Enhancing Visual Perceptual Learning

Through Reward and Sleep

Aaron V. Berard, Sc.M.
Brown University

Dissertation

Submitted in partial fulfillment of the requirements for the Degree of Doctorate of Philosophy in the Department of Cognitive, Linguistic, and Psychological Sciences at Brown University

PROVIDENCE, RHODE ISLAND
MAY, 2016

This dissertation by Aaron V. Berard is accepted in its present form by the Department of Cognitive, Linguistic, and Psychological Sciences as satisfying the dissertation requirement for the degree of Doctor of Philosophy.

Date_____ _____
Dr. Takeo Watanabe, Advisor

Approved by the Graduate Council

Date_____ _____
Dr. Yuka Sasaki, Reader

Date_____ _____
Dr. Leslie Welch, Reader

Approved by the Graduate Council

Date_____ _____
Peter M. Weber, Dean of the Graduate School

Curriculum Vitae

Department of Cognitive, Linguistic,
and Psychological Sciences
190 Thayer st., Box 1821
Providence, RI 02912

Aaron V. Berard
May 1st, 2016
aaron_berard@brown.edu
(781) 223-0315

Education

Brown University

Ph.D ., Cognitive Science **2012-2016**
M.Sc., Cognitive Science **2012-2014**

University of Massachusetts Amherst

B.Sc., (Honors) in Neuroscience **2008-2012**

Research Experience

Brown University

Laboratory for Cognitive and Perceptual Learning 2012-2016

Project: Frequent video game players resist perceptual interference

- Results: Frequent video game players showed enhanced sleep-dependent learning compared to a non-gaming population.
- Article has been published by PloS ONE (first author).
- Article featured in TIME Magazine, MSN, and several other media outlets.

Project: Sigma activity originated in the early visual cortex during sleep associated with visual perceptual learning

- Results: Spontaneous, localized sigma band activation during sleep in the visual cortex reflected wakeful training on a visual task suggesting a new mechanism of visual sleep-dependent learning.
- Article in preparation.

Project: External reward facilitates visual perceptual learning over a night's sleep

- Results: Visual training paired with an external primary reward (such as water) enhanced learning over a period of sleep, which correlated with significant changes in sleep architecture.
- Article in preparation.

Project: Visual perceptual learning in Alzheimer's patients

- Results: Clinical investigation into Alzheimer's patients' ability to learn visual skills and consolidate memories. Data collection in process.

University of Massachusetts Amherst

Cognition and Action Psychology Lab **2010-2012**
Project: Effects of sleep on category learning

- Results: Implicit and explicit categorical learning behaves differently over a period of sleep

Boston University

Psychology Vision Lab **2007-2011**
Project: The role of contiguity and contingency in visual perceptual learning

- Results: Different mechanisms for visual perceptual learning were found in classical conditioning format compared to instrumental conditioning.

Teaching Experience

CLPS 0510: Perception, Illusion, and the Visual Arts	**Spring 2014**
CLPS 0010: Elementary Psychology	**Fall 2014**
CLPS 0710: Psychology of Happiness	**Spring 2015**
CLPS0010: Elementary Psychology	**Fall 2015**

Skills

- Doctorate-level skill in experimental psychology
- Strong background in behavioral psychophysics and sleep research
- Advanced multivariate data analysis and software manipulation proficiency
- Programming languages: Matlab, R, SPSS, HTML, Python
- Experienced operation of EEG and PSG equipment – includes proficiency in EEG data analysis, sleep scoring, time-series analysis of brain wave oscillations, and cortical source localization.
  - Over 3 years of highly effective teaching experience – trained 4 students in EEG operation and analysis
- Experienced fMRI operation and data analysis
- Skilled in grant and academic paper writing
- Proficient use in all Microsoft Office products (PowerPoint, Excel)
- Over 5 years of training in public speaking and strong teaching experience
- Strong leadership, management, and teaching ability

Publications

(1) Berard AV, Cain MS, Watanabe T, Sasaki Y (2015) **Frequent Video Game Players Resist Perceptual Interference.** PLoS ONE 10(3): e0120011. doi: 10.1371/journal.pone.0120011

Conference Presentations

(1) (Poster) Berard AV, Miller T, Spencer RMC. **Effects of Sleep on Category Learning**, *17th Annual Undergraduate Research Conference*,

Amherst, MA. Apr, 2011.
(2) (Poster) Kim D, Berard AV, Seitz A, Watanabe T. **The role of contiguity and contingency in visual perceptual learning**. *11th Vision Sciences Society*, Naples, FL. May, 2011.
(3) (Poster) Berard AV, Cain MS, Watanabe T, Sasaki Y. **Do video game players resist interference with perceptual learning by training on a new task?** *13th Vision Sciences Society*, Naples, FL. May, 2013.
(4) (Poster) Tamaki, M., Berard, A., Watanabe, T., & Sasaki, Y. (2015). **Sigma activity originated in the early visual cortex during sleep associated with visual perceptual learning.** Journal of vision, 15(12), 1139-1139.
(5) (Poster) Shibata, K., Machizawa, M., Walsh, E., Bang, J. W., Chang, L. H., Berard, A., Tan, Q., Sasaki, Y., & Watanabe, T. (2015). **The neural mechanism of stabilization of perceptual learning revealed by the concentration of excitatory and inhibitory neurotransmitter.** Journal of vision, 15(12), 32-32.
(6) (Talk) Berard AV, Barnes-Diana T, Nanez, Sasaki Y, Watanabe T. **External reward facilitates visual perceptual learning over a night's sleep**. *15th Vision Sciences Society*, St Pete Beach, FL. May, 2015.

Awards and Honors

Dean's Honor List, University of Massachusetts Amherst **2008-2009**
Dean's Honor List, University of Massachusetts Amherst **2010-2011**
Honors 17th Annual Undergraduate Research Conference **2011**
Dean's Honor List, University of Massachusetts Amherst **2011-2012**
University of Massachusetts Amherst *Cum Laude* Graduation **2012**
NIH Vision Training Grant Recipient (Brown University) **2014-2016**
Sheridan Teaching Certificate I **2016**

Biography:

Aaron V. Berard was born at the Toby Hospital in Wareham, MA, on July 18th, 1989. Aaron attended the Commonwealth High School from 2004-2008 and graduated with honors status. From there, Aaron attended the University of Massachusetts Amherst from 2008-2012 where he graduated Cum Laude and received his B.S. in neuroscience. Since college, Aaron has been interested in perception-based psychology and the neuroscience behind sleep, learning, and brain plasticity. Aaron received his Sc.M in Cognitive Science from Brown University in 2014 and Ph.D. in Cognitive Science in 2016.

Preface and Acknowledgments

This dissertation offers a cumulative review, understanding, and concrete projection of the current research employed on investigating the neural mechanisms that contribute to the offline memory formation, integration, and destabilization within the domain of visual perceptual learning. Recent literature offers insights on how visual skills and memories are consolidated during sleep as well as potential frameworks for the mechanisms of these processes. While in the past 10 years sleep research has made noteworthy progress, the mechanisms that contribute to visual perceptual learning during sleep consolidation remain unclear. Recently, reward-based learning and dopamine modulation have been shown to interact with sleep consolidation. In this dissertation, reward processing in sleep consolidation and how this mechanism specifically affects visual plasticity will be discussed. I hope to demonstrate the significance of reward-based memory consolidation in enhancement of visual perceptual learning.

The present research utilized specific experimental conditions that have been thoroughly tested and refined within the Laboratory for Cognitive and Perceptual Learning. The studies are supported by the National Institute of Health (NIH R01EY015980, R01EY019466, and R01MH091801) and the Vision Training Grant T32 EY018080. Additional acknowledgments are extended to the Laboratory for Cognitive and Perceptual Learning as well as Brown University for providing the tools and support to conduct this research. I would additionally like to extend a special thanks to my friends and family for all their support.

Table of Contents

Figures and Tables

Abstract of "Enhancing Visual Perceptual Learning Through Reward and Sleep"
by Aaron V. Berard, Ph.D., Brown University, May 2016

Visual perceptual learning (VPL) is defined as a long-term performance improvement on a perceptual task as a result of perceptual experience. Although VPL is regarded as a manifestation of plasticity in the visual cortex, research has shown that factors beyond the visual cortex facilitate VPL, such as playing video games, reward processing, and sleep related enhancements. In the first experiment of this dissertation, we tested whether frequent video game players have more robust consolidation of VPL compared to non-gamers by employing an interference experiment. As a result, we found the gamers resisted the interference effect while the non-gamers did not, suggesting more robust consolidative mechanisms compared to non-gamers. Since reward is a significant portion of playing video games, this finding was further investigated in the second experiment by examining the effects of reward on VPL sleep consolidation. Four groups were trained over a 12-hour period where two sleep groups and two wake groups received reward and two did not. This experiment yielded a significant interaction between sleep and reward over VPL. We then examined the neural mechanisms of this interaction of reward and sleep on VPL in the third experiment, where two groups were trained (one with and one without reward during training) and then tested after a 2-hour nap. We replicated the behavioral performance results from the second experiment and found that sleep and reward specifically interacted over VPL during post-training REM sleep. This finding

was illustrated by extended REM durations found in the post-training nap in the reward group compared to the control group that did not receive reward. Additionally, during REM sleep, the reward group showed significantly different alpha and theta brain wave oscillation patterns compared to the control group that suggested reactivation of reward processing during REM sleep, which modulated visual processing contributing to the enhancement of VPL.

