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Measuring Cognitive Enhancement Through Pharmacology and Sleep Intervention

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Measuring Cognitive Enhancement Through Pharmacology and Sleep Intervention

DISSERTATION

submitted in partial satisfaction of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

in Cognitive Sciences

by

Tenzin Tselha

Dissertation Committee:
Professor Sara C Mednick, Chair
Associate Professor Alyssa A Brewer
Associate Professor Susanne Jaeggi

2022

DEDICATION

To
His Holiness the Dalai Lama,

my parents and teachers

in recognition of their kindness

"All the suffering there is in this world arises from wishing our self to be happy.
All the happiness there is in this world arises from wishing others to be happy."

— Shantideva,
The Way of Bodhisattvas

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FIELD OF STUDY

Sleep and Memory

PUBLICATIONS

"Tatti, R., Haley, M. S., Swanson, O. K., Tselha, T., & Maffei, A. (2017). Neurophysiology and regulation of the balance between excitation and inhibition in neocortical circuits. *Biological psychiatry*, *81*(10), 821-831."

"Tselha, T., Whitehurst, L. N., Yetton, B. D., Vo, T. T., & Mednick, S. C. (2019). Morning stimulant administration reduces sleep and overnight working memory improvement. Behavioural brain research, 370, 111940."

ABSTRACT OF THE DISSERTATION

Measuring Cognitive Enhancement Through Pharmacology and Sleep Intervention
by
Tenzin Tselha
Doctor of Philosophy in Cognitive Sciences
University of California, Irvine, 2022
Professor Sara C Mednick, Chair

Cognitive enhancement (CE) is the pursuit of enhancing and increasing the core mental capacity above the normal level. With the advancement of science and technology, many different approaches to carry out enhancement are available. The use of psychostimulants as the choice of cognitive enhancer is rapidly growing. Although anecdotal and subjective evidences claim that these drugs work, empirical evidence from studies in healthy adults show inconclusive evidences. One reason could be that these studies did not consider sleep as an important factor mediating the effect of stimulants on brain activities. My study 1 investigates the role of sleep in stimulant mediated CE. Along with sleep, there are other factors which are important when investigating the stimulants' effect of CE such as dosage, type of cognitive tasks, individual variability and bias of stimulant drugs toward certain cognitive domain. My study 2 investigates the evidences of bias by stimulants towards specific cognitive domain/s. Stimulants are addictive and comes with many side effects that may cause long term health issues. In my study 3, I investigated CE through targeted memory reactivation (TMR) which exploits the natural process of memory formation and strengthening during sleep with sensory stimulation to manipulate the memory strength. Specifically, in study 3 I developed a homebased- TMR protocol to selectively bias the weak and strong memories. This protocol was designed to carry out the

study amidst the COVID pandemic lockdown. I developed a brand-new spatial memory cognitive task for remote online participation. The TMR intervention protocol is suitable for real world and naturalist settings without the participants having to come to the lab. This new homebased-TMR protocol shows some promising results. With future improvement and refinement, it could be turned into fully automated unsupervised TMR system.

INTRODUCTION

Sleep Supports Cognitive Functions

Sleep is an evolutionary conserved brain state measurable in all species. The average human being spends one third of their life sleeping. During sleep the brain enters a unique state with low external interference. Along with its restorative processes, sleep is well known to be important and vital for a range of cognitive functions such as memory, attention, vigilance, etc. (Durmer & Dinges, 2005; Eugene & Masiak, 2015; Jackson et al., 2013). Generally, sleep is broadly classified into Non-Rapid Eye Movement (NREM) and Rapid Eye Movement (REM). NREM further consists of stage 1 (N1), stage 2 (N2) and stage 3 (N3) (Patel et al., 2020). N2 is characterized by the frequency of brain activity in the theta activity range (4- 7.5 Hz). This is interspersed by some unique features such as spindle wave of sigma activity (8-15Hz) and K-complexes (Steriade, 2000). Spindles event are marked by transient short burst of waxing and waning waves. Thalamocortical cell burst firing manifests as spindles, which look like their namesake in the EEG recording.

Sleep and specific individual sleep stages have been shown to support a wide range of cognitive activities in a significant body of studies (Diekelmann, 2014). NREM Stages 2 and 3 have been connected to the creation of long term memories (Rasch & Born, 2013) , whereas REM sleep has been associated to emotion processing (Walker & Helm, 2009). Sleep is also beneficial to working memory (WM). Kuriyama et al. found that sleeping rather than waking speeds up the improvement of WM performance (Kuriyama et al., 2008). Participants were trained on an N-back task with either 10 hours of wake time or 10 hours of overnight sleep in between re-testings. When compared to the wake group, the sleep group showed much better

WM improvement. Similarly, a recent study contrasted a period of wakefulness to a period of nocturnal sleep between WM test (Walker & Helm, 2009)

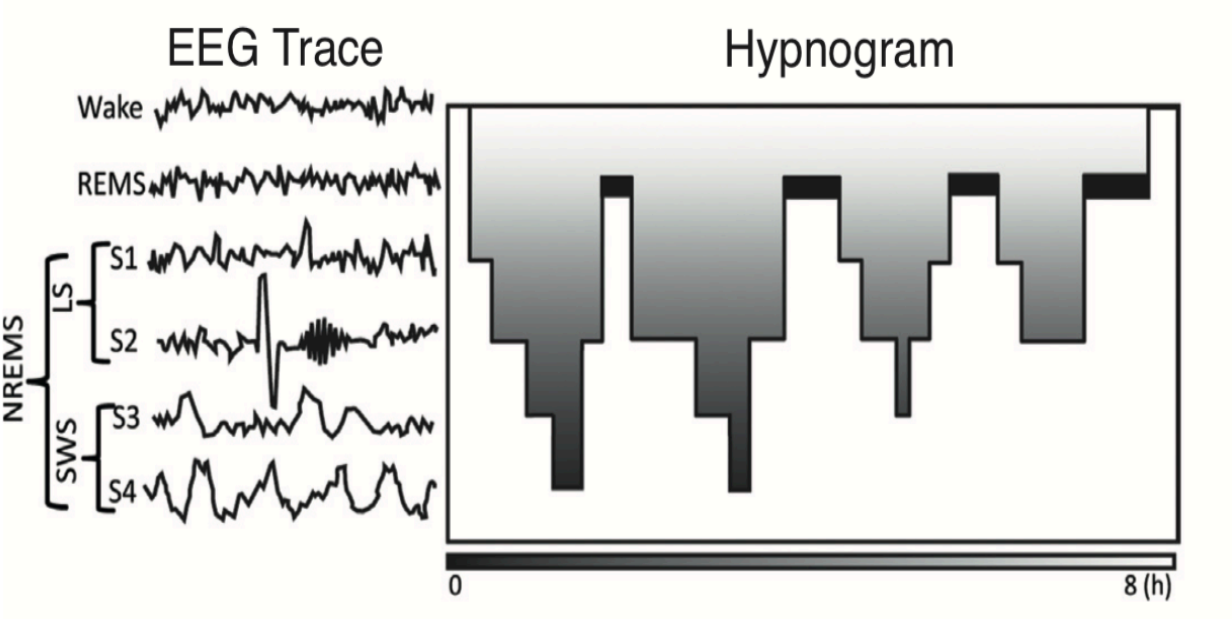

Figure 0.1: Sleep stages across a night of sleep with EEG signal representation of different stages. Hyponogram showing stages and duration in each stage. Figure taken from *Fonseca and Genzel, 2020. https://s100.copyright.com/AppDispatchServlet*

sessions, and found that both children and adults performed better during the sleep session than during the waking session (Zinke et al., 2018). In a similar vein, sleep deprivation has a deleterious impact on WM performance. During an extended duration of over-night awake,

healthy young volunteers were evaluated on an N-back task in one study. Their accuracy and reaction time declined in tandem with a rise in subjective and objective drowsiness measurements, including delta (0–4 Hz) and theta (4–8 Hz) frequency bands brain activity (Smith et al., 2002).

Cognitive Enhancement with Stimulants:

Advancement in science and technology, specifically in the fields like neuroscience and psychopharmacology have increased the possibilities for enhancing mental functions and capacities with different approaches. This motivation termed as cognitive enhancement (CE) is defined as amplification or extension of core capacity of the mind by improving the internal and external information processing systems (Bostrom & Sandberg, 2009). CE can be performed with different methods and approaches. Some of these methods are listed in the figure 1.

In the recent times, there has been increasing trend of non-medical use of prescription of stimulants. There has been a roughly more than a 10 fold increase in the use of off-label stimulant for cognitive enhancement in the last 2 decades (Klein-Schwartz, 2002; Wilens et al., 2008).

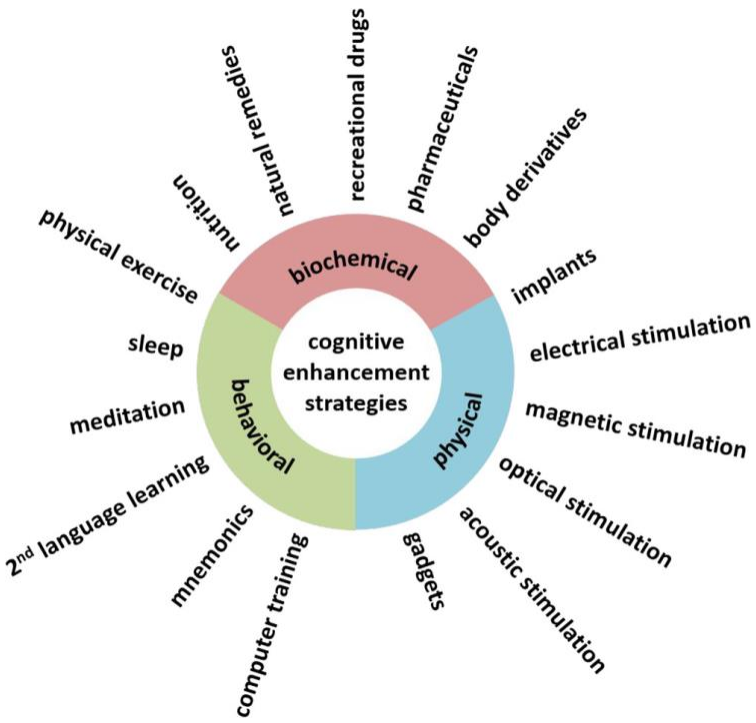

Figure 0. 2: Different approaches for cognitive enhancement. Figure taken from *Dresler et al., 2019*

Conservative estimates suggest roughly 11 million people in the US alone report using stimulant medications for cognitive purposes (Swanson et al., 2011). Up to 35% of college students in some studies endorsed the use of stimulant medications for cognitive gains. Motivation for using stimulants increasing concentration, increasing awake time, enhancing cognitive performance to improve overall professional and academic productivity. In demanding situations like military and shift workers where extended wakefulness is necessary, there are data to suggest that these drugs may help promote cognition. In these contexts, stimulants help to maintain alertness, visual attention, and they have also been shown to support planning and spatial working memory. However, in normal circumstances and people with relatively good health the results are quite mixed with differential effects across cognitive domains (Smith & Farah, 2011).

Additionally, there are also mixed effects within cognitive domains, specifically the memory domain, with a few studies showing that stimulants can boost memory, and others showing that is not the case (Repantis et al., 2010; Smith & Farah, 2011). However, these studies have not considered sleep which is an important factor necessary for supporting normal cognitive function. One of primary reason for off-label stimulant use is to increase wakefulness and alertness. Research show that individuals with a history of off-label use report decreased subjective sleep quality as well as increased nighttime sleep disturbance (Stein et al., 2012) . Additionally, psychostimulant (PStim) drugs are known for reducing both the quality and quantity of nighttime sleep (Comer et al., 2001). Sleep benefits cognition, and the interaction between stimulants, sleep, and cognition in healthy adults has received little attention. My completed study 1 attempts to investigate the effect of stimulants on sleep and working memory.

Many of the previous studies investigating the effect of stimulants in healthy adults under normal circumstances show inconclusive results in terms of cognitive enhancement capability of stimulants. There are different factors besides sleep which may explain the mixed findings. Different studies reported the effect of PStim on cognitive abilities using different drug doses which varies by types of Pstim used. Also, different studies have used multitude of different cognitive task testing long term memory (LTM), WM, selective attentions and other executive function task. One important factor is the diversity in individual baseline for cognitive capacity. Studies have shown that Pstim is more efficient for low baseline individuals (Mattay et al., 2003). This may be directly related to differences in individual dopaminergic activity level with benefit of Stim for low baseline activity levels (Dresler et al., 2019). Last but not the least, previous studies did not consider the limitations in cognitive capacity resources and inter-domain competition for the limited resource (de Jongh et al., 2008; Dresler et al., 2019). Such that gain for one domain can mean loss for other.

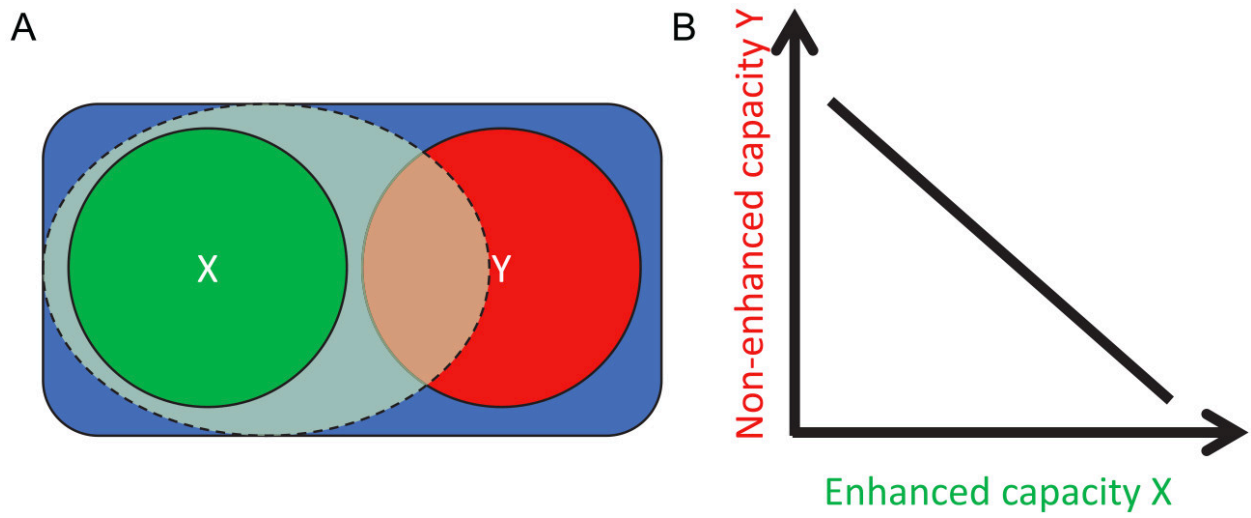

Figure 0.3: The principle of neural competition. In the figure A, X and Y represents two cognitive domains. When X is enhanced and utilizes more resources, it takes up the resource of Y leading to Y domain's compromise. Similarly, figure B, shows that as X domain capacity is enhanced, Y capacity decreases. Figure from *Colatzo et al, 2021* *https://creativecommons.org/licenses/by/4.0/*

According to the theory of Neural-Competition the interaction between brain's subsystems is net zero-sum such that, subsystems are competing for the limited resources of the brain (Colzato et al., 2021). In my completed study 2, I investigated the differential influence of stimulant dextroamphetamine on working memory and spatial selective attention in the form of multiple object tracking.

