration of the diagnostic criteria for adult-onset ADHD.

In addition, SK endorsed several items on the Sluggish Cognitive Tempo (SCT) Scale, scoring in the 94th percentile. These items indicated issues with daydreaming, maintaining alertness in boring situations and processing information slower than other people. The Barkley Deficits in Executive Functioning Scale revealed high percentile rank scores reflecting problems with self-management to

to time (90%), regulation of motivation (93%) and regulation of emotion (97%). SK's scores on the CPT before the administration of KB220z suggested inattention problems but were inconclusive because he used a very conservative response style, trading speed for accuracy.

Method

Material: KB220z Liquid Nano Variant

This KB220z variant has been developed as an aqua –10-20 nano-sized, non-trans- fat formulation. Specifically, this variant of KB220z is comprised of the following ingredients at validated, evidence-based intake levels: thiamine, 15 mg, vitamin b6, 10 mg; Chromium poly nicotinate (as ChromeMate®) 200 mcg and Synaptose a fixed dose combination of herbs and amino acids. Synaptose is comprised of DL-phenylalanine, L-tyrosine, passion flower extract, white pine bark extract, and spirulina, Rhodiola Rosea (as RhodiGen™), L-glutamine; 5-hydroxytryptophan (5-HTP), pyroxidal-5-phosphate, pyridoxine HCl and a Metalloglycoside™ Complex. The Metalloglycoside™ Complex contains Arabinogalactans, N-Acetylglucosamine, Astragalus, Aloe Vera, Frankincense Resin.

LORETA Methodology

Nineteen channels of EEG data was acquired with a Deymed, Tru-Scan 32 amplifier, and Tru-Scan Acquisition software. The EEG data was gathered at 70 microvolts sensitivity and digitized at a rate of; 256 samples/second/channel. The EEG was analyzed with Neuroguide 2.8.4 software from Applied Neuroscience, Inc. The EEG data was collected during an "eyes closed", "eyes open" and a "working memory task", in that order, before and one hour after consumption of 30ml of KB220z. The EEG was collected for 4.5 minutes during the eyes open and eyes closed conditions, and until the subject (SK) made three consecutive errors during the working memory task.

The working memory task required the participant to listen to a random list of numbers and letters and then recall the sequence of numbers in ascending order and letters in alphabetical order. The lengths of the items are progressively increased.

The EEG data was corrected for eye movement, drowsiness and muscle artifacts, and artifact free epochs were selected for LORETA analysis. Regions of Interest (ROI) on the right side of the brain were chosen, based on their known relationship to brain networks sub-serving attention and working memory. We examined the anterior cingulate cortex (Brodmann area 32) at Talairach coordinates x = 4mm, y = 43mm and z = 15mm, as well as the dorsal cingulate cortex (Brodmann Area 24) at x = 4mm, y = 6mm and z = 38mm, and the posterior cingulate cortex (Brodmann Area 31) at x = 4mm, y= -57mm, and z = 23mm. While we did not have an a priori pre-conceived notion as to what ROIs KB220z would activate following the memory task, one of us (BS) carefully reviewed the resultant data first under the 7- Hz paradigm and found significant activation of the right dorsolateral prefrontal cortex. Then we analyzed the entire data set across all frequencies (4-13 Hz) and conditions and report herein our findings involving a number of ROIs. The ROI's were located in Brodmann areas 8, 9 and 46. Five of the regions were located in the right middle, frontal gyrus, and a sixth was located in the right superior, frontal gyrus.

LORETA Testing

The patient had been taking KB220z for approximately three months before this experiment. He

ceased taking KB220z for at least five days to allow for a washout period before LORETA testing. Baseline LORETA testing was followed by a retest one hour after oral administration of 30mls of KB220z.

Results

A QEEG analysis was performed on the baseline, Eyes Closed EEG record, to study the distribution of power across frequency bands and locations. QEEG analysis revealed a broad, distribution of theta (4-8 Hz) and alpha (8-13 Hz) activity in central, frontal and temporal regions.