Chapter 1

1. Introduction

One of the most essential topics in cognitive science and perception research is how the brain selectively adapts to changes in the environment and how these changes are prioritized. Although the brain needs to respond to new and important environmental changes, it must also protect itself from becoming too malleable so that the constant bombardment of irrelevant information does not destabilize the system. This problem is known as the 'stability-plasticity dilemma' (Spanis & Squire, 1987) and remains largely unresolved in cognitive science.

In order to address the 'stability-plasticity dilemma' and related perceptual questions, scientists have studied the visual system as a guide for understanding brain plasticity. Visual perceptual learning (VPL) can be defined as long-term performance improvement on a visual task as a result of visual experience and is regarded as a manifestation of visual plasticity in the adult brain (Sasaki et al., 2010; Fahle & Poggio, 2002). A prominent example of VPL can be seen in the field of radiology, where doctors are given extensive training on how to properly read x-ray scans (Sowden et al., 2000). To the untrained eye, diagnosing tumor presence in an x-ray scan can be almost impossible. Radiology training requires constant, continuous exposure to these x-ray scans in order to hone the ability to identify potentially life-threatening signs of illness. This repeated exposure is an example of VPL, where over time, a radiologist will gain the ability to identify physiological markers in an x-ray scan that are otherwise impossible for the average eye to detect.

In order to understand visual plasticity, it is crucial to investigate the neural changes that occur with the initiation, process, and completion of VPL. A dominant view on VPL processes is that they require focused effort on the part of the observer. However, recent studies have suggested that VPL can occur even without conscious effort (Ahissar & Hochstein, 1993). Research has also suggested that VPL occurs in association with changes in the primary visual cortex, as well as higher cortical areas such as attentional systems, decision-making areas, and reward-processing areas (Law & Gold, 2008). Additionally, it is thought that during the time course of VPL, learning consolidation plays an important role. This includes processes that occur during both wakefulness and sleep that lead to the stabilization and consolidation of VPL (Sasaki et al., 2010). Thus far in research, it has been proposed that VPL is affected by numerous mechanisms, many of which originate beyond the visual cortex and contribute to promoting visual plasticity.

In this dissertation the question of how these processes that facilitate VPL can be *enhanced* is addressed. To date, there exists a solid foundation of scientific research that examines the neural changes that occur with VPL and attempts to identify the root causes that explain how visual plasticity functions. Given evidence that suggests that factors beyond the visual cortex influence visual plasticity, the current work approaches the concept of enhancement by utilizing these known factors in VPL in an attempt to determine their efficiency so as to maximize learning. Here, factors that may affect the consolidation of VPL are investigated with the aim of refining their nature and speeding up learning

acquisition and stabilization. This includes investigating the effects of specialized behavioral training methods on VPL, such as playing video games, as well as the roles of reward processing in VPL consolidation. By examining these processes, new methods for enhancing VPL can be introduced that promote faster, more accurate learning consolidation.

1.1 History of Visual Perceptual Learning

For quite some time, visual plasticity was regarded as a manifestation of neural modulation in the early visual cortex only during the early stages of development that is then hard-wired in maturation into adulthood. This view was substantiated by studies that focused on the visual critical period in early life where rapid neural development occurred for only a period right after birth. For example, binocular vision depends on sustained, patterned visual input from both eyes simultaneously during the critical period in kittens (e.g. Wiesel and Hubel, 1963). Specifically, the limitations of sensory plasticity in this manner was heavily studied and thought of as a primary explanation for the rapid adaptation to selective features in development.

In contrast to traditional definitions of early visual processing, studies of visual plasticity using a multitude of techniques such as psychophysics and single-unit recordings illustrated that performance thresholds for either detection or discrimination of specific stimuli can be lowered and refined to a very high degree (Fiorentini & Berardi, 1980; Schoups et al., 1995). This research identified some of the key foundational aspects of VPL in the manner of defining visual

plasticity at the lower levels of cortical processing. Many earlier studies on visual learning concluded that plasticity can take place in the lower-level visual cortex because learning was only evident in the trained, but not untrained, eye (Fahle et al., 1995). This conclusion would be due to the fact that not many visual cortical cells possess monocular receptive fields past the early portions of the primary visual cortex. Additionally, multiple reports of retinotopic specificity were found in research through various psychophysical tests examining simple visual features such as direction (Ball & Sekuler, 1987; Watanabe et al., 2001) and orientation (Fiorentini & Berardi, 1980; Schoups et al., 1995). These studies provided evidence for plasticity in the early visual cortex.

In addition to psychophysics and behavioral research, low-level visual plasticity has been found through various electrophysical methodologies such as single-unit recordings in animals and functional imaging in humans. For example, single-unit recordings of the early visual cortex in monkeys revealed long-lasting activity changes in response to training with specific stimuli (Schoups et al., 2001; Li et al., 2004; Yang & Maunsell, 2004). Along with these data, MR signal changes in V1 of humans (Schwartz et al., 2002; Furmanski et al., 2004) and the human MT homologue (Vaina et al., 1998) demonstrated plasticity at early sites in the visual cortex, suggesting VPL involves lower-level plasticity. In addition, evidence at other sensory areas support the hypothesis of on-site plastic changes occurring with learning, this has been observed in somatosensation (Dinse et al., 2003) and motor functions (Pascual-Leone et al., 1999; Li et al., 2001) within their respective primary cortical areas. It is important to note that this body of

research has provided evidence that supports the modification of primary sensory and motor areas in response to learning, but does not rule out intervention from top-down processing or higher-order cognitive functions.

One of the quintessential studies in VPL, conducted by Karni and Sagi (1991), demonstrated the significance of early visual plasticity in VPL. This research demonstrates how we may apply properties of visual plasticity to other forms of plasticity in the brain. Participants in their study were given a novel VPL paradigm that, today, is used in a multi-purpose fashion (Yotsumoto et al., 2009a; Sasaki et al., 2009). This is called the Texture Discrimination Task (TDT) and can be manipulated to form both task-relevant and task-irrelevant stimulus features that impact perceptual training (Figure 1.1).

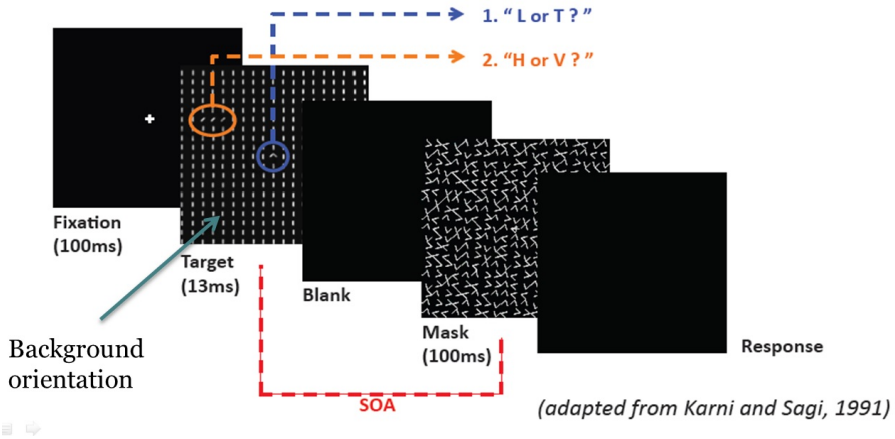


Figure 1.1: An adapted version of the Texture Discrimination Task. The primary target is highlighted in orange (H or V) and is the measure of performance in the task. The secondary target is highlighted in blue (L or T) and is designed to hold fixation. SOA is indicated in red. The shorter the SOA, the more difficult the task becomes. Here, the background orientation is indicated in green and is task-irrelevant. Background information can be manipulated to demonstrate interference properties of VPL.

The task for the subject is to discriminate an array of obliquely-oriented lines imbedded in an array of horizontal or vertical line segments. The target can be

presented in any of the four visual quadrants in the subject's peripheral vision. An additional task is employed in order to confirm fixation in the center of the stimulus. TDT can be varied in difficulty through changing the Stimulus-to-mask Onset Asynchrony (SOA). SOA defines the time between the presentation of the stimulus and the presentation of the mask, designed to prevent further bottom-up processing, where a smaller SOA corresponds to more difficult detection. One of Karni & Sagi's findings was the learning curve over time for the TDT. Moreover, The improvement was found to last years after the training was conducted (Karni & Sagi, 1991; Watanabe et al., 2002).

In addition to the lasting effects on performance from TDT training, Karni & Sagi observed three key features of the training that had significant implications for understanding the plastic nature and functionality of the visual system. The first finding was that training in one of the four visual quadrants did not transfer to other quadrants. Improved performance being limited to a specific peripheral quadrant demonstrated location specificity for VPL seen in studies mentioned above. The second was no inter-ocular transfer of learned TDT features. If the subject was trained only using their right eye, the training did not carry over to the left eye highlighting monocular lower-level plasticity in the visual system. Finally, learning was also specific to the background line-segment orientation. Even if the subject were trained for a substantial amount of time on a specific visual quadrant, when the background lines were changed from say, horizontal to vertical, then performance improvement would not be seen, as if the subject never were never trained at all. All of these characteristics together

demonstrate a high degree of *learning specificity* to the stimulus characteristics that is a key feature of VPL.

1.2 Top-Down Influences and Higher-Order Cognition

In light of the discussed lower-level mechanisms of VPL, the question of how the organism decides *what* to learn remains open. Research has converged on the theory that focused attention in the stimulus features to be learned is required for VPL, engaging higher-order cognition as a director for what needs to be learned and to what degree. This type of VPL is referred to as 'task-relevant' (Seitz & Watanabe, 2005).