Manipulating Sleep for Cognitive Enhancement:

Sleep is a non-homogenous brain state with diverse stages and features. As discussed earlier, these stages and features play unique role in supporting different cognitive functions. The offline, low- interference state of the sleeping brain provides a fertile ground for the brain to

consolidate the previously encoded memories without any external interference. This view of sleep state as an opportunity for hippocampus-related memory consolidation to occur when the hippocampus is not actively encoding new memories is put forth by the Opportunistic theory of cellular and system consolidation (Mednick et al., 2011). Various studies have underscored the important role sleep plays in memory consolidation such that the memory performance is superior after a period of sleep when compared to an equal duration of a wake period between the learning and the testing (Marshall & Born, 2007). This is true for multiple domains of memories such as declarative, procedural and emotional. For instance, long-term memory formation is supported by NREM sleep stage 2 (Rasch & Born, 2013), whereas REM sleep has been linked with the processing of emotions (Van Der Helm and Walker, 2009).

In the light of vital cortico-hippocampal dialogue necessary for memory consolidation as encompassed in the System Consolidation theory described above, several studies show the evidences supporting sleeps role in in this dialogue. For example, the reactivation of memory traces during sleep was seen in the rat brain. In the study, rats' hippocampal place cells displayed a pattern of brain activity during SWS that was similar to the brain activity pattern during wake learning period (Wilson & McNaughton, 1994). This phenomenon was also seen in the human brain where, with the use of neuroimaging approach, it was found that the brain regions active during learning period undergo similar activation during SWS (Peigneux et al., 2004). Adding to the System consolidation theory, subsequent theories like Active System Consolidation (ACS) theory added more details to the mechanistic understanding cortico-hippocampal interaction related to consolidation process and how sleep uniquely facilitates this.

Active System Consolidation (ACS) theory laid down a more detailed role of unique sleep features involved this interaction. It proposes that an active consolidation process is caused by selective re-activation of memories during sleep (Diekelmann & Born, 2010; Marshall & Born, 2007; McClelland et al., 1995). Specifically, according to the ACS, SO events during SWS

provide the temporal framework for the hippocampal-neocortical interactions, such that large depolarizing up-state of the SO drives the hippocampal reactivation of the memory network. Furthermore, activation of cortico-thalamic network during the SO up-state leads to the generation of spindles, a key player in the interaction. Spindle generation along with hippocampal SWR lead to reactivation of memory trace in the hippocampus and concurrent reactivation in the neocortical network leading to re-distribution and stabilization of memory traces for long-term storage. The coincidence of SO, spindle and SWR is proposed to be the key feature in the dialogue for memory consolidation (Sirota et al., 2003). The unique roles of these features can be manipulated to modify the memory formation process and thus influence the strength of the memory.

Targeted memory reactivation (TMR), a type of CE through sensory stimulation, exploits memory consolidation mechanisms to manipulate the strength of memory consolidation, which refers to the process of transforming the vulnerable memory trace into a lasting state by increasing its resistance to interference (Lechner, 1999). This technique involves reactivating a memory trace via sensory cues during sleep that were earlier associated with memory events during their encoding. Memory trace represents learning induced change in neuronal circuit and activity (Thompson, 2005). The manipulation of memory trace or representation during sleep with the introduction of TMR is dependent on specific stages of sleep, specific sleep features and the coupling of these features. Targeted memory reactivation (TMR) attempts to influence memory-consolidation processes by leveraging the natural memory reactivation during sleep. In a typical TMR protocol, sensory cues are associated with objects during the wake-encoding phase. When these formerly associated cues are reintroduced at suboptimal strength during sleep, these cues are believed to drive spontaneous re-activations above the natural level (Cellini & Capuozzo, 2018; Schouten et al., 2017). Considering the findings so far, TMR represents a promising avenue for CE without the involvement of drugs. In my study 3 I

developed a home based TMR protocol to bring about CE by selectively strengthening the weak memories above their natural memory strength level. The details of the study are explained in the relevant chapter.

Chapter 1:

Study 1: Morning stimulant administration reduces sleep and overnight working memory improvement

1. Introduction:

As human society has gradually evolved to value mental capabilities over physical ones, the desire to enhance mental aptitudes seems a befitting response to the demands of the modern world. This compulsion to compete and outpace others is a motivation behind the pursuit of cognitive enhancement, in which individuals seek to 'amplify and extend core mental abilities' to improve performance on a range of cognitive domains, including working memory, attention, and control processes (Bostrom & Sandberg, 2009). Many are turning to pharmacology, including readily available stimulant drugs like caffeine and nicotine, that have been shown to improve alertness, vigilance, and attention (Newhouse et al., 2004; Tieges et al., 2004). Another growing trend in students and young professionals is the off-label use of prescription psychostimulants to promote wakefulness and boost cognitive performance. These drugs, such as methylphenidate (MPH), dextroamphetamine (DEX), and mixed-salt amphetamine, prescribed for the treatment of Attention-Deficit-Hyperactivity-Disorder (ADHD) are currently being diverted into college campuses and work-places for their perceived cognitive enhancing effects. Though, compared with PBO, psychostimulants enhance performance in the context of sleep deprivation (Gill et al., 2006; Repantis et al., 2010), studies in healthy non-sleep deprived

adults show conflicting findings (Smith & Farah, 2011), with positive (Ballard et al., 2012; Linssen et al., 2012; Soetens et al., 1993, 1995), negative (Elliott et al., 1997; Ilieva et al., 2013), and null effects (de Wit, 2002; Mommaerts et al., 2013).

Working memory (WM) is widely believed play a core role in cognitive ability, and has been shown to correlate with broad measure of cognitive ability and fluid intelligence (Fukuda et al., 2010; Johnson et al., 2013). Studies of psychostimulant effects on WM in healthy, well-rested adults report a mix of findings. Among the positive outcomes, a within-subject study compared the impact of 10mg and 20mg of DEX to PBO on a WM digit span task in healthy young adults. Compared with PBO, DEX showed a dose- dependent improvement in performance (de Wit, 2002). Additionally, Mattay et al. (Mattay et al., 2000) investigated the effect of D-amphetamine (0.25 mg/kg body weight) on an N-back task performance. They found that D-amphetamine benefitted the more demanding 3-back vs 2-back condition (Mattay et al., 2000). On the other hand, Ilieva et al. (Ilieva et al., 2013) administered 10 mg mixed salt amphetamine in healthy young subjects to study the objective and subjective effects of the drugs on a range of cognitive tasks, including WM (digit span and object-N-back) and found no stimulant-related benefit for WM. Accordingly, a meta-analysis found that the overall effect of psychostimulants on cognitive enhancement is inconclusive (Smith & Farah, 2011), and that the literature is plagued by several issues that make comparison across studies difficult, including different subject demographics, drug compounds, and dosages.

Sleep is another unconsidered factor that might help explain the discrepant findings across studies. Sleep is usually categorized into Non-Rapid Eye Movement (NREM) sleep and Rapid Eye Movement (REM) sleep. Within NREM sleep, the stages of sleep (1–3) progress into lower frequency, higher amplitude waves on the electroencephalographic (EEG) recordings. REM sleep is characterized by high frequency, mostly desynchronized waves that show a similar pattern to wake. A large body of research has demonstrated that sleep, and specifically

individual sleep stages, support a wide range of cognitive processes (Diekelmann, 2014). NREM Stage 2 and Stage 3 supports long-term memory formation (Rasch & Born, 2013), whereas REM sleep has been linked with the processing of emotions (Walker & Helm, 2009).

Sleep also supports WM. Kuriyama et al., showed that sleep, compared with wake, accelerates improvement in WM performance (Kuriyama et al., 2008). They trained participants on an N-back task with either 10 h of wake or nighttime sleep between retesting. Significantly greater WM improvement was seen in the sleep group compared with the wake group. Similarly, a recent study compared a period of wake to a period of nocturnal sleep between WM test sessions, and showed an improvement in performance across the sleep session, compared to wake in both children and adults (Zinke et al., 2018). Along the same lines, sleep deprivation negatively affects WM performance. In one study, healthy young subjects were tested on an N-back task during an extended period of over-night wakefulness. Their task accuracy and reaction time deteriorated in conjunction with an increase in both subjective and objective measures of sleepiness; including brain activity in the delta (0–4 Hz) and theta (4–8 Hz) frequency bands (Mehringer et al., 2001).

Importantly, amphetamines promote wakefulness by reducing total sleep time, sleep efficiency (total sleep time/minutes in bed), minutes in REM and Stage 3, and increasing Stage 2 (Barbanoj et al., 2007; Rechtschaffen & Maron, 1964). However, the impact of psychostimulant sleep disruption on cognitive processes has not been thoroughly investigated. One unexamined question is whether the deleterious impact of stimulants on sleep may play a role in the drug's impact on cognition. Most studies examining the effect of these drugs on cognition do not measure sleep. Given the growing trend in use/ abuse of these drugs and recent understanding of the importance of sleep for health and cognition, the goal of the present study was to measure the impact of psychostimulants on WM and sleep. Using a double-blind, placebo-controlled, repeated measures design, we examined the effect of dextroamphetamine (DEX, 20

mg) on repeated WM testing and overnight sleep. We administered DEX in the morning on Day 1 and tested WM several times across the day, subjects then slept in the lab while monitored with polysomnography and were tested on WM in the morning. We hypothesized that DEX would promote a temporary boost to WM compared with PBO. In addition, we predicted a significant deterioration in nighttime sleep in the DEX group, compared with PBO, followed by significant decreases in WM performance the next morning.

2. Methods

A total of 46 healthy (22 female), non-smoking participants between the ages of 18–39, with no personal history of psychological, neurological, or chronic illness participated in the study. To control for prior sleep, subjects were required to keep a specific sleep schedule. Specifically, subjects went to sleep and woke up within a two-hour bedtime and wake time window-Bedtime: 10:00PM-12:00AM; Wake time: 6:00−8:00AM. Subjects were asked to maintain this regular sleep schedule for 7 days prior to each experimental visit to ensure approximately 7 h of sleep each night. For the night before the study day, the subjects had to ensure that they get at least 7 h of sleep and adjust their sleep schedule to report to the lab the next day by 8:00am. This schedule was confirmed via daily sleep diaries and a wrist-based activity monitor (Philips Respironics, USA). Participants gave informed consent to participate in the experiment, which was approved by the Western Institutional Review Board and the University of California, Riverside Human Research Review Board. Participants received monetary compensation for their participation in the study.

We used a double-blind, placebo-controlled design in which all subjects experienced both drug conditions. Each visit occurred a week apart to allow for drug washout. Each visit corresponded to one of the drug conditions, DEX or PBO, and drug conditions were counter- balanced across participants. Participants were extensively screened for their eligibility to participate in this study

and were excluded if they did not follow a regular sleep schedule or if they reported: personal history or familial history of a mental illness, substance abuse, personal history of head injury with a loss of consciousness greater than two minutes or seizures, irregular sleep/wake cycles, history of parasomnias, and any cardiac or respiratory illness that may affect cerebral metabolism. Eligibility was determined during an in-person assessment in which research personnel conducted a structured clinical interview for DSM- IV psychological disorders as well as reviewed a series of self-report health and wellness questions as approved by the study physician. In addition, we administered the Assessment of Hyperactivity and Attention (Mehringer et al., 2001) to screen for symptoms of ADHD. After the in-person eligibility interview, participants underwent a standard health and physical exam conducted by the study physician to certify their health and eligibility. Participants were then required to submit to a urine toxicology test to ensure they had not used any substances not permitted by the study prior to their participation. All subjects were naïve to or had limited contact with (< 2 lifetime uses and no use in last year) the active medication in the study.

On each experimental day, subjects arrived to the lab at 8:00am (Fig. 1). After confirming that the subjects followed the required sleep schedule and adequately slept the night before, they were given breakfast. Their subjective sleepiness of the initial morning (AM1) was assessed with the Karolinska Sleepiness Scale (KSS) questionnaire (Kaida et al., 2006). The baseline performance for the WM task (details discussed below) was assessed at 8:30am. At 9:00am, participants received their first drug administration, which was either DEX or PBO. Seventy-five minutes later, another WM assessment was taken (Test 1), followed by a break during which participants could watch television, eat lunch, or work on their computer. After drug administration, subjects' vital signs were monitored every hour. Subjects were allowed to leave the lab after 4 h of monitoring if their: 1) systolic blood pressure was below 140 and diastolic blood pressure was below 90, 2) resting heart rate was below 100 beats per minute, 3) gait

measurements were sufficient, and subjects did not report experiencing a racing heart, dizziness, headache, or nausea. Upon their departure, subjects were told to refrain from caffeine, naps, and exercise during their time out of lab and were asked to confirm abstention upon arrival back to the lab. Subjects returned to the lab for another WM testing session at 9:00pm (Test 2). After completion of the task, subjects were then attached with 32-channel electroencephalogram (EEG) cap to monitor their sleep throughout the night (see below). Lights out occurred at 11:00PM and subjects were provided 10 h of time in bed. This was to ensure that the subjects had enough sleep opportunity. Subjects were awoken the next morning at 9:00am. After taking a KSS questionnaire (AM2), the subjects were tested on the WM task at 10:30am (Test 3) before being permitted to leave the lab at 11:00am. Before leaving, subjects were provided a final blood pressure reading, pulse reading, and gait assessment to ensure subjects' safety upon leaving the lab. For all subjects, the on-call doctor was regularly consulted throughout the study and for any concerns about subjects' ability to leave the lab.

We administered 20 mg of DEX, a stimulant drug that inhibits the reuptake of catecholamines, dopamine, and noradrenaline, prepared by MDMX Corona Pharmacy. DEX is an FDA approved drug to treat ADHD (Daughton & Kratochvil, 2009). We chose 20 mg dosage as previous works by De Wit et al. (de Wit, 2002) showed an improved performance in WM digit span task at this dosage. The PBO as made of microcrystalline cellulose and contained no active medications. DEX powder was encapsulated and visually indistinguishable from the PBO capsules.
We utilized an operation span task (Fig. 1) that measured a subject's capacity to maintain and actively manipulate information in WM prior to a response time. We chose the operation span task as it engages and captures both the memory retention and online processing capacity of WM. Participants were shown a string of letters (4–8) on a computer screen and were asked to remember each letter in the exact order they were presented. Between the letters, subjects were shown simple mathematical equations (e.g. 4 + 2 = 6 and 6 + 3 = 5) and were prompted to

use keyboard response to determine if the presented equations were correct or incorrect. Participants were provided three seconds to respond to each equation. The mathematical task was utilized as a distractor task to discourage online rehearsal of the letters. After each trial, subjects were provided a short break and moved to the next trial after a keyboard press. Subjects were required to maintain at least 70% accuracy on the mathematical distractor for the trial to be included in the analyses. Subjects were given practice trials at the start of each test session. Test trials were grouped into “short” versus “long” conditions in which short trials were defined as 4–5 to-be- remembered letters and long trials were defined as 6–8 to-be-remembered letters.