In the figures power is measured in microvolts^2. The data are presented as z scores (standard deviation units), representing the deviation of power in each area of the brain from the values in a normative database of EEG records (see enclosed color scale). The top panel represents data for Absolute Power, the amount of energy in each frequency band, and the bottom panel present Relative Power, the amount of energy in each frequency band as a percentage of the total energy across all of the frequency bands. The small white circles represent electrode placements that conform to the; 10-20 International Electrode System.

The baseline QEEG data are presented in Figure 1. The data are shown as z-scores (standard deviation units) representing SK's percentile rank for absolute power in the EEG, for his age and gender, relative to a normative database of EEG records [24]. The QEEG indicates that theta and alpha power are 2-3 standard deviations above the values observed in the normative group.

The QEEG data for the Eyes Closed condition, following consumption of 30ml of KB220z, are presented below, in Figure 2.

The changes in z scores for QEEG absolute power, pre and post consumption of KB220z are summarized in Table 1.

Table 1 indicates that KB220z produced increased average z scores for QEEG absolute power, across 19 channels, in the theta and alpha frequency bands, with a decrease occurring in the high beta band. Beta power (12-25 Hz) remained essentially the same. The mid-line locations (Fz, Cz and Pz) demonstrated increased absolute power in response to KB220z, in the theta, alpha and beta bands, with high beta power decreasing or remaining the same. Finally, three right hemisphere locations (FP2, F4, and P4) demonstrated increased absolute power in the theta, alpha, and beta frequency bands, in response to KB220z, with a decrease in the high beta band.

The QEEG data show a general increase in the topographic distribution of theta and alpha activity, with the administration of KB220z. In light of the dominance of theta and alpha activity in the QEEG, we focused our LORETA analysis on theta (4-7 Hz), low alpha (8-10 Hz) and hi alpha (11-13 Hz) activity.

Several features of the data in Table 2 are noteworthy. A comparison of the average current source density values (represented as z-scores) for the baseline and the KB220z conditions reveal that theta, low alpha, and hi alpha power increased with the application of KB220z for the anterior cingulate gyrus (ACG), dorsal cingulate gyrus (DCG) and posterior cingulate gyrus (PCG). In almost all cases, the z-score for each frequency band and each condition increased with Kb220z.

With the change from Eyes Closed to Eyes Open, theta power decreased, and low and high alpha power increased during both the baseline and KB220z conditions, except for the low alpha power in DCG.

We examined the z scores for LORETA current source density for the Eyes Closed, and the Working Memory conditions, during baseline and following consumption of KB220z. We focused on theta, low alpha and hi alpha activity in five ROI's in the right middle, frontal gyrus and one ROI in the right superior, frontal gyrus. These ROI's were all located in Brodmann areas 8, 9 and 46, three anatomic regions that are common to the dorsolateral prefrontal cortex, an area known to be involved in working memory operations.

The data in Table 3 demonstrates that the average z scores for the right dorsolateral prefrontal area increased with KB220z for the theta and low alpha ranges during the eyes closed conditions, and increased for all frequency ranges during the working memory condition. The exception to this trend was high alpha activity, which decreased to a small degree, under eyes closed with KB220z. Notably, without KB220z, LORETA z-score values declined from the Eyes Closed to the working memory task, suggesting a relative reduction in the activity of the dorsolateral prefrontal ROI's. In contrast, under KB220z, theta activity increased during working memory, whereas low and high alpha declined. We should note that SK's performance on the working memory trial improved from 13 correct letter-number sequences (baseline) to 14 correct sequences with Kb220z.

It is noteworthy that with SK's approach to the Conner CPT, trading accuracy for speed, errors were minimal, but reaction time was unusually slow. Following consumption of KB220z, SK's reaction time shortened slightly, but was still slow, his response style was more balanced for speed and accuracy, and he made fewer perseverative errors (random, anticipatory or late responses). The decrease in perseveration errors suggests improved control over response inhibition.

The z-scores for SK's current source density in the cingulate and dorsolateral cortices, for theta and alpha frequencies, were high, indicating above average current flow relative to the normative group. This finding is consistent with data from [26] demonstrating a positive relationship between current source density and I.Q. The elevated z-scores for SK are consistent with his superior intelligence.