Through studying the neural mechanisms underlying VPL, it has been suggested the attention is a key element and VPL may not occur unless it is present (Shiu & Pashler 1992; Ahissar & Hochstein, 1993; Herzog & Fahle, 1998; Gilbert et al., 2001; Schoups et al., 2001). Successful learning has been demonstrated repeatedly in VPL with task-relevant features, although task-irrelevant or unattended features within these experiments can be sparsely learned (Schultz et al., 2000). A prominent example is an early foundational study conducted by Ahissar & Hochstein (1993). They found that there was little to no transfer of learning when subjects were instructed to judge two features (such as orientation and local elements) within the same stimuli. Specifically, subjects were given a dual-task stimulus containing a local 'pop-out' target (to judge whether or not it is present) and a global target (asking whether or not the entire stimulus presented is vertically aligned or horizontally aligned). The results

showed no transfer of each task to new stimuli, suggesting that in addition to feature specificity in VPL, there is a top-down processing element that is also task-specific. Meaning, learning is specific to the trained task due to attention and not just simple features. In another study, when subjects were asked to attend to the stimulus brightness rather than the target orientation, discrimination of that orientation did not improve (Shiu & Pashler, 1992). These two behavioral studies provide evidence that attention plays a key role even in VPL of basic visual features. This evidence is also supported by single-unit recording studies with monkeys, including research that showed visual plasticity in the form of sharpened tuning curves in V1 for the target location in a stimulus (Schoups et al., 2001). This study did not find any evidence of tuning curve changes for the task-irrelevant portion of the stimulus, even though it was presented along with the target in the experiment trials.

The body of research on task-relevant learning and attention was challenged however, when Watanabe and colleagues discovered that a form of task-irrelevant VPL could exist (Watanabe et al., 2001, see Figure 1.2). Subjects were given a series of sessions in which a foveal task-relevant RSVP stimulus consisted of 2 white letters which subjects were required to identify at the end of each trial. During the rapid task-relevant presentation, a specific sub-threshold task-irrelevant motion was presented during the exposure portion of the experimental trial. This motion was invisible to the subjects, as the motion was so obscured by noise that it could not be detected by conscious effort. Despite this, the motion that was presented with the RSVP task showed increased performance

discrimination when tested at the end of the experiment. These results suggest that, even though subjects were not attending to the motion, plasticity still occurred allowing for that specific motion direction to be learned.

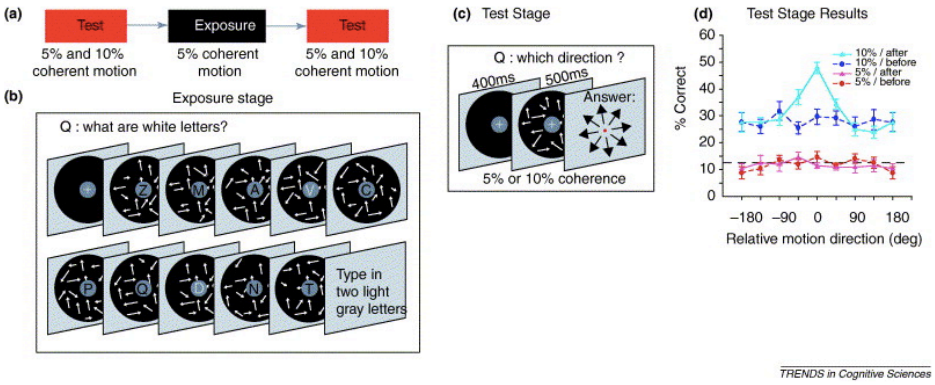


Figure 1.2: Outline of experimental procedure and essential findings from Seitz & Watanabe (2005). (a) A pre-test and post-test procedure was employed to measure performance change with an exposure training session in between. (b) Exposure stage properties. Subjects were required to identify two white letters in a stream of black letter distractors. The letters were presented at the fovea, with the surrounding peripheral space composed of 5% coherent motion that was consistent in direction for each subject across the exposure stage. (c) Test stage procedure. 5% (subthreshold) or 10% (suprathreshold) coherent motion displays were presented in each trial. 500ms after presentation, subjects were required to indicate which direction was present by choosing 1 of 8 directional arrows on screen. (d) Average subject performance at the pre- and post-test stages. 10% and 5% coherent motion discrimination performance before and after exposure yielded significant performance increases at the 10% motion direction paired with the white letters. There was no improvement for the subthreshold stimuli.

In addition to this unexpected finding of task-irrelevant VPL, follow-up studies reported similar effects indicating that attention might not be necessary for VPL to occur. It was found that task-irrelevant learning was highly specific to local motion and was not found for global motion. This type of learning suggested that task-irrelevant VPL was specific to simple visual features (Watanabe et al., 2002). Another study found that mere exposure to a stimulus resulted in VPL of some of the tactile information in the presentation (Dinse et al., 2003). These

studies taken together, suggest that it is possible for VPL to occur without attention given the right conditions.

Following the research line on task-irrelevant VPL, the next question pertains to exposure alone or some form of active participation that leads to task-irrelevant VPL. This is especially interesting because some task-irrelevant learning does not suggest that everything passively observed in our visual field induces plasticity (Watanabe et al., 2002). In 2003, Seitz and Watanabe conducted a study in a similar manner, but attempted to parse out whether mere exposure was sufficient for task-irrelevant VPL to occur. In this experiment, subjects were presented with a similar RSVP task where two white letters in a stream of black letters were to be reported at the end of each trial. Four coherent motion directions were presented during the exposure portion of the experiment, but only one was consistently paired temporally with the presentation of the target white letters. The result of the experiment was that motion discrimination learning occurred only for the motion that was paired with the target white letters, and not the other three directions. If task-irrelevant VPL were a result of purely passive exposure, all 4 motion directions would have been learned. Given that only the motions paired with the targets were learned, the research suggests that there is some element other than mere exposure that is required for task-irrelevant VPL to occur (Figure 1.3).

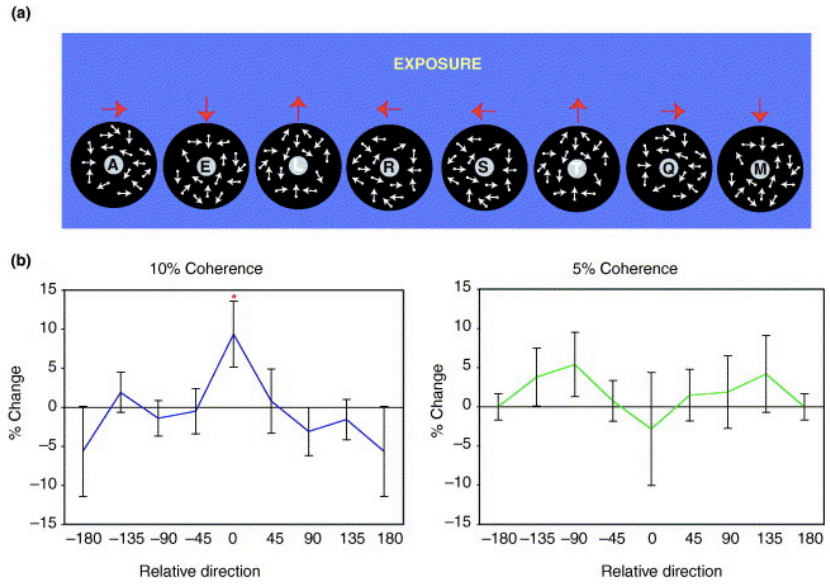


Figure 1.3: Methodology and results from Seitz & Watanabe, (2003 as shown in Seitz & Watanabe, 2005). (a) The 5% subthreshold coherent motion paired with the white letters is shown represented as the up arrow. Three other distractor directions were paired with the black letters. (b) Percent change for motion discrimination results from the pre-test and post-test stages. A significant difference was found for the 10% coherent motion paired with the white letter. Nothing was significant for the 5% coherent motion condition.

The studies by Watanabe and colleagues highlight some interesting properties of VPL, yet do not seem to be in accordance with some prior literature. Seitz and Watanabe considered this issue, and concluded that prior studies that should have demonstrated task-irrelevant learning did not have sufficient pairing of the irrelevant task or feature and the relevant target stimulus. For example, in Ahissar and Hoshstein's work (1993), which did not show task-irrelevant learning, the experimental procedure included trials where the 'pop-out' target (task-relevant) was not presented with either the global target (task-irrelevant) or a blank trial background. There may have been learning had the 'pop-out' target been paired temporally with the global target during every trial instead of presenting the 'pop-out' target sometimes with and sometimes without the

presence of the global target. In Shiu and Pashler's work (1992), the presentation of two task-irrelevant line orientations coincided with the presentation of the two levels of brightness (task-relevant). If one orientation had been selectively paired with a specific brightness level there may have been task-irrelevant learning of these features when that corresponding brightness level was present. Given this evidence, it seems that it is necessary to explain the mechanism for task-irrelevant VPL in order to create a fully formed model of this research.

1.3 Unified Model of Visual Perceptual Learning

In 2005, Seitz and Watanabe established the "Unified Model of Perceptual Learning" in an attempt to reconcile different findings on task-relevant and task-irrelevant VPL (Seitz & Watanabe, 2005). The model proposes that both task-relevant and task-irrelevant learning result from the same properties of the attentional system where diffuse reinforcement signals, triggered by task recognition and completion, drive task-irrelevant learning as long as it temporally coincides with task-relevant targets. Essentially, the primary difference between task-relevant and task-irrelevant learning depends on whether or not they lay in the same temporal and nearby spatial area of attentional focus (does not have to be the exact same spatial location). Task-irrelevant learning can be achieved as long as is it paired with a relevant task that requires attentional resources (Figure 1.4).