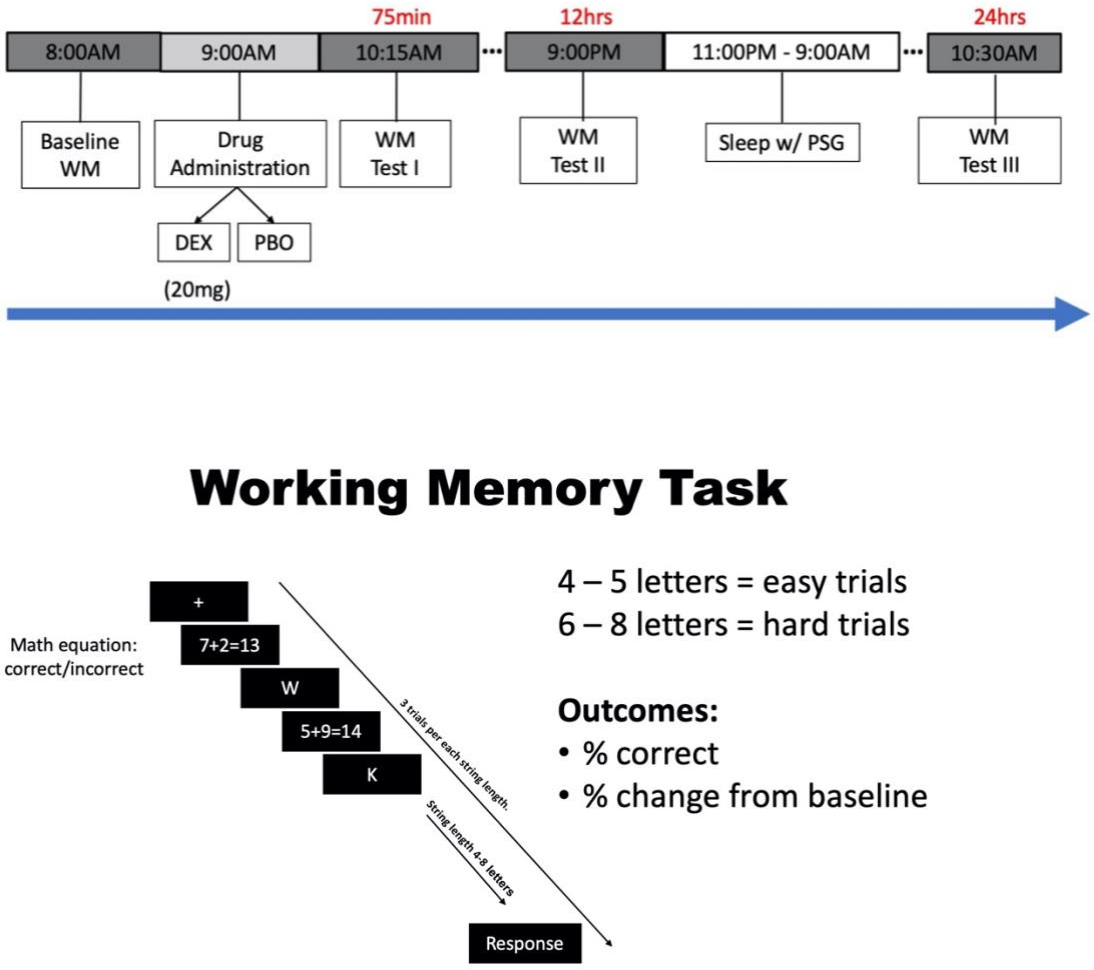

Fig. 1.1. Protocol and Task Figure.

We employed the Karolinska Sleepiness Scale (KSS), a 9-point scale to measure the sleepiness of the participants throughout the study day visits. KSS was tested at the onset of the initial morning visit (AM1) and the morning after the experimental sleep night (AM2).

2.1 Data Reduction

12 subjects did not complete both visits due to scheduling conflicts. For these subjects, we used their behavioral and sleep data, when applicable, and degrees of freedom are reported with each analysis for clarity.

2.2 Statistical Analysis

For prior sleep data analysis, we used paired t-tests to compare total sleep time (TST), WASO (Wake After Sleep Onset), SE (Sleep Efficiency) of the 7 days of sleep prior to each visit (DEX vs PBO) and the night before each visit (DEX vs PBO). Average bed/wake times and delay between wake time and test time are also reported. We ran 2 (DEX vs PBO visits) X 2 (AM1 vs AM2) RM ANOVA to investigate if the KSS score between PBO vs DEX visits and AM1 vs AM2 are comparable. To investigate the effects of the two drug conditions on the sleep quality, we used paired sample t-test. We examined the impact of DEX or PBO on nighttime sleep variables via a t-test on variables of: SE, TST, WASO, minutes in S1, S2, SWS and REM. To compare WM performance in the two conditions (DEX vs PBO), we first examined raw performance across each test and employed 2 (string length) X 2 (drug condition) X 3 (Performance Test) RM ANOVAs to compare the performance change between the DEX and PBO conditions across each Testing instance (Test 1: 75 min. post drug; Test 2: 12 h post drug; Test 3: 24 h post drug). To examine performance change, we calculated difference scores between baseline and each test and utilized the same 2 (string length) × 2 (drug condition) × 3 (Performance Test) RM ANOVAs. To control for differential drug absorption rates across our subjects due to weight, we entered weight (mean centered) as a covariate in each of these analyses. We also considered sex as a covariate in our analysis but performance nor sleep outcomes varied as a function of sex, so it is not included in the presented analyses. Lastly, we employed Pearson's correlations to examine the relationships between sleep features and WM performance. We consider $p < 0.05$ as significant and report effect sizes wherever applicable. For paired t-tests,

we used repeated measure design effect size(dRM) calculation which takes correlation coefficient into account (Morris & Deshon, 2002) and for ANOVA we report partial eta squared. IBM SPSS Version 25 software was used for all statistical calculations.

3. Results

3.1 Prior sleep

We first confirmed that there were no significant differences in actigraphy for the seven days prior to the in-lab visits. Sleep features were similar for both the week prior and the night before for PBO vs DEX visits: TST ($t28 = 0.114$, $p = .91$, $dRM = 0.022$), SE ($t28 = 2.0$, $p = .055$, $dRM = 0.44$), WASO ($t28 = -2.139$, $p = 0.041$, $dRM = 0.43$) and eve of the experimental day: TST ($t28 = -0.62$, $p = .53$, $dRM = 0.118$), SE ($t28 = 0.8$, $p = 0.42$, $dRM = 0.146$), WASO ($t28 = -1.63$ $p = 0.1$, $dRM = 0.33$). During the seven days prior to each experimental visit, subjects slept an average of 7 h 53 min of sleep, and for the night before each experimental visit, subjects slept an average of 7 h 6 min of sleep. For the week before each experimental visit, the average bed and wake times were 11:57 pm and 7:47 am for PBO visit, and 11:52pm and 7:40 am for DEX visits. The average bedtimes and wake-up times for the eve of the experimental night's sleep were 11:30pm and 6:48am for PBO visit and 11:22pm and 6.53 am for DEX visit. These times indicate that subjects may have been sleepier on the experimental morning, but that this sleepiness was similar across DEX and PBO conditions. On the study day visits, the mean delay between wake-up time and test-time was 102 min for PBO and 97 min for DEX. Morning sleepiness assessed by the KSS in the AM on Day 1(AM1) and Day 2(AM2) was not significantly different across drug conditions or sessions (AM1 vs AM2). With 2 × 2 RM ANOVA on KSS score (Drug condition visit (PBO vs DEX)) X Session (AM1 vs AM2), we did not find a significant main effect $F(136) = 0.133$, $p = 0.717$ partial eta square = 0.004 or interaction effect, Drug X Session : ($F(136) = 0.456$, $p = 0.504$ partial eta square = 0.013). The mean KSS score were DEX: AM1=3.43, AM2=3.6 and PBO: AM1=3.37 and AM2=3.86. In sum, we confirmed that

the prior sleep was similar for the two drug conditions, and sleepiness did not differ between drug conditions.

3.2. Stimulant vs placebo and nighttime sleep

To examine the impact of stimulants on subsequent nighttime sleep, we measured the effect of DEX vs PBO on seven polysomnographically-measured variables using paired samples t-tests: TST, Stage 1, Stage 2, SWS and REM mins, SE, and WASO using a paired samples T-tests (Table 1). Compared with PBO, the DEX condition showed lower SE ($t33 = 5.47p < 0.001$), lower TST ($t33 = 4.68$ $p < 0.001$), higher WASO ($t33= -3.71$, $p = 0.001$), decreased minutes in REM sleep ($t33 = 4.54$, $p < 0.001$), S2 ($t33= -2.06p = 0.047$), and SWS ($t33 = 2.41$, $p = 0.022$), whereas S1 duration was significantly longer ($t33= -3.48$, $p = 0.001$). Also, onset to REM, S2 and S3 duration was longer for DEX ($t33 = 4.71$, $p < 0.001$, $t33 = −2.06$, $p = 0.001$ and $t33 = 3.95$, $p < 0.001$, respectively).

Next, we examined the impact of DEX vs PBO on WM performance both pre- and post-sleep. First, we confirmed that there were no differences in baseline performance across the two experimental days with a paired t-test. For both short trials ($t33 = −318$ $p = 0.752$ dRM = 0.07) and long trials ($t33 = −1.77$ $p = 0.084$ dRM = 0.29), no significant differences were found. Using a 2 × 2 X 3 RM ANOVA (string length (short vs long) X drug condition (DEX vs PBO) X Test Performance (Test 1, Test 2, Test 3), we found a main effect of string length ($F(1,32) = 190.437$, $p < 0.0001$, partial eta square = 0.856), with short strings having better performance, but no main effect of drug ($F(1,32) = 0.203$, $p = 0.655$, partial eta square = 0.006), or session ($F(2,64)=) = 0.922$, $p = 0.403$, partial eta square = 0.028). We did find a significant string length X drug condition X test performance interaction ($F(2,64) = 4.04$, $p = 0.022$, partial eta square = .112). Post hoc analysis revealed a significant difference between Test 1 and 3 for PBO (dRM = 0.45, $p = 0.009$,) but no such (dRM = 0.08, $p = 0.72$) (Fig. 2A).

Table 1.1 Sleep Variable Analysis

Sleep Variables Analysis.

	Placebo	Dextroamphetamine	
TST (min)	537 ± 44	488 ± 69	*
SE(%)	92 ± 5	84 ± 9	*
WASO(min)	30 ± 26	52 ± 34	*
Stage 1 (min)	13 ± 8	20 ± 10	*
Stage 2 (min)	285 ± 50	267 ± 53	*
SWS (min)	108 ± 38	97 ± 33	*
REM (min)	130 ± 32	102 ± 36	*
Stage 2 Onset(min)	10.37 ± 1.41	22.43 ± 3.57	*
REM Onset(min)	56.03 ± 9.755	65.79 ± 11.45	*
Stage 3 Onset(min)	20.63 ± 1.69	33.96 ± 3.90	*
Stage 1 (%)	2.59 ± 1.60	4.357 ± 2.3	*
Stage 2 (%)	52.99 ± 8.21	55.48 ± 8.34	*
SWS (%)	20.27 ± 7.26	22.44 ± 14.7	
REM (%)	24.129 ± 5.192	20.739 ± 5.89	*

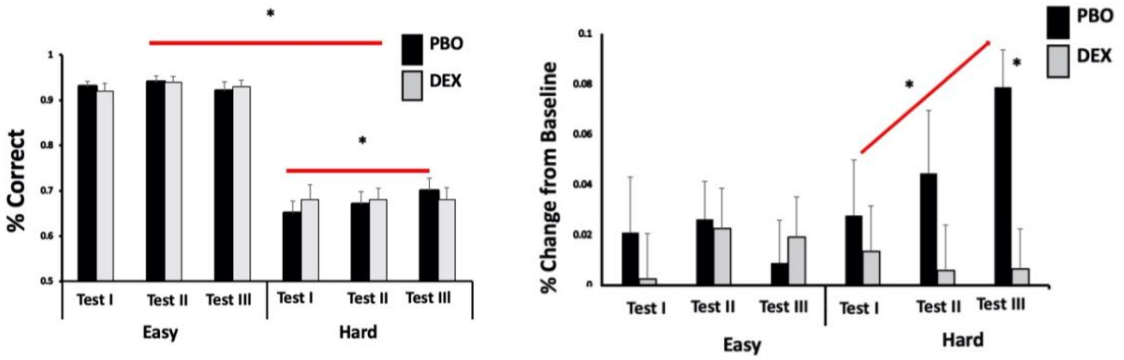

Fig. 1.2. Stimulants disrupted normal task improvement. A. Working memory performance at various time points (after 75min, 12 h and 24 h). *Signifies over-all interaction effect. B. Working memory performance improvement at various time points (after 75 min, 12 h and 24 h) from the baseline. *Differences between PBO and DEX at Test session and improvement.

Next, we calculated difference scores to examine the change in performance from baseline to Test 1 (Day 1 AM), Test 2 (Day 1 PM) and Test 3 (Day 2 AM). Again using a 2 × 2 × 3 RM ANOVA (string length (short vs long) X drug condition (DEX vs PBO) X Test performance difference from baseline (at Test 1, at Test 2, at Test 3), we discovered no main effects of string length ($F(1,32) = 1.124$, $p = 0.297$, partial eta square = 0.034), drug ($F(1,32) = 1.945$, $p = 0.173$, partial eta square = 0.057), or session ($F(2,64)=0.922$, $p = 0.403$, partial eta square = 0.028). However, a significant string length X drug condition X test performance interaction emerged ($F(2,64)=4.04$, $p=0.022$, partial eta square=0.112) (Fig. 2B). Post hoc analysis revealed for long trials, individuals performed better after PBO compared to DEX at Test 3 only (post-sleep) (Δ = 7.2%; $p = 0.012$). Additionally, for long trials, participants showed a significant 5.1% increase in performance from Test 1 to Test 3 in the PBO condition ($p = 0.009$), however no difference from Test 1 to Test 3 was present in the DEX condition (Δ = 0.07%; $p = 0.72$). Lastly, individuals showed more improvement for long trials at Test 3 compared to short trials (Δ = 7.0%; p = 0.013). No other significant differences across conditions or sessions were detected for short trials (Δ's < 2%; p's > 0.86). Taken together, these results suggest WM training may benefit from a night of sleep and that DEX may block overnight WM performance enhancements.

3.4. Sleep and WM correlations

Lastly, to determine if WM improvement was correlated with nighttime sleep variables, we correlated sleep features with performance change (Test 3 - baseline WM performance) and at Test 3. We did not find significant correlations amongst any of the variables (all p values > 0.5) for both short and long trials.

Discussion

The present study examined the immediate and delayed impact of a psychostimulant on WM and sleep in well-rested, healthy adults. We found that stimulants administered in the morning

significantly disrupted nighttime sleep. Importantly, contrary to our hypothesis, no significant difference in WM performance between DEX and PBO was present at either the 75-min or 12-hr post-drug delay. However, after a night of sleep (24 + hrs post-drug administration), the DEX condition performed significantly worse than the PBO condition. Even more, in the PBO condition, performance after sleep showed significant WM improvement compared to Test 1, but no such improvement was pre- sent in the DEX condition. These results suggest good sleep may be important to WM training and that sleep impairment, in this case induced by stimulant administration, may block WM performance gains.

One caveat to our findings is that subjects' night time sleep before the experiment was curtailed due to the early experimental start time (8AM), and this may have elevated levels of sleepiness and sleep inertia at the start of the study. However, this restriction pertained for both PBO and DEX conditions, and no differences in total sleep time was found for the week prior or the eve of the experimental day, suggesting that poor prior sleep could not completely explain the drug differences on performance. Also, with a mean delay time between wake-up and test time of more than 1.5 h for the both visit days, our participant would have typically recovered from sleep inertia (Ferrara, 2000; Jewett et al., 1999; Tassi & Muzet, 2000). This is also supported by average low score on the KSS at AM1, which did not differ across drug conditions.