Discussion

ADHD is considered to be a hypodopaminergic trait in which the tonic pool of dopamine is attenuated [2]. Administration of stimulant medications raises the tonic pool by blocking dopamine transporter (DAT) and improves clinical symptoms. Our data demonstrate that KB220z, a pro-dopamine regulator, increases electrical activity in regions of the brain known to be involved in attention and behavioral self-regulation. Increases in the absolute power of the theta and alpha frequency bands were observed and measured with a quantitative analysis of 19 channels of EEG data. These increases in EEG power were notable in mid-line locations (Fz, Cz and Pz), generally overlying the anterior cingulate, dorsal cingulate and posterior cingulate regions.

Table 2 indicates that current source density (represented as z-scores) increased reliably in the theta, low alpha and high alpha bands, in the anterior cingulate, dorsal cingulate and posterior cingulate cortex, in response to KB200z. The anterior cingulate is the hub of the brain's anterior attention system [27-29] and moreover, has a vital role in integrating affect with action. The dorsal cingulate, however, is known to be involved in control over cognitive activity [30]. The improvement that SK showed in current source density in these two regions is consistent with his improved performance on the working memory

task; before (13 letter number sequences) and after KB220z consumption (14 letter number sequences), as well as, his improved reaction time and perseveration score on the Conner CPT.

With KB220z, the QEEG revealed increased theta and alpha power in right, pre-frontal regions (FP2 and F4). FP2 and F4 are areas that contribute to attention and working memory functions. The increase in electrical activity in Pz and P4, as well as FP2 and F4, with KB220z, is also interesting in light of prior research [21] demonstrating increased alpha and low beta power in the EEG of individuals with a D2 receptor, A1 allele. KB220z increased frontal and parietal activation in individuals believed to be less sensitive to dopamine. It is also important to note, that SK, experiences many of the symptoms of RDS and has shown a strong, positive response to KB220z.

Table 3 presents z-scores that represent current source density values for theta, low alpha and hi alpha frequencies for six ROI's in the right, dorsolateral prefrontal cortex. These values are presented for the eyes closed baseline condition and the eyes closed working memory task, both before and after consumption of KB220z.

Theta and low alpha activity increased in the right dorsolateral prefrontal area during baseline and the working memory task, following KB220z ingestion. The z-score for high alpha activity remained approximately the same during baseline and with consumption of KB220z without an information processing demand. However, z-score for high alpha activity increased with KB220z-with the information processing demand of the working memory trial. Also, without KB220z, average theta, low alpha, and high alpha z-scores all decreased in value, from baseline to the working memory task, indicating a reduction in right, dorsolateral, current flow under conditions of working memory demand. In contrast, with KB220z, theta activity increased during the working memory task, whereas low and hi alpha z scores decreased in value. These data are interesting in light of SK's improved working memory performance with KB220z. The literature documents the importance of theta activity for encoding semantic information in working memory [8-9] and the correlation between increased theta power and the accuracy of recall of semantic information [11]. Finally, across baseline and KB220z conditions, the reduction in low alpha power, during the working memory task is consistent with the increased attention demands of semantic processing [8].

The data from this case study indicate that KB220z produces an increase in absolute power QEEG in theta and alpha frequency bands, across a broad distribution of cortical areas. Also, LORETA analysis reveals that KB220z also increases current source density in mid-line structures (anterior cingulate, dorsal cingulate and posterior cingulate) known to be involved in attention and the cognitive control of behavior [31]. Finally, the LORETA data demonstrate that without KB220z, in a sample of ROI's from the right dorsolateral cortex, electrical activity decreases, relative to baseline, in the theta frequency range during a working memory task, however, electrical activity increases in this frequency range with KB220z, pro-dopamine regulation. This increase in dorsolateral prefrontal activity was associated with an improvement in SK's working memory performance.