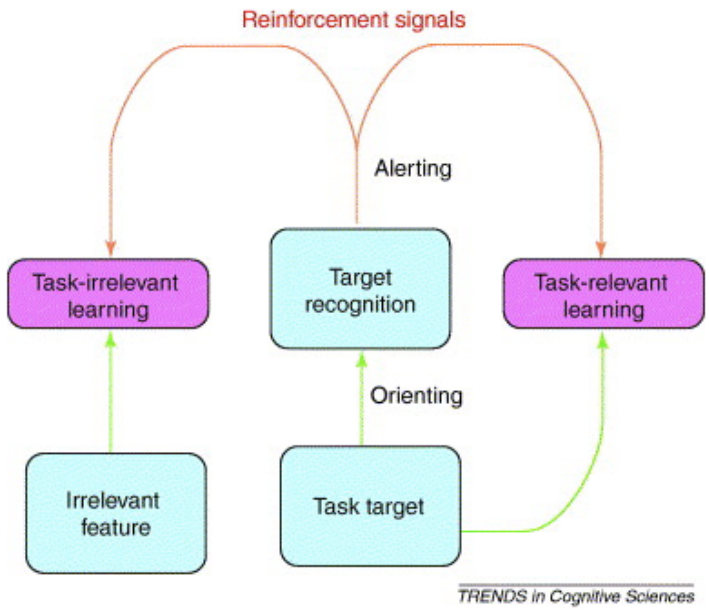


Figure 1.4: The unified model of perceptual learning as proposed by Seitz & Watanabe, 2005. First, a task-relevant feature draws focused attention (orienting) followed by successful task recognition and completion (alerting). This causes diffuse reinforcement signals to be released which triggers task-relevant learning. When this learning is temporally paired with a task-irrelevant feature, this initiates task-irrelevant learning, suggesting that the same mechanism is at work for both task-relevant and task-irrelevant learning.

An important factor that drives these two types of learning is the presence of reinforcement signals from target recognition. In VPL, it is well known that reinforcement is a crucial element to successful learning. Research has shown that reinforcement encouraged through successful task recognition or completion aids in VPL (Karni & Bertini, 1997; Herzog & Fahle, 1999). Additionally, reinforcement has been even shown to play a significant role in VPL at a subthreshold detection level (Seitz et al., 2005).

Another aspect of the unified model of perceptual learning by Seitz and Watanabe utilizes key elements from attentional subsystems, as defined by Posner and colleagues (Posner & Petersen, 2012; Fan et al., 2002). It has been widely accepted that the term 'attention' may be too broad to capture the essence of the

many things that really happen on a neural mechanistic level. Thus, attention can be thought of in three subsystems, two of which contribute to the unified model of perceptual learning. The first of the three subsystems is alerting, which controls a non-specific state of arousal. The second is orienting, which involves directing and concentrating resources to a specific feature or detail. The final subsystem is executive control, which denotes solving task conflict or establishing priority in attentional focus. In the unified model of perceptual learning, a subject would orient to the task target using this attentional subsystem. Then, due to the presence of the target, the alerting subsystem is triggered which contributes to the processing of task-relevant and task-irrelevant features. These attentional subsystems contribute to defining the degree to which top-down attentional intervention plays a role in task-relevant and task-irrelevant VPL.

In the broader scope, VPL can occur in many forms, either involving attention or even through sub-threshold detection (Watanabe et al., 2001; Seitz & Watanabe 2005). This, in addition to the learning specificity of the earlier levels of the visual cortex, suggests a high degree of versatility in what drives VPL. However, studies have indicated trends in VPL where performance increases over a span of a few days (Karni & Sagi, 1991). It is thus important to consider what allows for VPL to increase and persist over days of training. There is a growing body of evidence suggesting that an off-line sleep-dependent component is heavily involved in the consolidation of long-term VPL.

Chapter 2

2. Consolidation, Sleep, and Visual Perceptual Learning

Before discussing the connection between VPL and sleep, it is necessary to identify and explain the neural phenomenon that typically occurs after task learning. This phenomenon is referred to as 'consolidation' and is defined as the progressive post-acquisition stabilization of long-term learning. Essentially, there is a window of time after learning a new task or forming a new skill, when that piece of information is fragile and not yet 'solidified' within the storage system of the brain (Alvarez and Squire, 1994; Karni et al., 1994; Brashers-Krug et al., 1996; Karni et al., 1998; Plihal and Born, 1999; Maquet, 2001; Dudai, 2002; Fischer et al., 2002; Gais et al., 2002; Seitz et al., 2005; Stickgold and Walker, 2005a; Born et al., 2006; Ellenbogen et al., 2006b; Walker and Stickgold, 2006)). Consolidation is what is occurring during this time window, and the end result of this process is observable learning or reliable recall of memories (Sasaki et al., 2009). Research has suggested that in addition to wakeful consolidation, there is evidence for the relevance of sleep (Plihal and Born, 1999; Gais et al., 2002; Gais and Born, 2004; Stickgold, 2005; Stickgold and Walker, 2005b, a; Born et al., 2006; Ellenbogen et al., 2006b; Ellenbogen et al., 2006a; Walker and Stickgold, 2006; Ellenbogen et al., 2007; Rasch et al., 2007 Yotsumoto et al., 2009b). This form of sleep consolidation can thus be thought of as 'off-line learning' (Walker and Stickgold, 2006).

Sleep has been studied in great detail partly because of its strong connection to memory consolidation and learning. A wide variety of human operations have been found to associate not only with sleep in general, but tend to

correlate to specific sleep stages or brain wave oscillation frequencies (Stickgold et al., 2005; Stickgold & Walker 2005a+b; Walker & Stickgold 2006). While the details are under debate, it is generally thought that sleep plays some crucial role in solidifying newly learned skills or memories. Some specific skills, such as motor tasks, have been found to have strong sleep-dependent links, along with retaining episodic memories (Nishida & Walker, 2007).

It should be noted however, that perceptual learning is thought to involve plasticity primarily in the visual cortex and not the hippocampus or other memory related areas (Fahle and Poggio, 2002; Sasaki et al., 2009). This may suggest that the sleep-dependent links associated with perceptual learning may allude to dissimilar mechanistic consolidation. Perceptual learning could show a completely different relationship with sleep or even wakeful consolidation. Given our understanding of the visual system in other respects, however, it is thus important to investigate the neural components involved in sleep-dependent perceptual learning in order to differentiate this from other systems. The findings of this project could yield a new perspective on the processes of VPL or even a better understanding of learning as a general, unified concept.

In prior research, perceptual learning has been shown to have certain connections to sleep, just as other performance tasks such as motor, (emotional) memory, and word-pair tasks (Walker, 2009). Specifically, TDT has been tested extensively and found to be the quintessential VPL paradigm that demonstrates off-line performance improvement thought involve sleep consolidation (Karni and Sagi, 1991, 1993; Stickgold et al., 2000a; Stickgold et al., 2000b; Stickgold et al.,

2001; Mednick et al., 2002; Schwartz et al., 2002; Mednick et al., 2003; Walker et al., 2005; Censor et al., 2006; Yotsumoto et al., 2009b). Specifically, TDT performance improvement was found to be strongly connected to sleep when examined both through behavioral methods and through neuroimaging techniques. Such experiments included sleep deprivation paradigms where control groups trained on visual discrimination were allowed to sleep compared to experimental groups that were deprived of sleep (Stickgold et al., 2000). Further behavioral techniques included segmenting sleep into various portions and training TDT before specific phases of a normal night's sleep (Gais et al., 2000). In addition to the massing behavioral evidence, researchers also conducted fMRI experiments in order to identify local brain modification by TDT training. Studies reported enhanced BOLD signal activation (compared to a group who received no training) during post-training wakefulness corresponding retinotopically the trained hemisphere in the visual cortex after sleep (Schwartz, et al., 2002; Walker et al., 2005). Also, studies with sleeping participants in fMRI scanners revealed significantly enhanced BOLD signals in the trained area of the visual cortex during the first sleep cycle (Yotsumoto et al., 2009b).

In addition to the overnight performance improvement seen with TDT training, there is also a solid platform of evidence concerning how even a short napping period can facilitate consolidation. Researchers found that sleep can improve performance on certain perceptual tasks with just one 60-90 minute nap between training and testing (Mednick et al., 2003). This is similar to the findings from Yotsumoto and colleagues (2009b), where V1 reactivation was found

specifically within the first sleep cycle of an overnight period. It is thus not unreasonable to expect that a nap would benefit TDT performance. Not only was napping found to increase TDT performance, but also napping during the day was reported to rescue TDT performance deterioration typically seen when subjects are trained too much in TDT over the course of wakefulness (Mednick et al., 2002). Given the recent findings on the interaction of sleep and perceptual learning, it is safe to conclude some reorganization of the brain happens during sleep that differs from a wakened state, allowing for long-term consolidation. Specifically, although sleep is correlated with performance improvement on visual tasks, the mechanisms underlying this improvement are still unclear (Sasaki et al., 2009)

2.1 Theories of Sleep-Dependent Learning

To date, the mechanisms of sleep consolidation have been separated into two major theories. These theories aim to explain the specific processes that occur during sleep and how they relate functionally and anatomically to the regions of interest given a certain human operation. The two leading theories are the *learning-consolidation model* (Born et al., 2006; Sasaki et al., 2009) and the *use-dependent model* (Stickgold et al., 2001; Tononi and Cirelli, 2003), each of which attempts to tackle the specifics of off-line information consolidation (Miller, 2007).