Few studies have investigated the cost of off-label prescription psychostimulant use for sleep and cognitive performance in healthy, well-rested adults. This is surprising given that sleep is important for proper cognitive function, and the primary outcome of stimulants is increased wakefulness. In the present study, we noted that DEX impaired sleep quality, with lower sleep efficiency, increased WASO, and decreased SWS, as well as dampening sleep-dependent enhancement of WM performance. Thus, even a morning administration of DEX deteriorated nighttime sleep and post-sleep WM performance. Contrary to our expectations, we did not find increased WM ability after stimulants at either the 75-min or 12-hr delay. Previous studies have

also failed to find an acute impact of stimulants on cognitive performance. For example, Ilieva et al. (Ilieva et al., 2013) found no evidence of cognitive enhancement after 75min with a 20mg dose of mixed-amphetamine salt in an N-back WM task. However, other studies reported a significant benefit of stimulants for WM performance (de Wit, 2002; Mattay et al., 2000). One potential reason for our null results relates to the inverted U-shape theory of baseline WM capacity (Cools & D'Esposito, 2011) and optimal arousal theory (Yerkes & Dodson, 1908), which posits that beneficial effects of stimulants would be maximum for individuals with low baseline performance, and minimal benefits would occur for individuals at moderately high baseline performance (Garrett et al., 2015). Our subject pool of healthy, young adults is likely at the peak of their working memory capacity (Cansino et al., 2018), and in the context of this argument, positioned at the peak of inverted U. As such, they may not have been able to reap as much benefit from stimulants as individuals at lower performance capacities. Consistent with this idea, a study using methylphenidate showed that baseline performance was negatively correlated with errors made on a spatial working memory (SWM) task. The investigators noted that the lower the baseline performance, the more the stimulant group showed improvement in error reduction (Mattay et al., 2000). Future studies might examine this by comparing samples with lower and higher performance capacities.

Given the growing trend in off-label stimulant drug usage in healthy, well-rested adults (Smith & Farah, 2011), these findings have implications for public health, with a specific impact on the debate of stimulant use for cognitive enhancement. Along with the known adverse side effects from these drugs including addiction, psychosis, cardiovascular disease and sudden death (Greenhill et al., 2001), disruption of sleep and impairment of sleep-dependent cognition should be taken into consideration. An effective alternative approach of sleep hygiene education and napping interventions may better support a wide range of cognitive and health functions.

Study 2: Dextroamphetamine Biases the brain Towards Enhanced Spatial Selective Attention Compared to Working Memory.

Introduction

There is a growing trend in the non-medical use of prescription psychostimulant (PStim) in healthy adults (de Wit, 2002; Mommaerts et al., 2013). Findings from a govt. survey in 2016 revealed that over 1.4 millions individual aged >12 reported non-medical use of Pstim (Faraone et al., 2020) . According to recent CDC data, there was a 48% increase in Pstim overdose death in the year ending April 2021 compared to the previous year (McPhillips, 2021). The reason for off-label use of these drugs vary. The motivations of PStim use range from increased concentration, increased awake time, enhanced cognitive performance to improve overall professional and academic productivity (Sharif et al., 2021). One of the main reasons for increased usage of PStim is due their perceived benefit on attentional capacity (Rabiner et al., 2009; Teodorini et al., 2020). In an online survey study, college students who used off-prescription stimulants revealed that 84% of them used it for motivations related to improving "attention/focus" (Teodorini et al., 2020). The above motivations point a desire for cognitive enhancement (CE) which is driving this trend for increased PStim used (Smith & Farah, 2011). CE is defined as an "amplification or extension of core capacity of the mind by improving the internal and external information processing systems" (Bostrom & Sandberg, 2009) . In other words, CE is seeking to increase and enhance the core capacities of different cognitive domains mostly through the use of PStim. However, the question asked by Smith and Farah in their 2011 review remain relevant: "Are prescription stimulants smart pills?" To put it simply, do PStim make you smarter? Evidences from empirical studies points to an inconclusive answer.

The experimental studies that examined the effect of stimulants in healthy adults across a range of cognitive domains show mixed findings. The results from these studies range from positive to

no benefit of PStims on CE. For example, in the cognitive domain of WM, De Wit and colleagues studied the effect of PStim dextroamphetamine (DEX) on WM using a digit span task. They found that DEX improved the participants' WM only in a dose dependent manner (de Wit, 2002). Likewise, another study found a beneficial effect of DEX on WM using an N-back task. The beneficial effect of DEX was dependent on difficulty of the task such a difficult task 3-back task benefitted more compared to 2-back version (Mattay et al., 2000) . Another PStim, Methylphenidate, has also been shown to have a beneficial effect on spatial WM performance (Elliott et al., 1997). However, some studies have found no clear benefit of PStim. A 10 mg DEX dose failed to show benefit in different WM tasks. Similarly, a study by our group also showed no benefit of DEX on Ospan WM performance across a period of a day. However, it in fact lead to decrease in the performance at the next morning. A recent study by Repantis et al compared different types of PStims showed that methylphenidate and modanafil did not have any benefit on sustained attention (Repantis et al., 2021). This inconclusive evidence of CE by PStims is underscored in many systematic reviews conducted by multiple groups (Battleday & Brem, 2015; Repantis et al., 2010; Smith & Farah, 2011). The reasons behind mixed findings can be interpreted and attributed to different factors related to the studies.

The underlying factors which can reasonably explain the mixed findings are PStim dosage, type of cognitive task, individual baseline and trade-off. Firstly, PStim dosage influence neurotransmitter activity in the brain (Moreira da Silva Santos et al., 2017) and consequently any relevant behavior changes. Different studies report the effect of PStim on the tested cognitive abilities using different drug doses which vary by type of PStim. Only a few studies compared the effect of different dosages. A study compared the effect of 10mg, 20mg d-Amphetamine and placebo pills on different cognitive tasks and reported that performance on WM digit span increased with dose (de Wit, 2002). Similarly, another study reported that PStim methylphenidate dose (0, 10, 20, and 40 mg) dependently increase the percentage of simple

arithmetic problems completed correctly in an allotted time of 50 minutes (Stoops et al., 2005). Reviews by Repantis et al and Smith & Farah highlights how different studies have used different doses of PStim and found diverse results.

Another factor that might have contributed to the mixed result is the type of cognitive task used. Different cognitive tasks testing long term memory (LTM), WM, selective attentions and other executive function task have been used to represent the cognitive enhancing effect of PStims (Repantis et al., 2010; Smith & Farah, 2011). Even within a cognitive domain different tasks have been used. For example, to investigate PStims' effect on WM, different tasks like digit span task, item recognition task, n-back task, spatial WM task etc. were used. WM performance tests also varied in terms what aspects is being measured; capacity, resistance to external interference or persistence over time. Given the multitude of tasks, different studies report different effects of PStim of WM. One study found dose dependent improvement in digit span task (de Wit, 2002), while another study did not find any effect in N-back tasks (Mattay et al., 2000, 2003; Mintzer & Griffiths, 2007). The benefit of PStim also seem to depend on the complexity of the tasks. In participants with low baseline performance, dextroamphtamine (DEX) improved performance in the more complex 3-back task but not in the simpler 2-back task (Mattay et al., 2000). This study also leads us to another factor contributing to mixed findings i.e. individual variability of participants.

Different people have different levels of baseline cognitive abilities and this differential baseline may influence the amount effect (both positive and negative) PStim may have over them. For example, Mattay et al., found that 10 mg DEX boost the 3-back performance of the low baseline individuals. On the other hand, DEX caused deterioration of the performance in individuals with high baseline WM capacity. Potentials for mixed findings due to individual variabilities in cognitive performance can be understood through the lenses of inverted U-shape theory of baseline WM capacity (Cools & D'Esposito, 2011) and optimal arousal theory (Yerkes &

Dodson, 1908). Individuals with low baseline capacity who gain positive benefit from PStim as they move up the slope towards peak level in both WM and dopamine related arousal level. On the contrary, PStim deteriorates the capacity of those individual with high baseline WM and are already at peak level but move down the slope with excess stimulation (Mattay et al., 2003). In the CE studies that have shown inconclusive results, it may be possible that the at individual level there is mixed of positive and negative effects of PStim lumping these individual effects together mask the influence and leading to an overall no-effect finding.

Another factor which could explain the mixed findings CE literature is the concept of trade-off. Concept of trade-off is related to limitation of brain resources. These limitations have to do with both the overall processing capacity limitation of the brain and limitations in the individual cognitive domains. Going beyond the constraints set by inverted U-shape curve, it is possible that when the situation demands, our brain is able to raise the optimal peak a of particular cognitive domain but at the expense of diversion of capacity and resources from another domain leading to its degradation or compromise. In fact, this is exactly posited by the theory of Neural- Competition principle proposed by Colzata et al (Colzato et al., 2021). This theory proposes that the interaction between brain's subsystems is net zero-sum such that subsystems are competing for the limited resources of the brain. Gain for one system means inevitable loss for others. There are various possibilities of trade-offs in the cognitive system. One such trade-off is between stability and flexibility of WM (de Jongh et al., 2008). Transient, phasic dopaminergic activity which underlies flexibility support updating and resetting of WM traces meanwhile a constant, tonic activity sustains stability of WM traces. A study investigated the presence of trade-off by using two groups of participants with val/val (phasic) and met/met (tonic) genotypes related to dopaminergic activity. Employing a cognitive task which demands ability transition between cognitive stability and flexibility, they found that val/val participants performed better on the task requiring flexibility and poorer on the task requiring stability

compared to the other group (Nolan et al., 2004). This finding underscores an important principle of our cognitive system which is that different cognitive domain and related tasks require different underlying brain activities. Therefore, different pharmacological interventions would be necessary to achieve optimal brain activities leading to enhancement in the related individual cognitive domains. It then follows that PStim manipulation to enhance one cognitive domain may impair another cognitive domain. There are evidences of such inter-cognitive domains trade-offs. A recent study by Chen et al., showed that by suppressing the vagal cardiac autonomic activity level and increasing sleep spindles during non-rapid eye movement sleep by administering a GABA agonist, leads to selective improvement in long-term memory (LTM) performance but decreased WM performance. In general, sleep supports the improvement in both LTM and WM but the pharmacological manipulation caused a trade-off between WM and LTM (Chen et al., 2021). Similarly, using a transcranial direct current stimulation (tDCS) researchers showed that stimulating a specific brain region leads to improvement one type of learning but impairs another (Iuculano & Kadosh, 2013). Despite these few studies investigating the trade-off due CE, there is a shortage of studies investigating the presence of trade-off by PStim related CE approach even though PStim is the most prominent route through which people seek CE.

This trade-off principle is directly applicable to CE such that enhancement in one domain may come at a cognitive cost in other. Despite some evidence of benefits of CE through PStims, some researchers have argued that CE may come with the negative consequence and a trade-off- i.e. enhancement in one cognitive skill may come at the price of compromising another skill (de Jongh et al., 2008; Maslen et al., 2014). When beneficial with a positive effect on a particular cognitive domain, it is possible that PStim may selectively bias the brain network to extend the capacity of the particular cognitive skill while brain resources for the other skill become simultaneously limited, thus leading to a compromising trade-off. This tradeoff in brain

may manifest various ways. Given the general lack of studies investigating this aspect of CE, our study which we investigated a potential bias of stimulant towards one of the two executive domains: working memory and spatial selective attention. We carried out a double blind, placebo-controlled study, with repeated measures design to investigate the differential influence of a stimulant drug (DEX vs PBO) on the cognitive skills of working memory (WM) and spatial selective attentive in the form multiple object tracking (MOT) across a period of a day. We compared the change in the performance of WM and MOT in DEX vs PBO conditions at 1) pre-drug baseline, 2) 75 minutes post-drug (peak concentration), 3) 12 hours post-drug intake (washout). We predicted that DEX will have no beneficial influence on WM performance across the day. DEX will have a beneficial rescuing effect on MOT performance, which will degrade across the day in the PBO condition. Overall, we hypothesized that there will be an overall bias by DEX towards MOT over WM at peak drug concentration in the DEX group above PBO level and that this bias will vanish after drug washout.

Method

We recruited healthy and young adult participants in the age range of 18-39 in this study. Participants' eligibilities were determined through in-person assessments at the lab. The in-person assessment screened the participants for their eligibility on the basis of sleep habits, personal mental and neurological health history, substance abuse, and any cardiac or respiratory issues which may affect cerebral metabolism. The researchers carried out the assessment through a structured clinical interview following the DSM-IV guidance and other self-report health and wellness question as approved by the study physician. In addition, assessment of Hyperactivity and Attention to screen for symptoms of ADHD was also

administered. To ensure that the participants had not used any substances not permitted by the study prior to their study involvement, they were required to provide a urine toxicology test.

Prior to the study, participants were requested to maintain a regular sleep schedule for 7 days such that they went to sleep and woke up within a two-hour window each day without extreme sleep pattern i.e bedtime around 10:00PM – 12:00AM and wake time around 6:00-8:00AM. For the night before their study visits the participants were required to get a minimum of 7 hours of sleep. To ensure and assess the quality of sleep, participants were asked to fill an online sleep diary each day for 7 days prior to their visits.

The study design was double-blind, placebo controlled, within subject with randomized, counterbalanced design. The study involved two visits with participants experiencing either the drug or the placebo (PBO) condition on each visit. The two visits were at least one week apart to allow for drug wash out. The drug condition involved administration of 20 mg dextroamphitamine (DEX) pill prepared by MDMX Corona Pharmacy. DEX is a stimulant drug that inhibits reuptake of catecholamines and is an FDA approved drug. The PBO pill was composed of microcrystalline cellulose capsule containing no active medication and as such it was made visually indistinguishable from DEX pills.

On each day of the lab visits, participants' baseline WM and MOT performances were measured followed by introduction of either drug or placebo pill. The WM and MOT performances were repeatedly measured again at 75 mins (Test 1) and 12 hours (Test 2) after the introduction of the drug. Significance of measuring at 75 mins is that this is the time when the drug concentration would be at peak concentration and would return back to normal concentration after 12 hours delay.

OSPAN Working Memory Task

Our task WM ospan task is exactly same to previous study (Tselha et al., 2019). We chose the operation span task as it engages and captures both the memory retention and online processing capacity of WM. On a computer screen, participants were shown a string of letters (4–8) and were asked to remember each letter in the correct order of their presentation. Presentation of each letter was interspersed with a mathematical task where articipants were shown simple mathematical equations (e.g. 4 + 2 = 6 and 6 + 3 = 5) and were prompted to use keyboard response to determine if the presented equations were correct or incorrect.

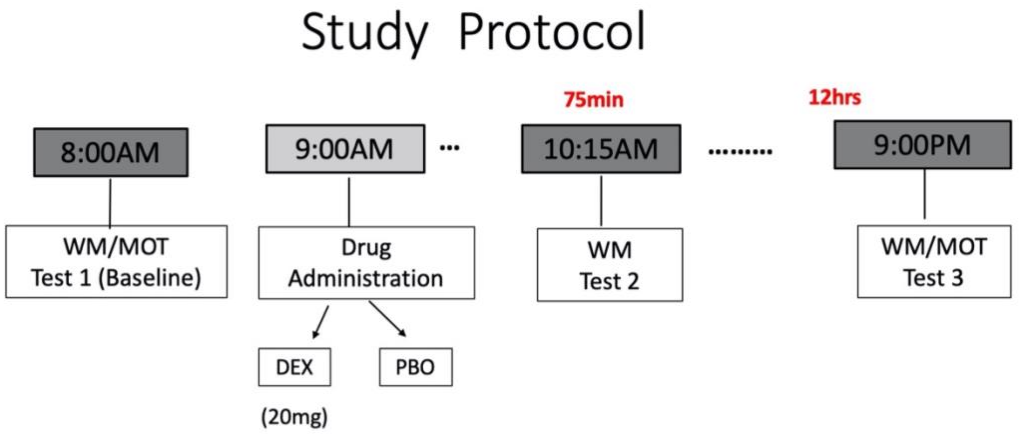

Figure 2.1: Study timeline and conditions.