Elevated theta activity is found in the EEG of children with ADHD [32], and has also been reported in the EEG of adults with ADHD, compared to normal controls [32-33]. The functional significance of this elevation in theta activity is not clear. Our data, summarized in Table 1, demonstrate that KB220z has a broad effect of increasing absolute theta across 19 cortical locations, including midline and right

prefrontal sites. Also, KB220z was associated with increased LORETA current source density values (z-scores), in the theta frequency range during the working memory task, for the anterior cingulate, dorsal cingulate and posterior cingulate regions (Table 2). These areas are important for attention and the cognitive control of behavior. Finally, we have observed increased theta activity (Table 3) with KB220z in the right, dorsolateral prefrontal cortex, at baseline and during the working memory task. This increase in theta electrical activity coincided with an improvement in SK's working memory performance. This improvement is consistent with studies demonstrating a positive relationship between theta power and the encoding of semantic information [8-9, 11], and the temporal correlation between increased theta and working memory operations [10]. Given these positive results, we theorize that KB220z is facilitating the operation of brain networks that subserve attention and working memory.

Limitations

In addition to the limitation of drawing conclusions from the exciting results of this single case study, there were some subject concerns. During the baseline and eyes open trials, SK was focusing on his breathing and practicing Mindfulness Meditation. He indicated on follow-up questioning that he does not practice meditation on a regular basis but focused on breathing during the trials to aid relaxation. While it is possible that focusing on breathing may affect the EEG, it is unlikely that this would occur in the absence of substantial experience with meditation. Also, the researchers visually examined the first 10 seconds of EEG data during the Eyes Closed, baseline condition (before breathing would have affected the EEG), and found that the EEG pattern was similar to that obtained during the full trial. Since SK used the same technique of relaxation before and following consumption of KB220z, any potential EEG effects of focusing on breathing would influence both the baseline and the KB220z conditions.

The second area of concern is that SK was using 2 mg. of Hytrin (Terazosin), an alpha 1 receptor antagonist, for the treatment of Chronic Pelvic Pain Syndrome. Recent research [34] with a mouse preparation demonstrates that treatment with Terazosin antagonizes the desynchronized EEG activity produced by Modafinil, inducing synchronous activity. It is well known that modafinil blocks epileptic seizures through enhancing GABAergic function and, as such, blocks the neuronal release of dopamine, which affects EEG synchronicity. We cannot determine if the dosage of Terazosin used by SK was a factor in the increased power of the theta and alpha frequencies. However, as is the case with SK's focus on breathing, the Terazosin would have operated equally in both the baseline and KB220z-conditions, and would not have been expected to have a differential effect.

Terazocin has been associated with increased EEG synchronization blocking modafinil effects [35-36]. Also, the subject (SK) reported that during both Eyes Close and Eyes Open conditions, he practiced focused breathing, with which he was acquainted from a continuing medical education training course on Meditation and Mindfulness. Overall, the combination of these factors may well have led to the predominance of slower EEG frequency observations.

Are Glutaminergic and Dopaminergic Pathways Therapeutic Targets for Reward Homeostasis?

It is recognized that glutamate and dopamine represent potential targets for novel treatments that modulate reduced functional connectivity, cocaine-seeking behavior and other RDS behaviors including ADHD [19]. Glutaminergic and dopaminergic pathways are affected by the chronic

psychostimulant administration. In cocaine self-administering rats, basal extracellular glutamate concentrations are reduced in the core of NAc, which also receives heightened PFC-evoked glutamate release. Evidence supports this heightened release and reduced tonic extracellular glutamate in drug reinstatement [19].

Additionally, it was recently shown that as cocaine intake escalates, phasic dopamine signaling in the ventromedial striatum is reduced [37]. The dopamine precursor L-DOPA was found to reduce escalated cocaine intake and restore striatal dopamine [37]. In ADHD, Badgaiyan et al., [2] found a reduced dopamine tone at baseline. Consistent with this result, in human subjects, L-DOPA was observed to increase functional connectivity between midbrain and striatal regions. This effect could presumably benefit ADHD individuals showing reduced functional connectivity in mesocorticolimbic circuitry [38].