The learning-consolidation model explains sleep consolidation with local mechanisms, suggesting that sleep consolidation works specifically on the cortical

regions that were used in a given task (Stickgold et al., 2001; Born et al., 2002). The use-dependent model however, approaches the problem of consolidation in more general terms. This model states that sleep initiates broader mechanisms that do not necessarily have a direct impact on learning, but help with learning consolidation as a by-product (Tononi, 2004). Specifically, the use-dependent model states that synaptic homeostasis correlates with slow wave activity (SWA) that occurs during sleep, and that we can measure learning by looking at the SWA originating from specific brain areas that were heavily used during the preceding wakefulness (for example, the visual cortex during VPL). This type of processing increases in local areas during sleep and has been found to correlate with learning, even though there is no direct mechanism meant to initiate learning and neuroplasticity. Instead, it is thought that learning itself is a by-product of synaptic homeostasis. The learning-consolidation model however, proposes a direct mechanistic connection to neuroplasticity and that there is a actual system originating in the brain that is specifically designed to initiate and modulate learning. This is thought to happen through four differently weighted theories (which are not entirely exclusive) that probe the possibilities of how exactly this mechanism operates on learning. The primary difference between the learning-consolidation and use-dependent models is that one proposes that sleep directly acts on learning while the other proposes a general mechanism that affects learning as a by-product.

2.11 *Use-dependent model*

The use-dependent model is based on synaptic homeostasis described most recently by Tononi and Cirelli (2003) in their work regarding brain wave patterns and spontaneous oscillations, building off of a long-time concept for memory function and learning during sleep (Diekelmann & Born, 2010). With spontaneous oscillations, namely SWA, synchronous neural firing during sleep can indicate synaptic homeostasis that produces learning as a by-product. This is the central theme to the use-dependent model. Spontaneous oscillations occurring in a general manner over the brain are thought to have higher activation in areas that have had training, producing a beneficial effect (i.e. learning) on task performance. When a task is performed, synapses used in the corresponding brain region are worked harder and exhibit more activity. During sleep, this increase in activity is downscaled in a homeostatic fashion, which results in a form of synaptic pruning. This pruning leaves only the specific synapses behind that were crucial to the task at hand, resulting in a higher signal to noise ratio, and equates to more efficient processing (Figure 2.1).

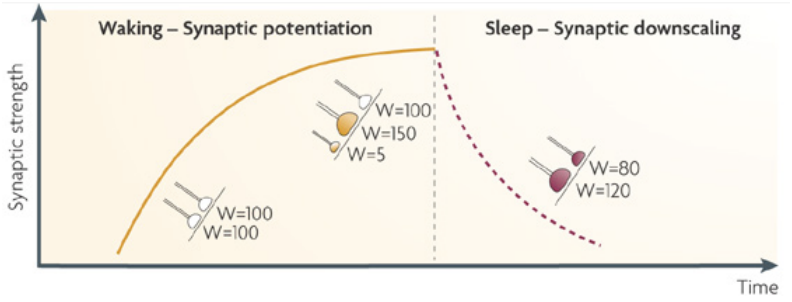


Figure 2.1: Use-dependent model representation from Diekelmann & Born, 2010. The core concept of the use-dependent model proposes that plasticity

> occurs as a by-product of synaptic downscaling during sleep. This results as a change in the weight of synaptic strengths depending on which synapses were most engaged during take performance during wakefulness. Synaptic strength and new connections are facilitated throughout the day and once sleep onset occurs, downscaling begins to prune out weaker synaptic connections. The synapses with the strongest weight based on wakeful usage will survive the pruning, unlike the less-used synapses. This results in a higher signal-to-noise ratio for the stronger synapses and effectively drives relevant learning plasticity.

There exists a plethora of research on SWA and its impact on learning, lending credit to the use-dependent model. TMS studies in rats for example, yield bursts of neural firing that are analogous to the SWA that occurs is the use-dependent model (Czarnecki et al., 2007). Another example includes studying synaptic activation during wakefulness in flies. Specific areas of activation display significant downplay in activity during sleep in accordance with this model (Donlea at al., 2009; Gilestro et al., 2009). Also, SWA was found to increase in the parietal region after an arm rotation task (Huber et al., 2004). This specific rotational task was found to be associated with the parietal motor areas in prior studies (Vyazovskiy et al., 2000). Given this extensive line of research as well as more recent contributions (Tononi, 2014), it would seem that when considering sleep-dependent learning, the use-dependent model must be considered.

It is important to revisit the important aspects of the use-dependent model. The use-dependent model does not focus specifically on the regions involved with leaning, but rather produces the results from learning as a by-product of global cerebral operations (Tononi & Cirelli, 2003; Huber at al., 2004). There are also data suggesting the direct

conclusion that learning is an epiphenomenon of synaptic homeostasis. In one study, arm immobilization was linked to a decrease in SWA in the corresponding motor area (Huber at al., 2006), suggesting that the decrease in SWA indicated less neuronal downscaling and therefore, no learning had occurred. According to the use-dependent model, synaptic downscaling is regulated by SWA and therefore, these results from Huber et al. ~~would~~ mirror the decrease in SWA expected from the model.

2.1.2 *Learning-Consolidation Model*

Unlike the central theme of the use-dependent model of processing, the key to the learning-consolidation model revolves around the idea that there is a specific mechanism operating directly on the cortical region used in task learning (Stickgold et al., 2001; Born et al., 2002). This process occurs during sleep and is uniquely responsible and necessary for consolidation of learning and memory. The learning-consolidation model can be further divided up into four hypotheses that could work either independently of one another or cooperate. These four theories are the dual process hypothesis, the sequential hypothesis, the spontaneous oscillation hypothesis, and the cortical connectivity hypothesis.

The dual process hypothesis explains sleep consolidation in terms of sleep stages and their specificity for different kinds of learning. The primary concept would focus on a contrast between SWS (slow-wave

sleep) and REM (rapid eye movement) (Born et al., 2006). Specifically, SWS was found to have some involvement in declarative memory consolidation while REM sleep processes procedural learning (Marshall et al., 2004; Born et al., 2006; Rasch et al., 2007). Long-term potentiation (LTP) is thought to be the primary model for the synaptic modulation occurring in this hypothesis. For example, the neural networks involved with declarative memory tasks would reactivate during sleep in order to strengthen their synaptic connections (Hasselmo, 1999; Born et al., 2006; Rasch et al., 2007), as opposed to the use-dependent model where SWA would encourage some form of synaptic pruning. There are other studies however, that have found results, which counter the above conclusions by Born and colleagues. For example, a perceptual leaning study found unique evidence suggesting that procedural learning could be consolidated during NREM instead of REM. The experiment utilized a special task, which trained the V1 region of the visual cortex, and then examined the effects of sleep. Activation of the V1 cortex was highlighted during NREM, suggesting learning may be occurring during NREM as opposed to the hypothesized REM stage (Yotsumoto et al., 2009b).

The sequential hypothesis on the other hand, views the significance of sleep stages together as opposed to apart. Instead of one sleep stage being responsible for a specific type of learning, both SWS and REM work together in a cyclic fashion to consolidate learned material. In essence, these two primary sleep variables operate in a dependent fashion,

where one would not able to perform its duties without the other. Research has suggested that during sleep, SWA presence is responsible for "preparing" the brain for the structural changes of synaptic plasticity. Although SWA is thought to prepare the brain for plasticity, the actual event of plasticity occurs during the following periods of REM sleep. Therefore, according to this theory, slow wave sleep (SWS) and REM operate on a dependent cycle where SWS initiates processes needed for plasticity to take place and REM sleep implements these processes (Guidditta et al., 1995; Ficca & Salzarulo, 2004). The idea of sleep being a "cycle" with separate components depending on each other for operation is not completely unheard of. Previous research has found that performance improvement from training on a certain visual task can best be explained by the interaction between SWS and REM sleep and not due to either alone (Gais et al., 2000; Stickgold et al., 2000b; Mednick et al., 2003).

The third hypothesis, the spontaneous oscillation hypothesis, attempts to view sleep consolidation as not bound by specific sleep stages but rather involving the spontaneous oscillations themselves. Both the dual process hypothesis and the sequential hypothesis are based on larger, core components of sleep: NREM and REM sleep. These hypotheses consider the extent to which SWS and REM sleep interact and depend on each other, whether they are both necessary for plasticity or simply mediate processes leading to plasticity. The extent however, to which SWS/REM

mediate consolidation of learning may seem some what limited, since each respective sleep stage contains a myriad of spontaneous neural oscillations with varying frequency bands (i.e. there is more than one frequency band to each sleep stage). Therefore, it may be too crude to organize theories of sleep consolidation simply around different sleep stages (Diekelmann et al., 2009). These spontaneous oscillatory activities that occur during each sleep stage are thought to arise from synchronous neural activity, which may be linked to offline consolidation. It is possible that during this spontaneous activity, different oscillatory frequencies may emerge and represent different roles for neural synchronization (von Stein et al., 2000; Engel et al., 2001; Vidal et al., 2006). Due to this evidence, more recent studies utilizing polysomnography (PSG) tend to encourage more detailed analysis of seep structure. Therefore, specific frequencies such as those representing sleep spindles (sigma band) or SWA are more closely investigated as opposed to simply examining at sleep stage patterning. There are several examples illustrating this point. In recent research, sleep spindle oscillations were examined with specific tasks during post training sleep. One study found that increased spindle activity during post-training sleep was linked to performance improvements with a verbal memory task (Gais et al., 2002). Another study found similar results regarding the properties of spindle activity with respect to motor learning (Nishida & Walker, 2007; Morin et al., 2008; Tamaki et al., 2008a, 2009). In addition to the significance of sleep spindle activity arising in modern research,

post-training sleep oscillatory SWA was found to correlate with performance improvements on a declarative memory task (Born et al., 2006), suggesting the importance of SWA frequencies. Another round of studies found evidence that electrical stimulation generating more SWA during sleep was found to be connected to better performance with declarative memory tasks (Marshall et al., 2004; Marshall et al., 2006). It is important to note at this point that both spindle activity and SWA are frequencies that generally occur during NREM sleep, although not always. Like these, theta activity, while typically occurring during REM sleep, is also seen throughout an entire sleep cycle. However, research has suggested the relationship between theta activity and firing neuronal patterns during REM sleep is altered due to learning (Poe et al., 2000). This all, taken together, suggests that close inspection of frequency properties could yield more information about the functional significance of sleep

The forth and final hypothesis concerning the learning-consolidation model is the cortical connectivity hypothesis. Research has suggested that during learning, the brain undergoes changes in cortical connectivity (Maquet et al., 2000; Laureyes et al., 2001; Robertson, 2009). Changes in cortical connectivity patterns during sleep suggest a possible connection to offline-learning and global reorganization (Massimini et al., 2005; Massimini et al., 2007). This hypothesis would be consistent with the learning-consolidation philosophy, where previous literature suggests

global cortical reorganization in response to learning as opposed to local neuronal downscaling associated with the particular brain region of use (Stickgold, 2001; Tononi, 2004).