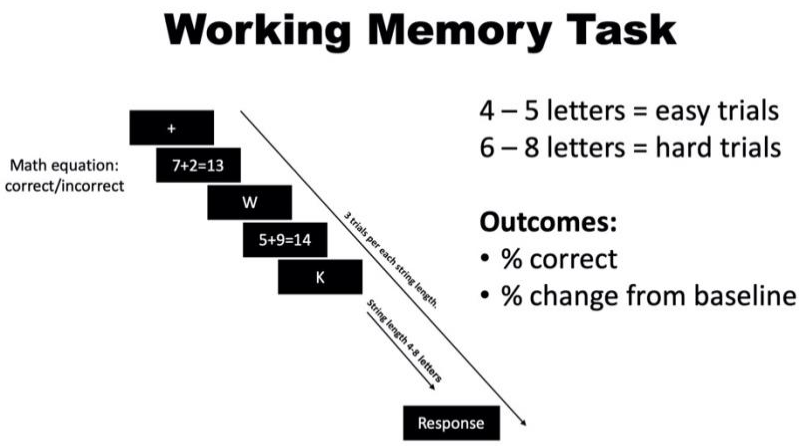

Figure 2.2: Working memory operation span task.

Participants were provided three seconds to respond to each equation. The mathematical task served as a distractor task to discourage online rehearsal of the letters. After each trial, there was a short break after which participants moved to the next trial after a keyboard press. Participants were required to maintain at least 70% accuracy on the mathematical distractor for the trial to be included in the analyses. Participants were given practice trials at the start of each test session. Test trials were grouped into “easy” versus “hard” conditions in which easy trials were defined as 4–5 to-be-remembered letters and hard trials were defined as 6-8 letters.

Multiple Object Tracking Task

We carried out the MOT task in similar fashion to the study by (Whitehurst et al., 2019). Psychophysical toolbox (PsychoPy) was used to implement MOT task. At the beginning of each trial a white fixation point (a black circle, radius = 0.15°) is displayed on a gray background. After that eight small, black circles (radius = 0.3°) were displayed on a computer screen, with four on either side of a centered fixation point. A subset of either 2 or 4 of the black circles began to flash at 2 Hz for 2 s marking them as the targets. Once the target circles cease to

flash, they became identical to the other circles. Then for next 5s, all circles moved on the screen in random, independent directions. The movement of the circle is restricted within a 6 × 6° region, centered 2° to the left and right of the fixation and bounced off the invisible edges of the square region. The circle moved at constant speed and repelled each other to maintain a spacing of 1.5°. When the motion stopped, two of the circles were highlighted red and participants were asked if the circles were or were not initial targets. Participants had to respond using predetermined keys on the keyboard.

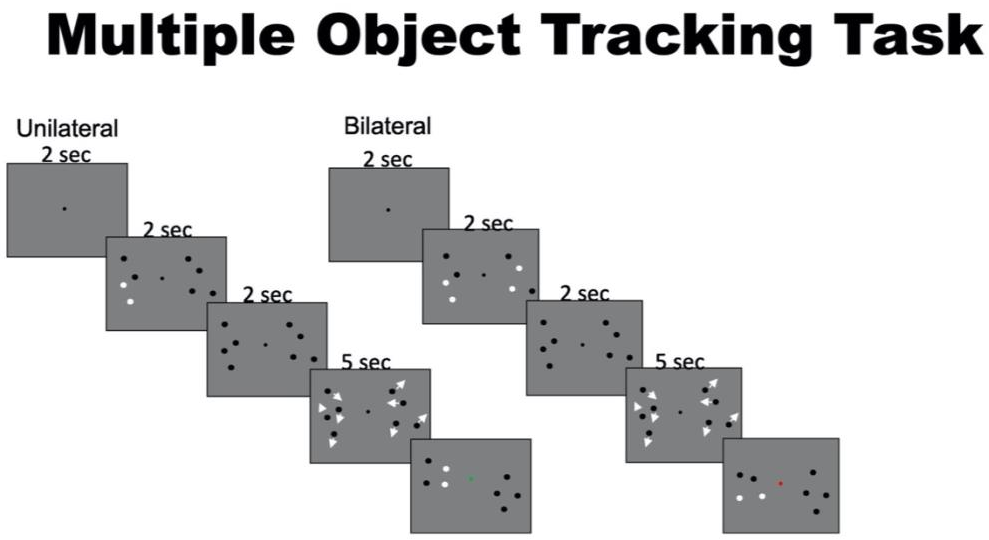

Figure 2.3: Protocol of the MOT task.

There were two distinct trial types in each session, unilateral and bilateral. For the unilateral trials, two targets were flashed on one side (left or right) of the fixation, however for the bilateral trials, four targets were indicated, two targets on each side of the fixation cross. This resulted in 4 trial types: unilateral left (UniLeft), unilateral right (UniRight), bilateral left (BiLeft, whereby the target will be tested in the left hemifield only) and bilateral right (BiRight;) Participants completed 16 trials per condition.

Statistical Method

To investigate how drug (or placebo) may influence WM and MOT differently over a course of day, i.e. at Test 1 and Test 2. We used Generalized Estimation Equation (GEE) analysis as it is a robust statistical approach for analyzing data with longitudinal and repeated measure design (Ballinger, 2004). GEE analysis model the estimates average response and the treatment effect for overall population (Hanley, 2003) .

For the analysis of WM performance, we used accuracy percentage as the dependent variable. The predictor variables in the model are Sessions (Baseline/T1 vs T2 vs T2), Drug condition (DEX vs PBO), and Trial_Type (Easy vs Hard). We also included an interaction term SessionXDrugXTrial_Type. Sample size for WM analysis was 58.

WM model

Accuracy ~ Session + Drug + Trial_Type +Session X Drug X Trial_Type

For the analysis of MOT performance, we used accuracy percentage as the dependent variable. The predictor variables in the model are Sessions (Baseline/T1 vs T2 vs T2), Drug condition

(DEX vs PBO), and Trial_Type (Unilateral vs Bilateral). We also included an interaction term SessionXDrugXTrial_Type. Sample size for MOT analysis was 59

MOT model

Accuracy ~ Session + Drug + Trial_Type + Session X Drug X Trial_Type

Cognitive Domain-Bias Analysis:

First, for each subject we calculated the difference between DEX and PBO condition performance at each session for both the WM and MOT separately. 1) For WM Easy trials:

DEX-PBO at T1, DEX-PBO at T2 and DEX-PBO at T3 2) WM Hard trials: DEX-PBO at T1, DEX-PBO at T2 and DEX-PBO at T3 3) For MOT Unilateral trials: DEX-PBO at T1, DEX- PBO at T2 and DEX-PBO at T3 4) For MOT Bilateral trials: DEX-PBO at T1, DEX-PBO at T2 and DEX-PBO at T3. Next, we used these difference score to calculate difference score between WM and MOT for the comparable trials at each session getting six difference scores i.e. For Easy vs Uni lateral: WM Easy -MOT Unilateral at T1, WM Easy -MOT Unilateral at T2, WM Easy -MOT Unilateral at T3. For Hard vs Bilateral: WM Hard -MOT Bilateral at T1, WM Hard -MOT Bilateral at T2, WM Hard -MOT Bilateral at T3.

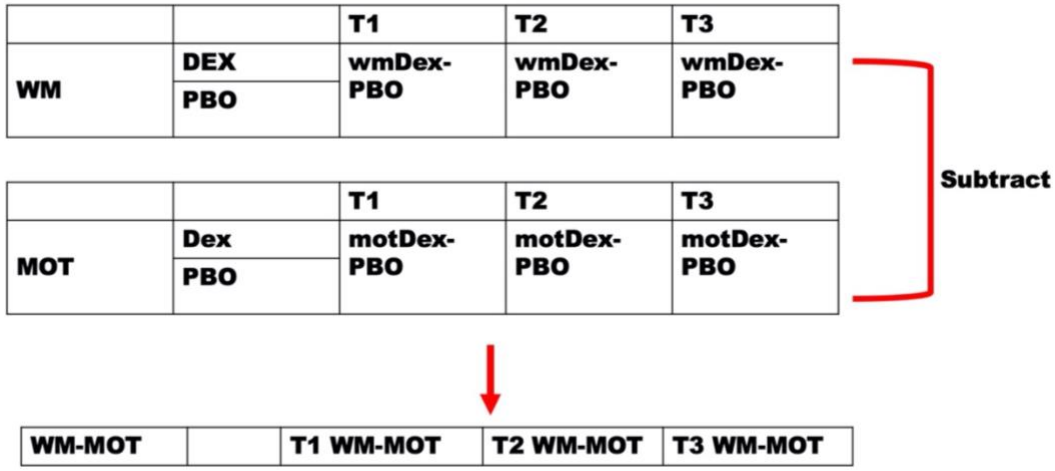

Figure 2.4: Difference scores calculation method.

The six resulting scores can range from -ve 1 to +ve 1. A positive score indicates that WM > MOT (WM dominance), negative score indicates that WM < MOT (MOT dominance), and 0 score means WM score same as MOT at that session for the individual participant. To generate individual difference score it was necessary to have no missing data for each task, drug condition and testing sessions. Therefore, we only chose the participants with complete data in both task types for this analysis. To assess if there is a significant fluctuation in the cognitive

dominance due to drug intervention across the day, we compared the difference score at T1, T2 and T3 using GEE. In the model, we use the difference scores as the dependent variable and Sessions as predictors.

We had 49 participants in this analysis as only these participants had complete data for both WM and MOT task.

WM vs MOT bias analysis model: Accuracy Difference Score ~ Sessions

We used python programming language for data preprocessing and analysis. Python packages of Stats model was used for GEE and Matplotlib for visualization.

Results

First, we investigated the effect of DEX on WM and MOT separately. GEE analysis on WM performance of the participants revealed that DEX does not significantly affect the WM performance at both the T2 (peak concentration period) and T3 (wash-out period); p values > 0.05 compared to T1 (baseline) Figure 4.

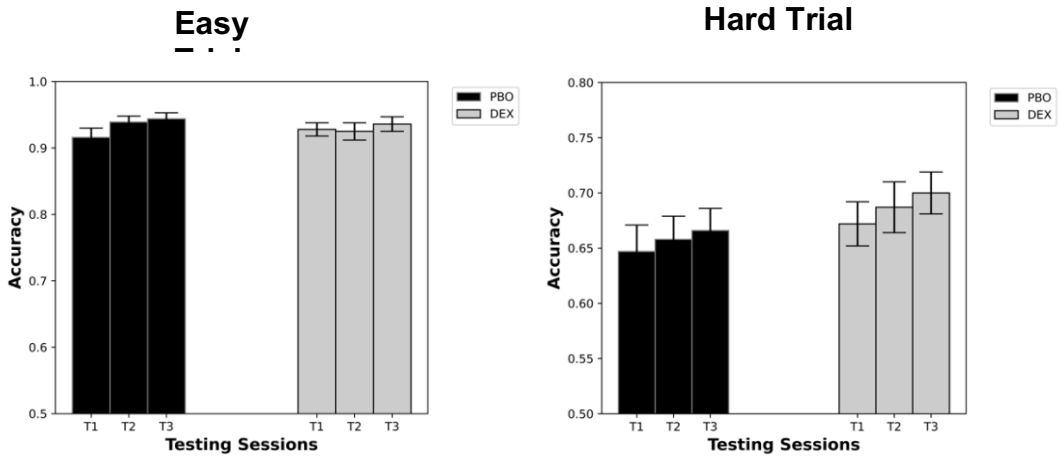

Figure 2.5: Effect of DEX on WM performance for easy and hard trials at various tests.

Furthermore, DEX performances were not significantly different from the PBO performances at the different tests. We also did not find any interaction effect between drug conditions and tests. However as expected, there was a significant performance difference between the trial types: short vs long trials, such that performance was better in the easy trials (Coef = -0.0159, SE = 0.015, $p < 0.001$). Overall, these results are in tune with our previous findings ((Tselha et al., 2019)) that a 20 mg dose of DEX does not have any measurable, objective benefit on WM performance over a wake period of 12 hours.

Similar to previous findings (Whitehurst et al., 2019), we showed that spatial selective attention deteriorated across the day (placebo), but that stimulants prevented this deterioration. In our data, DEX had a rescuing effect on MOT performance such that MOT performance in DEX condition did not degrade over the different testing periods. In the PBO condition, the MOT performance was significantly lower at T2 (Coef = -0.043, SE= 0.018 , $p = .016$) and lower (Coef = -0.043, SE = 0.023, $p=0.051$) at T3 when compared to the baseline testing of T1. Furthermore as expected, we found that there was significant performance difference (Coef = 0.0187, SE= 0.009, $p = 0.047$) between unilateral trial vs bilateral such that overall performance was better in the unilateral trials. We also found a Drug X Trial Type interaction effect (Coef = 0.06, SE = 0.025, $p = 0.017$). These findings are in line with previous work from our lab showing that DEX helps brain resists deterioration in sustained attention ability and maintains it at the baseline level over a wake period.

Next, we investigated if there was any bias from DEX on MOT over WM such that DEX's influence on it selectively enhances the cognitive domain over the other which remain unenhanced or even suppressed. We investigated this possible bias in both WM-easy vs MOT-unilateral and WM-hard vs MOT-bilateral comparisons. For WM-easy vs MOT-unilateral. For

WM-easy vs MOT-unilateral: GEE analysis of WM-MOT trade-off revealed a bias towards MOT processing at T2 (T 1 vs T2: Coef = -0.71, SE = 0.02, p = 0.004), compared to the baseline trade-off score. However at T3, the WM-MOT trade-off returned close to baseline level (T1 vs T3: Coef =0.03, SE = 0.02, p = 0.29). Similarly for WM-hard vs MOT-bilateral: GEE analysis of WM-MOT revealed a bias towards MOT processing at T2 (T 1 vs T2: Coef = 0.079, SE = 0.031, p = 0.011), compared to the baseline trade-off score. At T3, the WM-MOT trade-off returned close to baseline level (T1 vs T3: Coef =0.0391, SE = 0.033, p = 0.201).

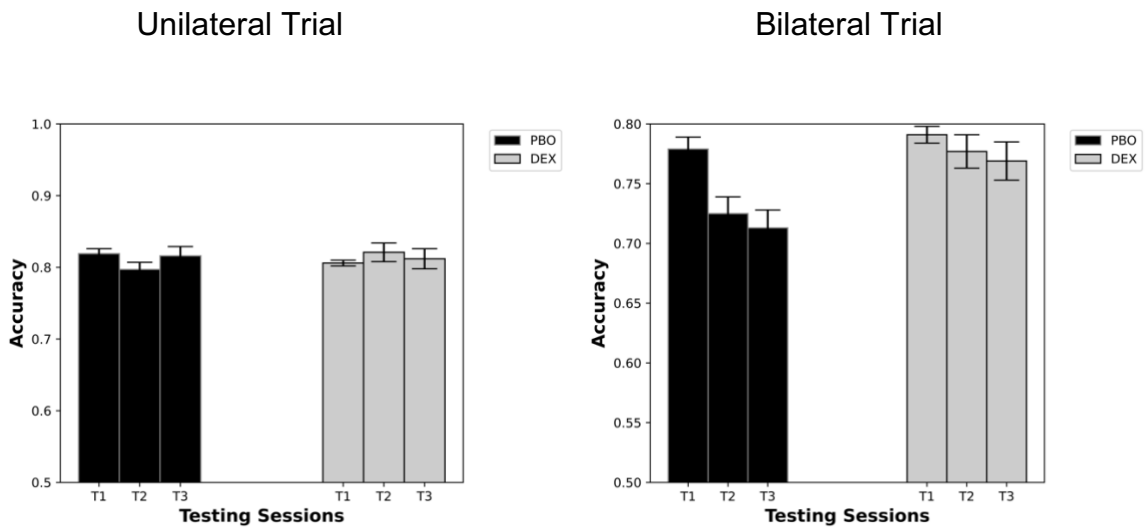

Figure 2.6: Effect of DEX on MOT performance at various tests. Left: Unilateral Trials. Right Bilateral trials.