Key ingredients in this complex act synergistically to replenish the pool of L-DOPA and facilitate its conversion to dopamine. The formulation is directed at re-establishing baseline connectivity through the dopamine biosynthetic pathway amongst other ingredients (L-Tyrosine and pyridoxine, which provides the enzymatic co-factor pyridoxal-5'-phosphate for L-amino acid decarboxylase conversion of L-DOPA to dopamine). KB220z variant has been tested in abstinent psychostimulant abusers and found to normalize QEEG abnormalities. Moreover, a preliminary double-blind cross-over study in heroin-dependent subjects shows increases in ventral striatal functional connectivity and connectivity volume [22]. Specifically, KB220z elevated functional connectivity between regions of the accumbens and the medial orbital cortex. These effects were supported in unpublished work that examined the effects of KB220z on functional connectivity and connectivity volume in rodents.

To reiterate, Willuhn et al. [37] reported that cocaine use and even non-substance-related, addictive behavior increase, as the dopaminergic function, is reduced. Chronic cocaine exposure and ADHD have been associated with decreases in D2/D3 receptors. Additionally, cocaine use has also been associated with lower activation by cues in occipital cortex and cerebellum. Therefore, dopamine homeostasis treatment strategies, like Pro-dopamine regulation therapy, such as KB220z that might conserve dopamine function, and Loretta Neurofeedback [24] may be a desirable approach to relapse prevention in ADHD and behavioral addictions.

Conclusion

Reduced resting-state functional connectivity has been found in naïve ADHD patients, compared to controls [38], and low dopamine tone at rest [2] in ADHD highlight the importance of seeking treatment options that improve dopamine homeostasis. Current psychostimulant treatment effects dopamine release in the NAc [14] but, is not optimal and has been linked to diversion and increased risk of the non-medical use of these drugs [39]. In fact, the NIH has encouraged scientists to seek alternative options. The pro-dopamine regulator, KB220z, is known to increase resting state, fMRI BOLD activity in human addicts and rodents [22]. Persistent issues with working memory [7] is another characteristic of ADHD. These first-ever findings using LORETA, albeit only involving one ADHD case, showed that KB220z was associated in this instance with activation of anterior cingulate and dorsolateral prefrontal cortices, resulting in enhanced EEG synchronization and improved working memory. To confirm these results and evaluate this potential nutraceutical treatment for ADHD larger randomized trials are required.

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Informed Consent and Ethics

The study was approved by the local ethical review board of the Path Foundation NY. The IRB approved the use of KB220 variants in the treatment of RDS in 2015. Written informed consent to participate was given by the patient before the study.

Figures

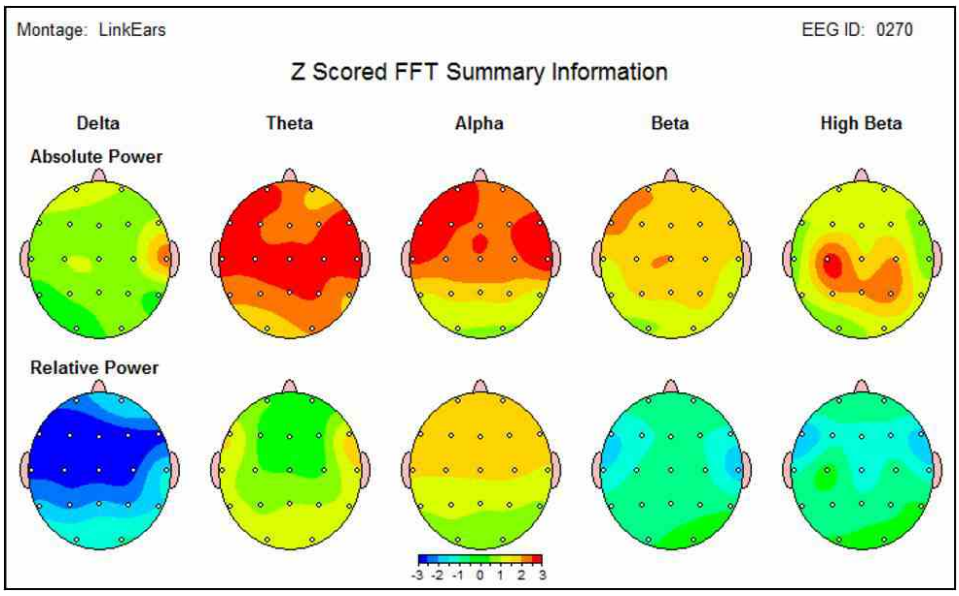

Figure 1: QEEG values (z-scores) for the Eyes Closed baseline condition
Eyes Closed, baseline, topographic map of power in the EEG in Delta (1-4 Hz), Theta (4-8 Hz), Alpha (8-12 Hz), Beta (12-25 Hz) and High Beta (25-30 Hz) frequency bands.