2.2 Interference and Stabilization in VPL

Consolidation during sleep, as illustrated above, contains many different theories, which not only outlines how the brain learns new skills but also suggests the importance of this phase of skill acquisition. Although the technicalities of sleep consolidation are on their own quite elaborate, it is important not to forget that the process of consolidation is not just about sleep. Consolidation, as a whole, undergoes a unique time course that spans from wakefulness to sleep. Research suggests that after a new skill is acquired it persists in the brain in a fragile state for a period of time before it reaches a point of stabilization (Müller & Pilzecker, 1900; Lechner et al., 1999), which is usually solidified with wakeful and sleep consolidative mechanisms. The period of time before a memory has become stable has been defined as fragile and momentarily not resistant to interference (Brashers-Krug et al., 1996). Specifically, it is possible to interfere with the consolidation of a new skill by disrupting or engaging the brain during the time period when the skill has not yet stabilized. This is referred to as interference and has been demonstrated VPL (Seitz et al., 2005; Yotsumoto et al., 2009).

Research of interference has first been studied through motor learning experiments. In a typical paradigm, subjects practice and adapt to a hand-reaching task where the force and degree of hand rotation, which is varied from what the

visual system would expect, is learned over time. Subjects typically display adaptation over several days and become quite good at applying the correct force and projection to complete the hand-reaching task. When interference is introduced, subjects will train on the same paradigm as described and will learn the specific force and projection to apply to complete the task known as "task A." The key difference is that instead of just training on task A, a second task known as "task B" is introduced to the experiment. Task B takes place immediately following task A. Subjects usually spend 30 minutes to an hour learning the force needed to adapt to task A and then are required to train on task B, a very similar task with the only differences residing in the parameters of force needed to apply adaption. When this competing task B is introduced after task A, the following day subjects do not display performance improvements on task A (Brashers-Krug et al., 1996; Caithness et al., 2004; Osu et al., 2004; Shadmehr & Brashers-Krug, 1997). This type of affect has also been shown in visual-motor sequence learning (Walker et al., 2003). The idea is that once the subject acquires task A, the brain needs a period of time in order for that new memory to stabilize and become resistant to interfering information. Since the tasks are so similar, training task B right after task A introduces a second memory that competes for the same physical neural space in the brain (Seitz et al., 2005). Simply put, unless there is time for the first memory to stabilize, similar types of memories can overwrite previous memories before consolidation takes place.

The most recognized study to investigate interference in VPL was performed by Seitz and colleagues in 2005 (Seitz et al., 2005). In this project,

interference in VPL was specifically investigated. Up until this point, motor and visual-motor learning studies had dominated the field investigating interference, which raised the question of what the characteristics specific to VPL were under neural interference. Seitz and colleagues applied a vernier acuity task that trained subjects on the ability to discriminate the alignment of three vertically stacked dots. Subjects were asked on a trail-by-trail basis if the center dot was in place with the other two. Over a period of 5 days, performance increased and subjects shoed better discrimination abilities for the task (Figure 2.2).

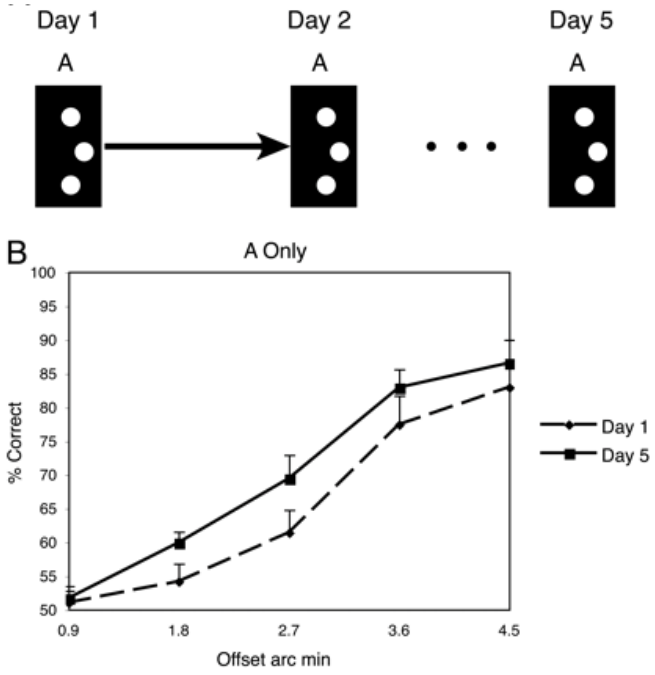


Figure 2.2: Control condition for Seitz et al., 2005. Subjects were required to focus on a central fixation throughout trial presentation. In each trial, the acuity task was presented in the lower right visual quadrant as three vertically aligned dots. Two presentations were given in each interval and subjects were required to identify if it was the first or second presentation interval that contained the offset dots. Difficulty was varied by the offset of the central dot in arc minutes from the other two dots. Over 5 days, subjects showed typical VPL and improved at all difficulty levels.

In the Seitz 2005 study, a key component was added that denoted the interference paradigm. As shown above, subjects improved over 5 days with "task A" in the vernier acuity training. In the experimental condition, Seitz and colleagues introduced a second task (task B), which was learned right after learning task A. This competing vernier acuity task was similar enough to the first task that performance increase was not seen in the first task as readily as the control condition (Figure 2.3). Additionally, unlike motor learning, which required a 6-hour period of wakefulness in between training task A and task B to not show interference, Seitz and colleagues found that this vernier acuity task only needed one hour of wakeful consolidation before the memory was resistant to interference (stabilized). This research not only demonstrated the properties of interference with VPL, but also suggested that the characteristics of plasticity in the visual system differ from other modalities.

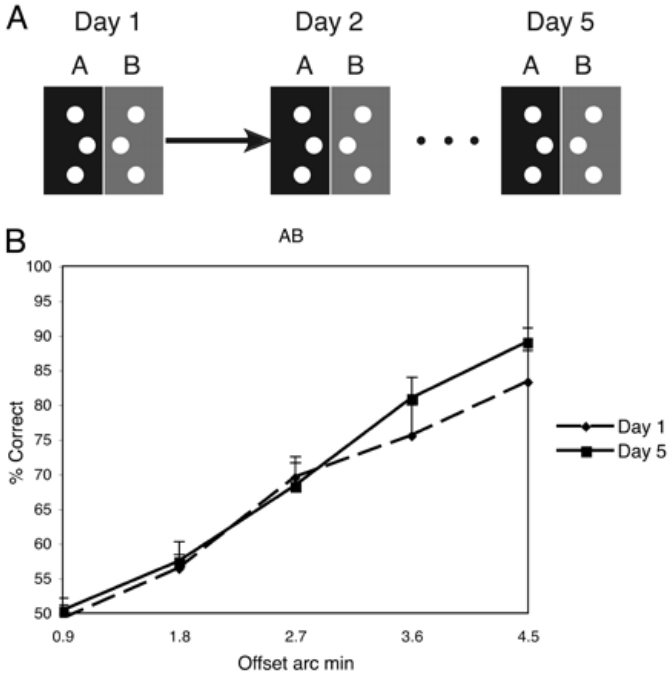


Figure 2.3: Experimental condition for Seitz et al., 2005. Procedure was identical to the control condition except subjects were given an additional task following the first acuity task. The difference in the two tasks was the direction (left or right) that the central dot was offset. Performance improvement was only seen on the easiest conditions although it could be described as negligible. This is a demonstration of the interference effect.

Given that Seitz and colleagues demonstrated interference in VPL only if the two tasks were not in different orientations, locations, or offset-orientations, we can conclude that the interference that occurs on a neural level is most likely a process of the early visual cortex. VPL is typically studied across many different paradigms and methodologies however, so the findings from Seitz and colleagues could be task-specific. This research was followed up by Yotsumoto and colleagues in 2009, where interference in VPL was tested against the widely-known and foundation methodology used in Karni & Sagi's research in 1991: the texture discrimination task (TDT) (Yotsumoto et al., 2009). Yotsumoto and colleagues varied different aspects of the TDT given to subjects in their series of experiments. One of the essential findings involved a display of interference, which occurred when learning two different but similar sets of the TDT. The results interestingly demonstrated that varying task-specific orientation in the foreground target did not produce and interference effect, but instead this was only seen when the background orientation was varied between task A and task B (Figure 2.4). This suggests that the low-level interference that occurs for VPL is specific to the background lines in TDT, but not the target orientation. This could have many implications and is important for the line of memory consolidation research in VPL.