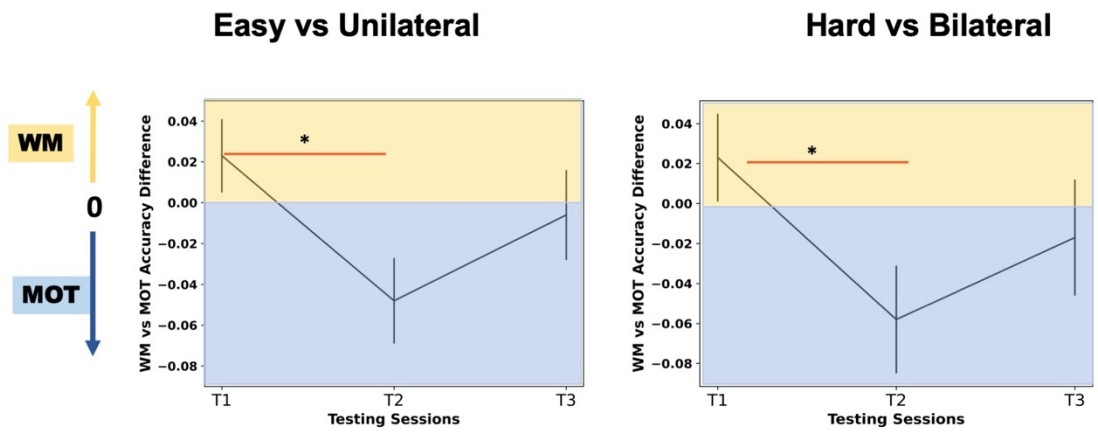

Figure 2.7: DEX biased influence on MOT compared to WM. Positive value indicate WM bias and negative value indicates MOT bias.

Overall, these findings suggest that stimulants drug selectively bias cognitive processing towards sustained attention at the cost of WM processing.

Discussion:

In the present study, our goal was to assess any differential effect of DEX on the cognitive domains of WM and MOT using a dual task paradigm. Using a DEX dosage of 20mg administered to healthy young adults, firstly we found that DEX did not have any overall significant effect on WM performance across a period of day compared to the placebo condition. Contrary to these WM findings, secondly, we found that MOT performance was rescued by DEX, unlike the placebo condition in which the MOT performance degraded over different testing periods across a wake day period. The main question of our study was whether administration of DEX caused any trade-off between MOT and WM. Here we found that during the peak concentration of DEX in the body (i.e at T2) MOT performance was significantly superior to that of the WM performance. This superiority of MOT over WM was not present

before the drug administration (baseline) and also returned to a level similar to baseline after a gap of 12hours; a significant gap period for the drug to be washed out from the system. Overall, our study findings suggest that DEX has a favorable bias towards MOT compared to WM and selectively enhances its performance when the brain is required to support both of these two cognitive domains concurrently.

The interaction between WM and MOT under the influence of this stimulant drug can be understood through how these two systems generally interact, through what mechanisms and how stimulants may influence these mechanisms causing selective bias and selective enhancement. Many studies have investigated the relation between WM and MOT by carrying out studies with concurrent tasks; i.e. having the participants do both a WM and a MOT task (Domkin et al., 2013; Fougnie & Marois, 2011; Medeiros-Ward et al., 2011; Tomasi et al., 2007). One view is that, WM and MOT may have a mutually synergistic relation; improvement in one domain has an overall positive effect on the other. This relation requires a common system which is used by both WM and MOT in non-competitive manner. Many researchers have highlighted the commonality between WM and MOT. Specifically, both WM and MOT have respective capacity limit around 4 items (Cowan, 2001; Pylyshyn & Storm, 1988; Scholl & Pylyshyn, 1999). This capacity limit may reflect the limit of an underlying cognitive feature which supports both WM and MOT skill. Some researchers propose that general attention may be this common feature (Endress et al., 2017). There are evidences from imaging studies which support the idea that WM and MOT tap into common brain areas and resources. An imaging study by LaBar et al., showed common activation pattern consisting of frontal, temporal, parietal cortices etc (LaBar et al., 1999). Additional studies by Tomasi et al., compared brain activation patterns during WM task of n-back and a Visual Attention task of tracking dots. Overall, they found that these tasks activated similar brain regions of prefrontal (PFC) cortex, medial gyri, middle frontal gyri, inferior and superior parietal lobes, thalamus and cerebellum (Tomasi et al.,

2007). Moreover, they found that as task load or difficulty increases there was an increase in activation of some common brain region whereas other brain regions showed differences in activation pattern. Overall, findings from our study are against this view of synergistic relation between WM and MOT. The rescuing effect of DEX on MOT was not visible in WM.

Another perspective is that WM and MOT may tap into common resources which are limited in nature, thus there is a competition between MOT and MW over this limited resource.
A study by Liu et al., showed that there is a negative interaction between WM and MOT but it is contingent upon the type of WM task used. They revealed that the MOT performance is negatively related to the spatial WM task performance whereas there is no relation between MOT performance and non-spatial WM performance (Liu-Qing et al., 2010) . The researchers concluded that this disproportionate effect of MOT on spatial WM may indicate that a primary spatial resource is common in both MOT and spatial WM performance. Thus, the evidences suggest that the interaction of WM and MOT differs depending on the feature of WM is engaged; spatial or non-spatial. However, our study used a non-spatial WM task and found that even without involvement of spatial component DEX tilts the needle of balance towards MOT instead of WM. This suggest a possibility of a different cognitive component which is limited in resource and reaps more reward from presence of stimulant in the brain. To answer these outstanding questions, future studies should carry out brain imaging studies with concurrent WM and MOT tasks with and without the influence stimulants in the body.

Our study findings are timely and relevant to the current trend of overall increase in the non-prescribed stimulants usage. Many people use the off-label stimulants believing it will increase their day-to-day productivity without considering the underlying cost. One of these costs is the possible tradeoff in performance of different cognitive domains. Our study shows that stimulants have bias towards specific cognitive domain such that it leads to improvement in only that domain. In the worst-case scenario, this could also mean that selective enhancement in one

domain may come at the cost of other. Illustrating this with an example; consumption of stimulant like DEX by a taxi driver may sustain their lane changing ability in bad traffic conditions but they might miss their exit on the freeway.

One of the caveats of our study is that the WM and MOT trials were not interspersed trial-by-trial in a manner that would simultaneously burden the brain. Rather our participants either first did WM or MOT separately. Therefore, our result cannot conclusively be tied to the simultaneous burden of WM and MOT tasks on the brain's limited processing capacity.

Chapter 3:

Home-Based Targeted Memory Reactivation to Bias Memories: A Pandemic Study

Introduction

Targeted memory reactivation (TMR) attempts to influence memory-consolidation processes by leveraging natural memory reactivation during sleep. In TMR, sensory cues are associated with objects during the wake-encoding phase. When these formerly associated cues are reintroduced at suboptimal strength during sleep, these cues are believed to drive spontaneous re- activations above the natural level (Cellini & Capuozzo, 2018; Schouten et al., 2017). Given the ability to manipulate memory formation process with TMR, it is a potential avenue for enhancing cognitive capability above normal level. TMR is also uniquely suited to manipulate long term memories.

In a groundbreaking study, Rasch et al. showed that visuospatial memory improved after previously associated olfactory cues were introduced during sleep. In the experiment, participants were shown images of various object pairs at different locations on a checker board like grid with rose scent as olfactory contextual cue. This olfactory cue was re-presented to the participants during SWS. At recall test, when the participants were tested on the location of the objects when shown the other pair, the participants had better memory performance than the control groups. The different control conditions were cues delivered during wake period, odorless vehicle delivered during sleep, no cue association, and odor cue delivered during REM sleep (Rasch et al., 2007). Subsequent studies showed that auditory cues can also be successfully used to improve memory performance through TMR. Rudoy et al. presented participants with 50 images of various objects on different locations on a screen with sound cues (e.g., cat/meow, kettle/whistle). Some of these were later replayed during the sleep period.

The memories of object locations were more accurate for the cued objects compared to non-cued on the subsequent test (Rudoy et al., 2009). This study showed the feasibility of applying TMR for individual memory, as unique sound cues can be used for each specific memory item. This is one advantage of using auditory cues over olfactory cues in the TMR protocol.

The successful increase in memory performance with the TMR protocol seems to result from the stabilization of memory following reactivation in SWS such that it is resistant to interference. In a follow up study by Rasch et al. using object-location and olfactory-cue paradigms, subjects were immediately woken up after odor-cue delivery in SWS and were introduced to an interference task followed by a memory test. Compared to the wake group, for which post-learning sleep TMR was replaced by wake TMR, in the sleep condition the post-TMR interference task affected the memory performance less. This showed that sleep reactivation results in memory stabilization rather than making it labile for memory trace re-distribution (Diekelmann & Born, 2010). According to the findings from one study, the benefit of the memory-performance increase with TMR application seems to depend on the strength of the initial learning. This was the question of a TMR study by Creery et al., who set to extend the prior study by Rudoy et al. described above. Using a similar object-location task, the experiments revealed a benefit of TMR intervention during sleep when young adult participants were tested on the object locations before and after the sleep. This benefit of TMR on the memory of cued-object locations was modulated by the strength of the memory performance before sleep (Creery et al., 2015; Rudoy et al., 2009). In another words, the cueing benefit during sleep seems to require a certain level of prior learning. Another TMR-related benefit is that its application seems to accelerate the memory consolidation process during sleep. Specifically, the increase in memory performance after a 40- minute nap with TMR was shown to be comparable to 90 minutes of sleep without TMR (Diekelmann et al., 2012).

Auditory TMR is uniquely suited to selectively and individually target a specific memory item and its trace by introducing individual cues or sounds. Auditory TMR is also simple due to the relative simplicity of delivering sound cues through simple gadgets like headphones or sound boxes. Most importantly, auditory cues can be delivered with temporal precision which endows it the potential to target not only individual memory items but also precisely target specific sleep stages and features. Given the unique potential for auditory TMR in targeting individual, it is worth investigating if we can selectively cue the weak memory items to the level of high memory. A previous study by Oudiette et al., has attempted to target what they refer to as 'high value' and 'low value' items. The high and low values in this particular study were associated with the amount of monetary reward the participants can receive by remembering specific items' locations. Although reward is a very strong motivation to effectively bias the memory into high and low value, it may be just too strong of a motivation such that participants completely dedicate all their brain's memory resources to the high value and ignore the low values. Therefore, low values may form traces that are very weak and beneath some specific threshold such that TMR is not able to reactivate and replay the trace. Fitting with this line of reasoning, the researchers did not find the benefit of TMR cueing in the low value items in their Sleep TMR experiment (Oudiette et al., 2013). To investigate the possibility of rescuing weak memory and selectively strengthening their memory, we designed our current study to bias the memory into different strengths and investigate if we can carry selectively strengthening of memory with TMR. At beginning stage of our study, the world-wide COVID pandemic happened which effectively ceased the opportunity for in-person lab testing. Therefore, we adapted out study and developed a robust home-based TMR protocol.

Materials and Methods:

Subjects:

Participants between the age range of 18-39 were recruited for the study. A total of 119 (80 females) healthy young subjects participated in the study. All the participants self-reported no history of sleep disorders. They also indicated no current or history of neurological disorders including hearing impairments. All participants were proficient in English. Those who met the eligibility criteria were invited to a virtual orientation over Zoom during which informed consent procedure was carried out. Participants gave informed consent to participate in the experiment, which was approved by the University of California, Irvine Human Research Review Board. During the study orientation the subjects were randomly assigned to different experimental groups. Those who were in the TMR intervention groups were additionally instructed on how to download an example sound file offline on their phones. To make sure the subjects had successfully downloaded the sound file they were asked to send back the screenshot of their phone Download folders containing the downloaded example sound file. This step was to ensure they knew how to successfully download the TMR sound cue file during the study day. Participants were either compensated with $20 or university course credits.

Design and Procedure:

The timeline of the study involved initial encoding phase when the participants were exposed to the image of different objects presented on different locations within concentric circles drawn on the computer screen along with a sound. Initial encoding was followed by the Training phase (Test I) where the participants' memory of the objects' spatial locations was tested following a feedback. For half of the items, a supplemental training was given to bias them to be trained better with higher memory accuracy. After the Training phase, Immediate Testing (T2) was carried out. Post sleep or wake period, the participants carried out the Delayed test (Test 3).

This study used a between-subjects, cross-sectional design; involving four experimental groups: 1) Sleep with TMR (n=26), 2) Sleep without TMR (22), 3) Wake with TMR (n=27, and 4) Wake without TMR (25). Wake only and Sleep only group served as the control conditions to the TMR intervention condition of the Sleep TMR. All four conditions carried out the Pre-intervention steps which included the steps of the Encoding, Training, Supplemental Training and the Immediate Test. After the Immediate test, the participants in the TMR intervention conditions notified the experimenter. In the case of wake control and wake TMR condition, pre-intervention phase occurred in the morning whereas in the sleep control and sleep TMR condition it occurred in the late evening/night. For the TMR intervention, the wake group listened to the TMR cue sounds on their phones in a quiet environment during the day. In the case of the Sleep TMR condition, participants played the TMR sound cue file on their phones by placing their phone near their pillow and going to sleep. Participants were instructed to set their phones on 'airplane' mode and set their phone sound volume to 30% of max volume. The Sleep TMR sound file was designed to play the sound cue during NREM sleep by including a 45 min silent part in the beginning section. While the sleep TMR group continued with their overnight sleep, the Wake TMR group resumed their normal daytime activity post TMR intervention. Retention testing occurred after a gap of 10 hours. In the wake TMR group this happened in the late evening/night and for the sleep TMR group this occurred the next morning.

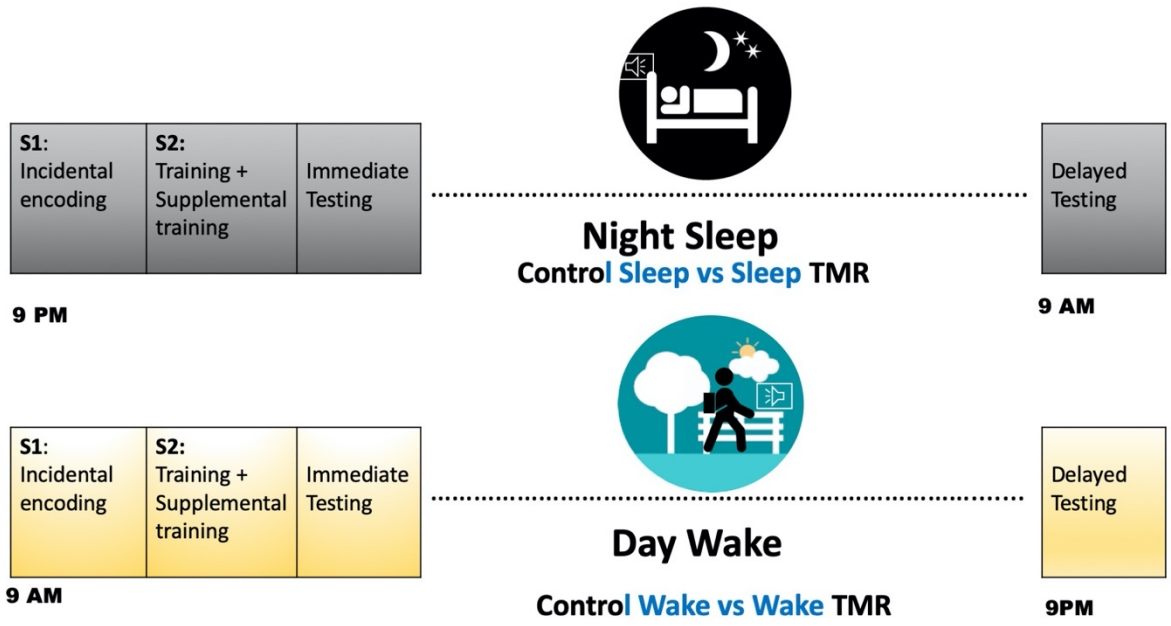

Figure 3.1: Homebase TMR study protocol and timeline

Cognitive Task:

The cognitive task was completely online i.e. the task was hosted on the online platform of pavlovia.com. On the study day, participants accessed the task through unique website links provided to them by the experimenters.