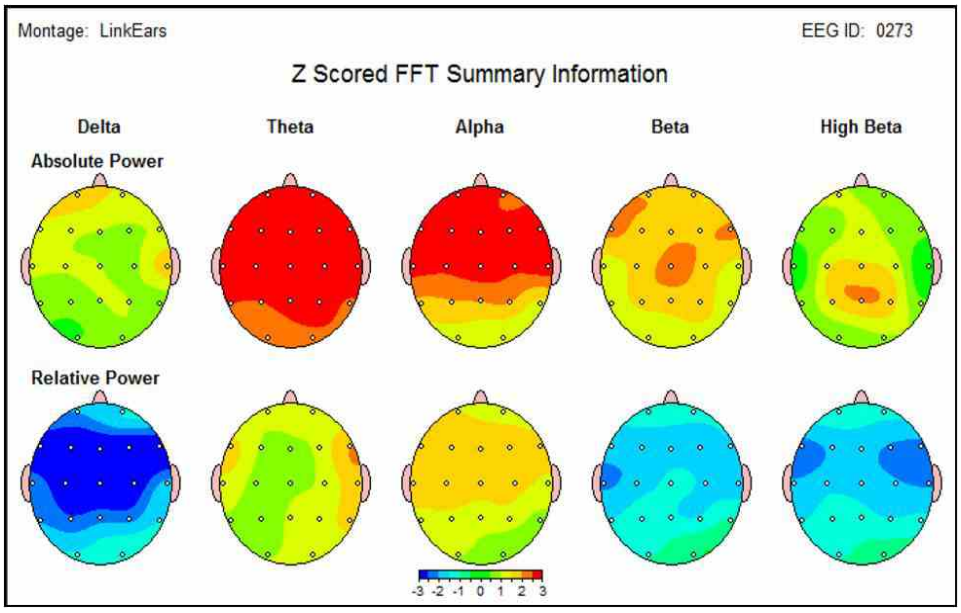

Figure 2: QEEG values (z-scores) for Eyes Closed, one-hour post consumption of 30ml KB220z.
Eyes Closed, post KB220Z, topographic map of power in the EEG in Delta (1-4 Hz), Theta (4-8 Hz), Alpha (8-12 Hz), Beta (12-25 Hz) and High Beta (25-30 Hz) frequency bands.

Tables

		Pre KB220z						Post KB220z		
Average of	Theta	Alpha	Beta	High Beta			Theta	Alpha	Beta	High Beta
19 Channels	4-8 Hz	8-12 Hz	12-25 Hz	25-30 Hz			4-8 Hz	8-12 Hz	12-25 Hz	25-30 Hz
Average	2.52	2.14	1.66	1.38		Average	2.92	2.34	1.67	1.00
Mid-line						Mid-line				
Locations						Locations				
Fz-Le	2.32	2.48	1.85	1.39		Fz-Le	2.96	2.7	1.9	1.26
Cz-Le	2.45	2.45	2	1.6		Cz-Le	3.29	2.74	2.11	1.59
Pz-Le	2.5	1.73	1.65	2.01		Pz-Le	2.9	2.03	1.79	2.02
Average	2.42	2.22	1.83	1.67		Average	3.05	2.49	1.93	1.62
Right Hemi						Right Hemi				
FP2-Le	1.96	2.31	1.58	1.14		FP2-Le	2.63	2.5	1.55	0.89
F4-Le	2.41	2.47	1.85	1.27		F4-Le	3.16	2.72	1.9	0.85
P4-Le	2.51	1.71	1.68	2.19		P4-Le	2.99	1.99	1.71	1.7
Average	2.29	2.16	1.70	1.53		Average	2.93	2.40	1.72	1.15

Table 1: Average z scores for absolute power by frequency band and electrode location before and after KB220Z.
Hz= one hertz equal to one cycle per second.