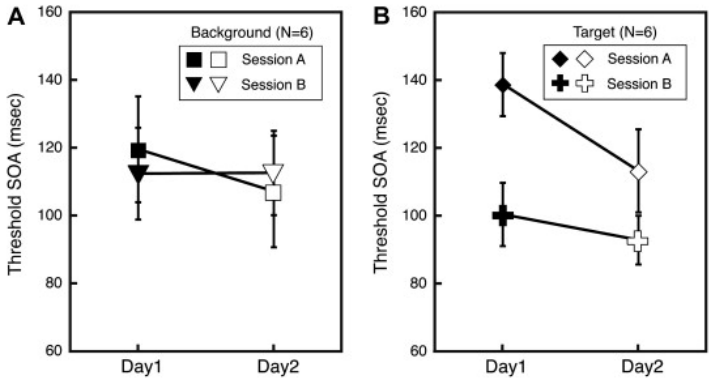


Figure 2.4: Results from the interference experiment in Yotsumoto et al., 2009. (a) Threshold SOA (measured as 75% point on the logistic curve fitted to the data with ascending SOA difficulty) when background orientation was varied. Between two background orientations, performance improvement was not seen on either background for either session. (b) Threshold SOA for target orientation variation. Significant performance improvement was found in this condition, demonstrating no interference effect, unlike what was seen in the background orientation variation experiment.

The results from Yotsumoto and colleagues illustrate very significant aspects of neural interference in VPL. In accordance with previous research (Mednick et al., 2003; Seitz et al., 2005), interference was established and characterized as a lower-level visual area modification, which housed the damage done by learning and interfering task. The key aspect of Yotsumoto and colleagues' work was that interference occurred for only the background change but not the task-relevant target change, which both contain low-level visual information features that are involved in the task. It is possible that interference occurred for the TDT background change due to its irrelevancy to the target in the discrimination trials. This could potentially assume that attention played a role in the interference process (Mednick et al., 2003; Yotsumoto et al., 2009), where focused attention on the relevant task disregarded feature change of the task which would have normally caused interference, but still remained susceptible to interference of information that was not relevant to the task. Both Yotsumoto's

and Mednick's group theorized that there could be two mechanisms at work during the interference process in VPL memory consolidation. Given this line of thought, it is possible that higher and lower level mechanisms are operating in VPL (in accordance to the unified model of VPL presented by Seitz and Watanabe) to the extent in which interference occurs. It may be the case that due to activity of each of these mechanisms, one or both may be responsible for deciding which information is critical when two memories are competing for the same neural space during memory fragility. Another possibility is that, due to background interference of TDT and not task-relevant changes, there may be modifications to perceptual templates that set the foundation for a visual space that is being learned and results in interference when that perceptual template is changed (Lu & Dosher, 2008). Given that there seems to be two processes at work, it may be possible that changing one or both could affect the other.

These findings above suggest a significant characteristic of memory consolidation and stabilization of VPL through work with interference. This finding is that the properties of consolidation can be modified, depending on task and situational circumstances. It may be possible to change or alter this pattern of consolidation to induce less interference and encourage maximization of information acquisition efficiency. Thus far, in models of VPL, sleep consolidation, stabilization, and interference, we have seen progress in understanding evidence and exceptions to memory formation and solidification in VPL that suggest concrete mechanisms for this type of neural plasticity. With respect to what we know, is it possible to hone and modify these mechanisms to

produce more efficient or faster learning? It may be quite possible that using all of this research, we can develop methodology that aims to improve and enhance VPL and plasticity, harnessing either or all of what we know on lower-level plasticity, high-level plasticity, consolidation, and stabilization, which could be used to expedite learning. Many academic groups have engaged the concept that the brain operates like a muscle, a muscle that can be trained. As such, various behavioral training methods have been explored in the effort to contribute to the facilitation of VPL. A popular topic is the study of video games and how they contribute to learning and brain plasticity.

Chapter 3

3. Video Games and Enhancement of Visual Perceptual Learning

Every day, more of our society is exposed to rapid video stimulation and virtual environments, ranging from television and movies to interactive games requiring active and vigilant participation. The frequency of exposure is becoming more prevalent in today's youth as well as among the general population, raising questions of how such activity affects our brain. In the past decade, studies have been conducted examining the differences in visual skill and function with frequent gamers compared to non-gamers. There exists a plethora of viable evidence suggesting differences caused by frequent exposure to video games.

One way to think about frequent video game playing is under the context of training and honing skills. Perhaps this is an analogue to going to the gym, practicing sports, or building athleticism, except for your brain. Can frequent video game playing influence brain plasticity? This is the question on many researchers ask as they study the cognitive effects of immersive gameplay styles in frequent habitual behavior. From the accumulating evidence, many theories are arising that suggest that frequent exposure to video games could modify attentional load, visual ability, cognitive control, and even visual perceptual learning.

3.1 Video Games and Cognitive Science

Studies with frequent video game players have revealed interesting side effects to their habitual activity. It is important to note that although there are numerous types of video games, from adventure and real time strategy games to

racing and sports simulators to simpler games like Tetris. The consensus seems to be that, just as various exercises at the gym offer various benefits for your body, these varieties of video games offer different effects for the brain (Green & Bavelier, 2010) The most widely-studied video games are first-person shooters (FPS) or adventure games since this essentially is the closest setting to virtual reality and could potentially offer "multidimensional" performance enhancements directly related to cognitive and vision science (Green & Bavelier, 2003; Green & Bavelier, 2007, Green & Bavelier, 2010; Li et al., 2009; Lu & Dosher, 2008). One particular study in 2003 by Green, Bavelier, and colleagues investigated frequent FPS game playing and the potential benefits on visual discrimination, field of view, attentional load, motion tracking, and object identification that could directly be related to basic elements in cognitive science and visual perceptual learning.

In Green and Bavelier's research, two populations were compared under a battery of cognitive and visual tests. One population was a control, designated as Non-Video-Game-Players (NVGPs), which consisted of individuals who did not frequently play video games. The other population, designated Video-Game-Players (VGPs), was defined as participants who engaged in action video game playing for at least 1 hour per day for 4 days a week in the past 6 months. The listed games for the VGPs were Grand Theft Auto 3, Half-Life, Counter-Strike, Crazy Taxi, Team Fortress Classic, 007, Spider-Man, Halo, Marvel vs Capcom, Roguespeare, and Super Mario Cart. All of these games have the first-person

perspective in common, as well as require quick reaction to adaptive visual stimuli.

The first task employed was a flanker-compatibility task, which was designed to measure attentional capacity by gauging the distracter effect in visual discrimination (Eriksen & Eriksen, 1974). The stimulus consisted of a fixation point, with identifiable squares or diamonds in the periphery that could be paired with additional information to distract participants from the target response of whether the presented image was compatible or not. The idea is that when the task is easy, a distractor effect occurs where surplus attentional resources 'spill over' to the irrelevant stimuli. This effect is less seen when the task is difficult, which is believed to be reflective of how engaged the participant is in the experiment (Lavie & Cox, 1997). The hypothesis was that, since VGPs are exposed to rapid visual information that requires constant attentional hold, they should have a higher attentional capacity, and therefore exhaust their attentional resources at a slower rate compared to NVGPs. As expected, VGPs demonstrated a constant distracter effect even when the task was difficult. This did not hold true for the NVGPs (Figure 3.1).

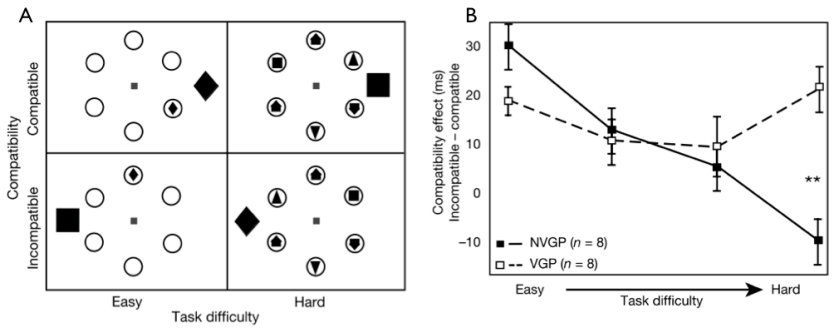


Figure 3.1: Flanker compatibility task used in Green & Bavelier, 2003. (a) Task stimulus. Subjects were required to fixate and were presented with two or more shapes. The target shape (square or diamond) was indicated as placed in one of the six circles surrounding the fixation point. A distracter shape was presented outside one of the circles. Subjects were required to indicate if the target shape was a square or a diamond. Difficulty was varied according to how many distracters were present in the stimulus. Compatibility was measured according to whether or not the primary distracter and the target stimulus matched. The processing speed between compatible and incompatible trials addressed the attentional resources of VGPs and NVGPs. (b) Flanker compatibility task results. Results showed that the compatibility effect (designated as attentional resources) decreased with task difficulty for the NVGPs. The VGPs however, remained constant across all difficulty levels suggesting increased attentional resources.