Initial Encoding: During the initial encoding, 40 different objects were presented on computer screen at random locations restricted to area between concentric circles. Each image was presented for the duration of 2 s with inter-stimulus interval of 4s. The presentation of each image was accompanied by a sound cue which is the name of the object in the image. For example, if image of an eagle was presented on the screen, the sound of word eagle would be played. Average duration of sound cues was 500 ms. The some of the sound cues were later used to carry out TMR.

Immediate Testing: In this section of the task, each image that was presented in the encoding phase was first presented on the center of the screen within the concentric circles for 2s. The image then vanished and was replaced by an instruction asking the participants to use the mouse to click on the location on the concentric circle where they had seen the image in the encoding phase. The participants had 4s to provide their responses. After each response, the feedback of the correct image location was provided. For half of the images, extra practice and feedback were provided to bias them for stronger memory.

Delayed Testing: Protocol of the delayed testing was similar to that of Immediate testing with the only difference that correct feedback was not given after each response.

TMR Cue Audio: After the immediate testing, the participants' response data were downloaded and analyzed with a custom-made python code. Specifically, the accuracy of the location memory recalls was calculated for each item. The individual recall score was sorted and median split into strong (less error) and weak memories (more error) groups. Strong items and weak items were then

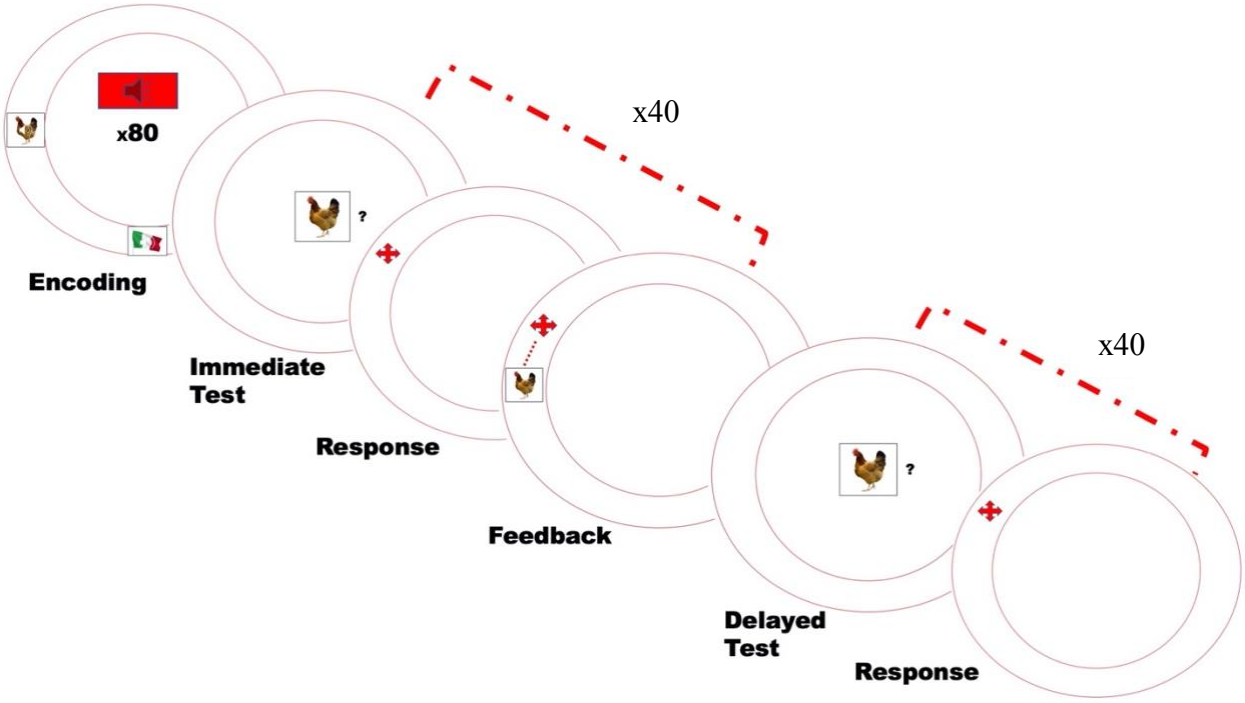

Figure 3.2: Spatial Memory task

shuffled within their groups and further divided into cued vs non-cued items. This resulted in four groups of Strong Cued items, Strong Non-Cued items, Weak Cued items and Weak Non-Cued items. Strong Cued and Weak Cued items' sounds were used to create the TMR cue playlist. The TMR cue sound playlist was created by shuffling the sounds and each cued item sound was played at least 3 times in the playlist. Furthermore, in order to target the sound cues presentation during the NREM sleep, the 45-minute-long silent audio was attached to the beginning of the TMR playlist. The TMR playlist audio files that were created customized for each participant were sent to the subjects through a google drive link 1 hour after their Immediate Testing. Subjects downloaded the audio file to their phones as demonstrated during the orientation session and sent a screenshot of their phone's download folder indicating successful download. In order to make sure that the sound file played without disruption during the TMR intervention session, the subjects were asked to keep their phone on 'airplane mode' or 'do not disturb' mode. In the case of sleep TMR, the subjects were asked to keep the phone

by their bed-stand or beside their pillow. The volume of the phone was set to 30 % of the max volume. In the case of wake TMR, the subjects sat in a quiet room on chair and listened to the audio file played through the phone on a nearby table or by using headphones to listen.

Survey: Surveys asking questions about alertness, sleep quality and whether the subjects heard the TMR sound cues during the sleep were conducted during the study. Surveys were designed using Qualtrics website.

Home-Based TMR Pipeline:

- Custom made online Spatial Memory Task.
- Spatial memory task implementation in PsychoPy and online hosting on Pavlovia.com.
- Customized Python and JavaScript codes to plot mouse click location on circle and save mouse click location for each.
- Python code for immediate analysis of Test I response.
- Generation of personalized cue playlist through custom made python code for audio editing.

Statistical Analysis:

19 subjects were not included in the final analysis due to reasons including failure to complete all tests, technical issues etc. Data were analyzed using repeated measure of analysis of variance (RM-ANOVA). Within subject factors were High vs Low, Cued vs NonCued, Immediate vs Delayed. Between subjects factors were Sleep vs SleepTMR vs Wake vs WakeTMR. Post hoc comparisons were done with t-tests. Statistical significance threshold was set to alpha value of 0.05..Means and standard errors are reported.

Result

Firstly, we compared the control sleep and control wake condition across the testing sessions.

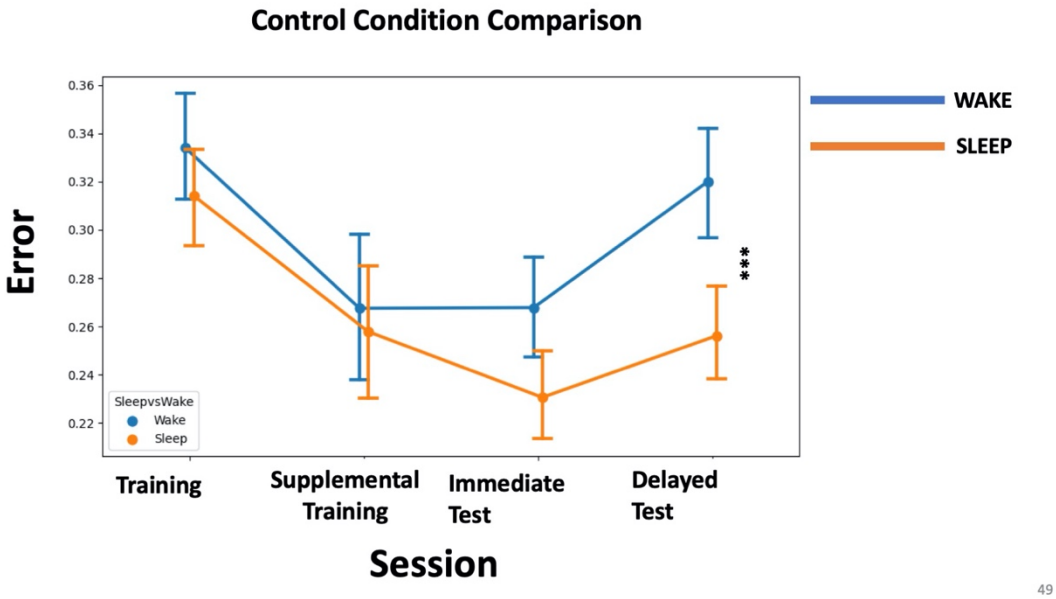

Figure 3.3: Comparison of the control conditions

We conducted a 2 (Sleep:Wake) x 4 (Sessions) RM-ANOVA which revealed the main effect of Sessions ($F(3,114) = 22.12$, $p < 0.001$) and interaction effect ($F(3, 114) = 3.45$, $p = 0.019$). Through a post-hoc t-test, we found that at the Delayed test, the Wake group had significantly higher errors compared to sleep group (Error 0.32± 0.027 vs 0.029 ± 0.023; $t = 2.6$, $p = 0.008$). This shows that a period of sleep helps to prevent memory degradation unlike the Wake period (Fig 3.2).

Next, we were interested in finding if sleep's support on memory stabilization has selective bias on the strength of the memory. For this we segregated the items' memory strength into high (less error) and low (more error) groups using a median split such that items with error less than the median were considered high memory strength and the items with error more than the

median were considered low memory strength. We tracked these items' error value from Immediate test to the Delayed test.

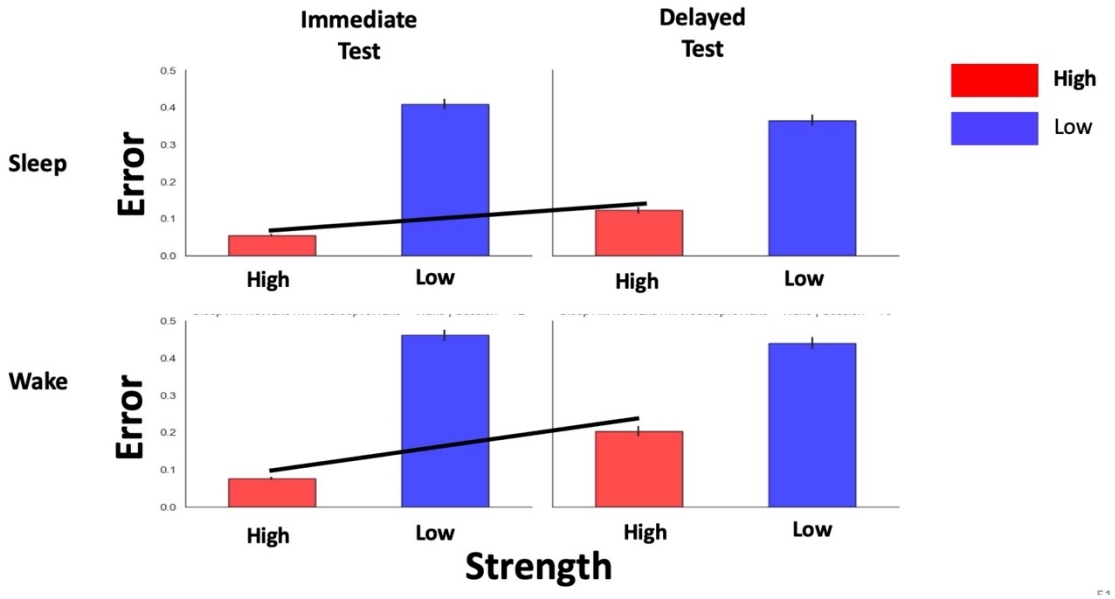

Figure 3.4: Control sleep and wake error for immediate and delayed test**.**

In Fig 3.4 we can see that the Sleep High Error group increased only a little while the Low Error group remained almost the same. On the other hand, in the Wake group High Error, it becomes much worse across the sessions. Meanwhile, the Low Error group maintains a similar performance in both Sleep and Wake conditions. To confirm this further, we calculated the error change from Immediate to Delayed Test for both high and low memory. We compared the error change from Immediate to Delayed Test (**Fig 3.4**).

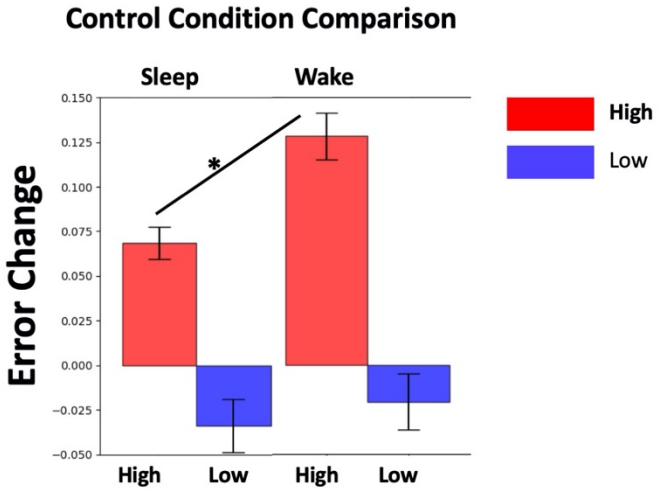

Figure 3.5: Control sleep and wake error change from immediate to delayed test**.**

We found a significant difference between the error change score of High Error group in Sleep vs Wake condition (error change 0.072 ± 0.007 vs 0.127± 0.01; $p < 0.001$). There was no significant difference in the Low Error group (error change -0.043 ± 0.002 vs -0.02 ± 0.0018; $p > 0.05$). Having found that sleep helped in mitigating memory degradation and that this effect is more pronounced for the higher memory strength items, next we investigated if TMR intervention can further help with memory stabilization in the sleep TMR and wake TMR conditions.

We tracked the memory performance of high and low memory strength items while cueing half of the high and low memory items during sleep and wake conditions.