Baseline	BA 32	ACG	4, 43,15		BA 25	DCG	4,6,38		BA 31	PCG	4, -57, 23
Pre-KB220Z	Theta	Low Alpha	Hi Alpha		Theta	Low Alpha	Hi Alpha		Theta	Lo Alpha	Hi Alpha
	4-7 Hz	8-10 Hz	11-13 Hz		4-7 Hz	8-10 Hz	11-13 Hz		4-7 Hz	8-10 Hz	11-13 Hz
Eyes Closed	1.20	1.60	1.21		1.37	2.13	1.72		1.37	1.21	1.09
Eyes Open	0.67	1.98	1.49		1.31	2.69	2.54		1.05	1.57	1.44
Working Memory	0.96	1.30	1.17		0.51	2.22	1.69		0.16	0.70	0.73
Average	0.95	1.63	1.29		1.06	2.35	1.98		0.86	1.16	1.08
Post-KB220Z											
Eyes Closed	1.38	1.83	1.17		1.84	2.66	2.12		1.84	1.51	1.09
Eyes Open	1.16	2.23	1.55		1.50	2.62	2.58		1.34	1.79	1.52
Working Memory	1.35	1.33	1.31		1.42	2.38	1.97		0.60	0.90	0.97
Average	1.30	1.79	1.34		1.59	2.55	2.22		1.26	1.40	1.19

Table 2: Average z scores for LORETA current source density in the anterior (ACG), dorsal (DCG) and posterior (PCG) cingulate gyrus, by experimental condition, before and after KB220Z.
BA=Brodmann Area; Memory=Working Memory

Baseline											
Pre-KB220Z						Eyes Closed			Working	Memory	
Right DLPFC				Location	Theta	Low Alpha	High Alpha		Theta	Low Alpha	High Alpha
BA	X	y	Z		Average	Average	Average		Average	Average	Average
9	53	17	32	Mid Frontal Gyrus	1.16	1.83	1.57		0.15	1.37	0.76
9	46	28	32	Mid Frontal Gyrus	0.87	1.62	1.45		-0.08	1.14	0.62
9	39	40	33	Sup Frontal Gyrus	0.58	1.34	1.21		-0.28	0.81	0.32
8	46	18	48	Mid Frontal Gyrus	0.93	1.64	1.50		-0.03	1.24	0.73
46	46	25	32	Mid Frontal Gyrus	0.91	1.65	1.50		-0.06	1.20	0.68
9	53	4	37	Mid Frontal Gyrus	1.15	1.75	1.52		0.13	1.38	0.84
				Average	0.93	1.64	1.46		-0.03	1.19	0.66
Post-KB220Z						Eyes Closed			Working	Memory	
Right DLPFC					Theta	Low Alpha	High Alpha		Theta	Low Alpha	High Alpha
BA	X	y	Z		Average	Average	Average		Average	Average	Average
9	53	17	32	Mid Frontal Gyrus	1.17	2.19	1.52		2.36	2.14	1.15
9	46	28	32	Mid Frontal Gyrus	1.03	2.13	1.42		2.23	2.02	0.97
9	39	40	33	Sup Frontal Gyrus	0.86	2.00	1.23		1.91	1.80	0.71
8	46	18	48	Mid Frontal Gyrus	1.11	2.17	1.49		2.34	2.10	1.09
46	46	25	32	Mid Frontal Gyrus	1.07	2.17	1.47		2.33	2.08	1.05
9	53	4	37	Mid Frontal Gyrus	1.23	2.17	1.53		2.32	2.11	1.23
				Average	1.08	2.14	1.45		2.25	2.04	1.03

Table 3: Average z scores for LORETA current source density in the right dorsolateral prefrontal cortex, by frequency band, for Eyes Closed and Working Memory condition, before and after KB220Z
BA=Brodmann Area; DLPFC=dorsolateral prefrontal cortex.

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