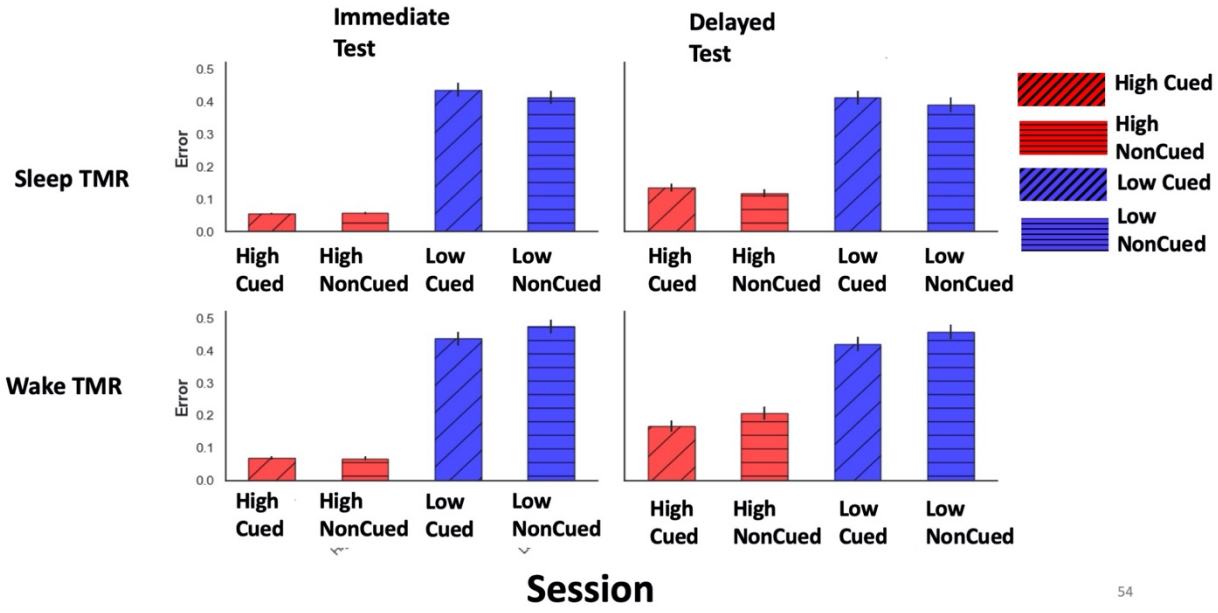

Figure 3.6: Sleep TMR and Wake TMR Error score for high vs low for cued vs noncued.

A 2(SleepTMRvsWakeTMR) X 2(T2 vsT3) X 4(HC:HNC:LC:LNC) RM ANOVA revealed no significant main ($p > 0.1$) and interaction effect ($p > 0.1$). In both sleep TMR and wake TMR, we found that at Delayed Test, there was no significant difference between High-Cued vs High - NonCued and Low-Cued vs Low-NonCued was not significantly different as well.

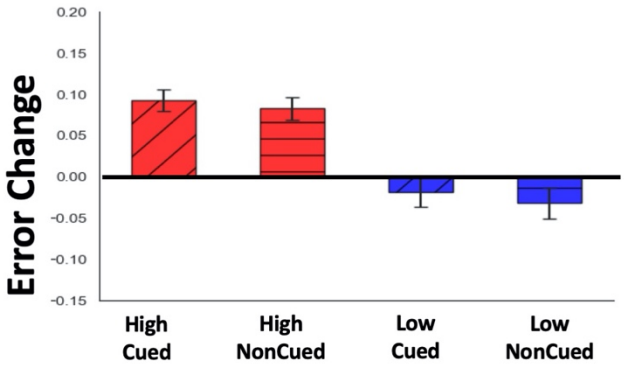

Figure 3.7: Sleep TMR error change from immediate to delayed test

Next for the sleep TMR condition, we compared the error change from Immediate to Delayed Test. We did not find any significant difference between Cued vs NonCued for both the High (0.093 ± 0.012 vs 0.082 ± 0.013 ; $p>0.1$) and Low Error group (-0.017 ± 0.018 vs -0.031 ± 0.018 $p>0.1$) (Fig 3.7).

Previously in our study, we had asked the participant at the Delayed Testing phase to report if their last night sleep was disturbed by the sound of TMR cues. We found that 6 participants had indicated that the they were disturbed by or heard the sound cues during sleep. We reasoned that disturbance by TMR sound cue could affect the memory performance as it reduces sleep efficiency and targeting of TMR cues during NREM could also fail. So next, we separately investigated the memory performance for the participant group who heard the sound cues and those who did not report any sleep disturbance by TMR sound.

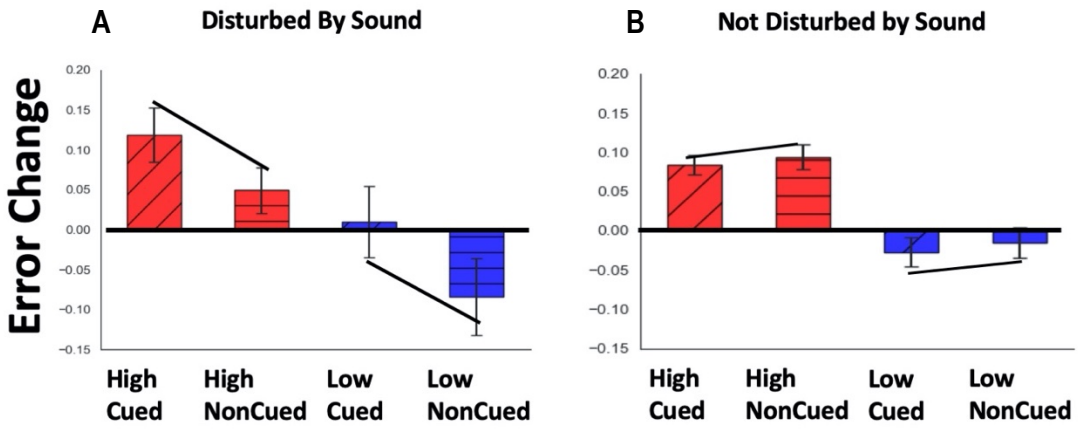

Figure 3.8: Sleep TMR analysis by disturbed sleep (A) and undisturbed sleep participants (B)

In Fig 3.6A, for those whose sleep was disturbed we can see that High Cued group has more memory degradation across sleep compared to the High NonCued (error change 0.0119 ± 0.0341 vs 0.049 ± 0.028) . Similarly, Low Cued group retains the memory performance while Low NonCued group has a slight sleep benefit (error change 0.01 ± 0.04 vs -0.08 ± 0.04).

We also investigated the group with no TMR sound sleep disturbance. We see a pattern that is reversed (Fig 3.6 B). Here the High Cued group has less memory degradation than the NonCued counterpart (error change 0.084 ± 0.012 vs 0.093 ± 0.015). And also, Low Cued has lower error than Low NonCued (error change -0.027 ± 0.018 vs -0.015 ± 0.019). However, we did not find statistically significant differences in the various comparison groups (All p values > 0.01). Our result is similar to that of Goldi and Rasch 2019 paper where they showed that in undisturbed sleep TMR participants, cueing benefitted memory performance but in the disturbed by TMR sound group cueing actually lead to decrease in the performance (Göldi & Rasch, 2019).

Discussion:

In this current study, first we show that the new spatial memory task that we designed from scratch and implemented using Psychopy and custom-made Python and Javascript codes is suitable for remote online testing with participants correctly following task instructions on their own. We also confirmed that newly designed spatial memory task was sensitive to sleep effect i.e the task performance was rescued by sleep in comparison to wake where spatial memory degraded from immediate to delayed testing phase. Previous studies show that spatial memory is generally consolidated and stabilized during sleep (Rasch & Born, 2013). The degradation of memory strength in the Wake condition is driven by higher memory strength items whereas low memory strength item retains their memory strength.

Overall, we did not find any significant effect of TMR on memory performance after one night or day of TMR intervention in sleep and wake conditions respectively. Since our TMR study was conducted in a naturalistic home setting and without supervision as opposed to control setting of lab where the TMR sound cues are targeted to be specifically played during NREM sleep and cues are stopped on arousal, one-fifth of our participants reported sleep disturbance by TMR sound. Disturbed participants had cued items error greater than noncued items, whereas in the undisturbed sleep participants cued items had less error than noncued items thus showing some sort of memory benefit of TMR cueing when the intervention goes well but the difference did not reach statistical significance. Considering our findings, for future Home TMR intervention studies to work with this current simple design we need more participants recruited since one-fifth of the participants in our study reported disturbed sleep. A previous study by Goldi and Rasch reported a similar trend; out of their 66 subjects only 15 had undisturbed sleep and

consequently showed TMR benefit after 3 night of TMR intervention (Göldi & Rasch, 2019). This brings us to the conclusion that multiple nights of TMR intervention may be need for memory benefit in home-based setting. However, the study also required the participant to continuously carry out the memory test for three consecutive days. So, we cannot positively conclude if the memory benefit was solely because of multiple nights TMR intervention or it was due to some interacting positive effect of repeated testing and multiple TMR interventions together.

One of the limitations of unsupervised TMR intervention is that we designed the TMR sounds to play 45 minutes after the participant hit the play button on their phone. This was designed with assumption that by the time TMR sounds start playing after 45 minutes, participants would be in their NREM sleep. While previous studies from our lab shows that on average majority of participants in the lab condition reach or are in NREM sleep by 45 minutes from beginning of sleep (Tselha et al., 2019), the sleep latencies may be different due to individual difference in the sleep latencies. Another factor influencing sleep latency in the home based setting is that (unlike a controlled lab condition where a single participant sleeps in one room), university students who makes up the bulk of our participants pool share room with other students who might have different sleep schedule might disturbed the sleep. Furthermore, our TMR study is honor based i.e as researchers even though we control and validate the success of each step, there is no way to absolutely tell if the participants played the TMR sounds other than trusting their self-report. In our study all participants included in the analysis reported that they played the TMR sound. Although our study did not show any statistically significant difference in the memory strength for cued vs non-cued in sleep and wake TMR, we saw a pattern of result which tend towards benefit of cueing in participants who had undisturbed sleep due to sound cues. This somewhat promising result calls for more refinement in the home-based TMR approach and method. One such area of refinement is use of wearable EEG to process the sleep signal in real time and target the TMR cue in NREM sleep and around slow oscillation.

Another area of improvement is to develop a system which keeps a log of whether the TMR sound was played or not and also logging the timestamps of each TMR sound cue. Additionally, regarding sound, the system should be able to auto adjust the sound to a volume level which does not cause arousal. This auto adjustment could work on the basis of a feedback system based on EEG signal. Finally, to fully automate the system, process of analyzing the immediate test result and generation of TMR sound cues can be structured to take place in cloud server which ingests the participants data directly from memory task app.

Overall Discussion:

My research works described above focused on investigating efficacy of pharmacological and sleep manipulation for CE. There are many other approaches which have potentials to achieve CE. To translate these potentials into consistent and generalizable result, each of these individual approaches should be continued to be investigated thoroughly to figure out what actually works and what does not? We need to consider all the factors that affect cognitive enhancement. Consequently, with each iteration of consensus on current state of the art, we must investigate where are the rooms for improvement and how to perfect the system further. My research work is an endeavor and scientific contribution in this regard. In the following section, I will discuss what I learned from my investigations, describe the current state of the art and direction for future.

In the case of CE with stimulant approach, although many works report mixed findings, it may be possible to separate the signal from the noise i.e within the mixed findings we can find potential clues of where stimulants do work and what factors may be involved. This leads us to consider different factor for stimulants in the CE. In my case I studied how sleep influences stimulant's impact on cognitive enhancement. My research showed that stimulants even if taken in the morning negatively impacts the night time sleep. This disrupted sleep then affect the next day's working memory. However, in my study, sleep quality was assessed with general measures of sleep like total sleep time, sleep efficiency, minutes in different sleep stages etc. However, we know from sleep research that beyond these general features, there are other sleep features like slow oscillation, spindles and the level of autonomic central coupling which play important role in supporting cognition. In fact, previous research on effect of a GABA agonist drug impact on sleep and WM show that the drug reduces the autonomic central coupling and leads to impairment in the WM performance. It is possible that stimulant use leads

to a suboptimal level of autonomic central coupling which is unable to support WM related process during sleep (Chen et al., 202). One factor beside sleep is individual differences. Different individuals have different baseline cognitive performance ranging from big room for improvement to already at peak capacity. Stimulants may only benefit individuals who have room for improvement in their cognitive performance. However, another way of looking at this is, what happens if the level of difficulty of the cognitive task is changed. For example, the OSPAN task can be modified to increase upper limit of test difficulty to the string level to 12. It is possible that stimulant may benefit the individuals in whom no benefit was seen earlier with a more complex task. A study by (Mattay et al., 2000) showed that in N-back task stimulant helped for the difficult 3-back task but not 2-back task. This also begs the question that do stimulants help the cognitive performance by improving the efficiency of the already existing neuronal network or do they bring change by stimulating some form of neuroplasticity. The second possibility of neuroplasticity is also important for considering the possibility of selective bias by stimulants on one cognitive domain over other.

In my second study we learned that stimulant dextroamphetamine have selective bias on spatial selective attention over verbal WM. Although many cognitive domains have similarity in the shared underlying cognitive processes but different domains also have different level or ratio of stability-flexibility balance. For example, cognitive domain like creativity may need a level that is more tilted towards flexibility than domains which demands more stability like focused attention. When a stimulant causes neuroplasticity related changes which favors certain level of stability-flexibility this may lead to compromise in the performance of other domain which may need a different level. This also predicts that multiple cognitive domain may also improve with stimulants if they share similar underlying properties.

My study on TMR to bias the strength of spatial long-term memory shows that basic feature for TMR related benefit is that cognitive domain needs to be sensitive to sleep effect. In other words, for TMR to have effect on a cognitive domain, sleep must play some important role in the natural process of the particular cognitive domain. TMR leverages the natural reactivation process which are mainly shown to occur during sleeping brain state. My study also supports the finding of an earlier study which showed that in a naturalistic setting of Home TMR, TMR sound cue related disturbance of sleep actually has negative effect on the memory performance. This phenomenon could be due to the disturbance of consolidation process by suboptimal sound cue which causes arousal. Specifically, the negative effect could be attributed to the fact the TMR cueing causes the trace to be labile and susceptible to interference. Instead of usual lability and subsequent strengthening process in optimal cueing, arousal due high-volume lead to catastrophic interference (Goldi and Rasch., 2019).

State of the Art: Sleep Manipulation with TMR

Many TMR research studies have made tremendous contributions to the field of understanding sleep process that support memory consolidation. Used as tool to unravel the mechanistic understanding of the process underlying consolidation, TMR have studies shown the pre-dominance of NREM sleep to how specific features like SO, Spindles and hippocampal SWR are involved (Hu et al., 2021). Most of the recent TMR studies have used the close-loop approach of targeted cue delivery during SO up-states in the NREM sleep. Furthermore, studies have also investigated the importance of cue delivery with respect to sleep spindle. Researchers have found that there is refractory period of sort after each cue delivery. Delivering cue within this refractory period does not benefit instead may disrupt consolidation process (Antony et al., 2018). Some researchers have also investigated the role of TMR in active

forgetting. A relevant motivation behind ‘TMR-to-forget’ could be to erase afflictive memories such as those associated with Post Traumatic Stress Disorder, etc. Furthermore, an understanding of the science behind TMR-to-forget could reveal an avenue to simulate the process involved in ailments related to memory erasure like amnesia and dementia. In a novel, pioneering study by Simon et al., the researchers confirmed that it is possible to lose parts of memory by introducing a ‘forget’ signal cue during TMR sleep. This feasibility of TMR-to-forget was subsequently supported by a study Schechtman et al. in a similar study (Schechtman et al.2020). Outside the declarative long-term memory, researchers have also attempted to use TMR in other cognitive domains like associative learning, procedural memory, language acquisition, emotional memory, cognitive bias modifications (Hu et al., 2020)

Future Directions:

The motivation for cognitive enhancement at the very heart is tied to our innate pursuit of happiness and productive life. In the coming future, both of these have tremendous societal implications and applications. In the realm of pharmacological intervention, the advancement of personalized medicine holds promising future where people will have their genetics, biochemical and psychophysiological data assessed through advance assessment tools and diagnostics followed by formulation of customized pharmacological agents which will be effective in cognitive enhancement for the particular individual. Similarly, continued development in the wearable technology and efficient-powerful processing chips together with fast internet can lead to many possibilities in the field of non-invasive wearable brain technology. A wearable EEG band or even recording chips could record brain signals which would be processed in real-time to classify and identify the current brain state of the wearer and send customized stimulation to the brain to keep it functioning at the peak level. These advancements can benefit individuals suffering from compromised normal brain function but also extend and amplify the capacity of normal, healthy individuals leading to cognitive enhancement.

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