Attentional capacity in VGPs was further investigated by employing an enumeration task. Here, a stimulus was presented briefly and participants were required to identify the number of squares that flashed on the screen. It is believed that there are two processes that the brain engages in order to complete this task. The first is an automatic "subsidizing" process, which is fast, accurate, and independent individual number. The second is a serial process, which is slower and can account for a larger number of items (Kaufman et al., 1949). Specifically, the number of items that can be subsidized is thought to be a direct reflection of attentional capacity, where the higher the number, the more capacity storage (Trick & Pylyshyn, 1993; Trick & Pylyshyn, 1994; Tuholski et al., 2001). Green and Bavelier found that VGPs could subsidize significantly more items than NVGPs, in accordance with the present theory (Figure 3.2).

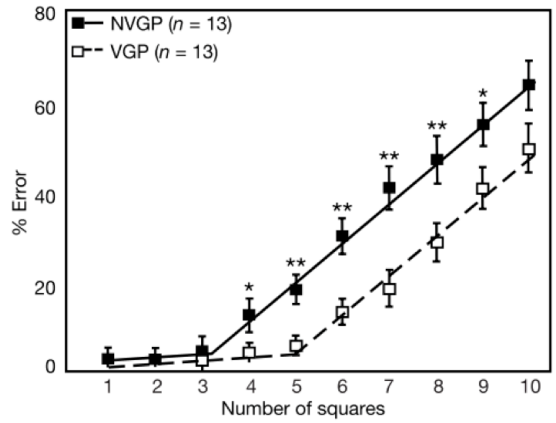


Figure 3.2: Enumeration task in Green & Bavelier, 2003. At all levels, VGPs displayed less error when reporting the amount of squares flashed on the stimulus. NGVPs displayed lower performance especially at difficulties where more than three squares were presented at a time.

An important aspect of these tests was that all information was displayed within a 5-degree eccentricity range. Along with the fact that most VGPs reported playing within an 18-degree eccentricity range, it could be said that visual improvements were specific only to this limit. Green and Bavelier used a useful field of view task on their two populations, in order to see if improvements in visual attentional ability remained within the specified eccentricity range or if there was a translational component. In this task, participants were required to identify a target amongst noise at different peripheral eccentricity ranges (Ball et al., 1988). The results demonstrated that VGPs not only out-performed the NVGPs at closer eccentricity levels but also continued to display dominance at far ranges such as 30 degrees (Figure 3.3). This finding is crucial, as this suggests that the benefits of frequent video game playing not only is specific to the game itself, but also extends neural modulation outside of the activity area. We can

speculate that if this is possible, other benefits could be seen from frequent video game playing that are translational and global.

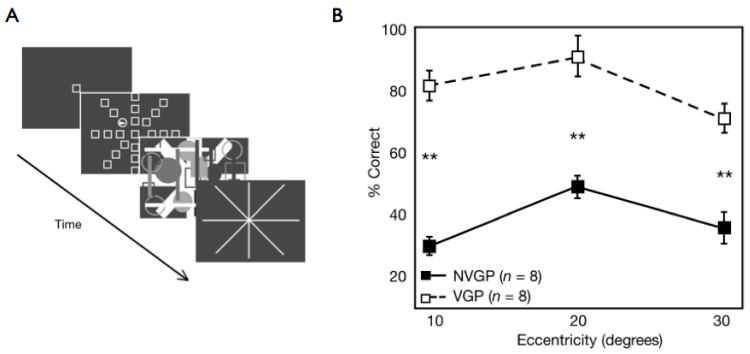


Figure 3.3: Useful field of view task as presented in Green & Bavelier, 2003. (a) Stimulus presentation. Subjects were required to fixate on the center of a computer display. A stimulus was presented in one of the 6 spokes surrounding the fovea fixation point followed y a sensory mask. Subjects were then required to indicate which spoke the target appeared on. Eccentricity values were varied according to how far away from the fixation the stimulus appeared. (b) Results of useful field of view task. VGPs displayed greater accuracy not only at all location but also at all eccentricities even up to 30 degrees. This amount was typical outside the area of affect for frequent video game playing.

The final experiment performed in the Green and Bavelier study was the classic attentional blink task. In every portion of this study, VGPs seem to have outclassed NVGPs in terms of attentional capacity. But the question remains if frequent video game playing modifies temporal attention and not just spatial. The attentional blink task measures an "attentional bottle-neck" where it is thought that resources are constricted temporally depending on if too much information is presented in a short amount of time (Raymond et al., 1992; Chun & Potter, 1995; Broadbent & Broadbent, 1987). In the task, the participant attends classic RSVP-style presentation of a stream of letters where they are required to pick out two targets shown closely together in time. If the two target letters are presented

within 200-500ms of each other, the second target is usually not seen due to attentional resources being constrained temporally by the presentation of the first target letter. Green and Bavelier were able to show that not only were VGPs better at the task in general (more accurate at all lag times), but also displayed abnormally high accuracy at the lag 1 portion of the trials (Figure 3.4). This suggests that VGPs not only have less of an attentional bottleneck in which to process more information quicker, but also have greater task-switching ability, where shifting attentional resources from one item to the next is accurate even in short temporal limits (lag 1 differences). A final note is that attentional blink is thought to be amodal (Chun & Potter, 1995; Arnell & Jolicoeur, 1999; Potter et al., 1998; Proksch & Bavelier, 2002), where tendencies seen are displayed not just through visual identification, but also span across other sensory systems as well.

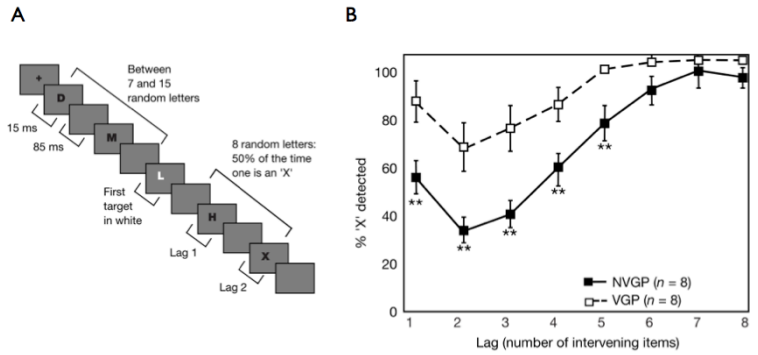


Figure 3.4: Attentional blink task employed in Green & Bavelier, 2003. (a) Stimulus presentation. Black letters were flashed in a RSVP style design, where one white letter was present somewhere in between. An 'X' was presented 50% of the time at a temporal location after the presentation of the white letter. Subjects had to indicate what the first target (white letter) was and then if whether or not the second target (the 'X') appeared. Temporal variation in space was denoted as 'lag time' and identified how close the second target was to the first in presentation. Typically the greatest attentional blink effect occurs in the first couple lag spots. (b) Results of the attentional blink task. VGPs outperformed NVGPs at all lag spots including the early temporal locations. As the attentional bottleneck decreased (further lag spots), VGPs and NVGPs began to show similar performance.

All of this evidence taken into context suggest that not only do VGPs have greater visual attentional ability than NVGPs, but also could translate performance improvements across all modalities and beyond training range. However, it is necessary to address some confounding factors of Green and Bavelier's work. One major controversy in cognitive research on video games is inherent population differences. Is it possible that some people are drawn to video games because they are naturally good at them? Or would people simply become better at video games by playing them over time? If some people were naturally better at video games, would this include enhanced motor skills used to operate the game? Would NVGPs have to divert attentional resources to motor control that could have skewed the results of this work? In order to address these questions, Green and Bavelier conducted a follow-up study where NVGPs were assigned to play an action video game, Medal of Honor, for 10 days for at least one hour a day. This group of participants was compared to regular controls that did not play any video games as well as an additional group of participants that played Tetris for 10 days in the same fashion as the Medal of Honor Players. Interestingly, the group that played Medal of Honor for 10 days demonstrated enhanced attentional abilities similar to frequent VGPs even after a short 10-day training period. Tetris and regular controls did not show this same effect (Figure 3.5). In conclusion, Green and Bavelier were able to show that frequent action video game playing led to enhanced visual attentional abilities which could be

translatable to amodal properties that can be formed in as little as 10 days of consecutive training.

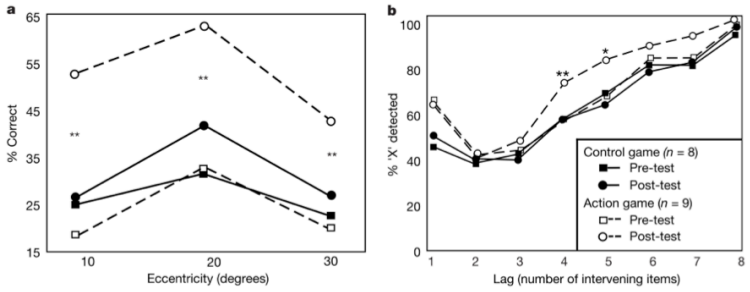


Figure 3.5: NVGP population training results as presented in Green & Bavelier, 2003. (a) Results from the useful field of view task. The NVGP group that was trained over 10 days performed better than their pre-test and control conditions upon post-test. (b) Attentional blink task. The NVGP group trained over 10 days recovered more quickly from the attentional blink effect than their pre-test in addition to outperforming the control group that played Tetris.

The study produced by Green and Bavelier is highlighted due to the concrete evidence that frequent video game playing can indeed offer multidimensional improvements not only in basic visual skills but higher cognitive areas in the brain as well. It can be theorized that these benefits to both upper and lower level brain processing systems could suggest that engaging all of these systems together would engage not only the tools used in these skills but skill acquisition itself.

3.2 Video Games and Perceptual Learning

The line of work seen with Green and Bavelier's interest was continued throughout the 2000's. Numerous studies reported population differences between frequent gamers and non-gamers when compared on a variety of visual and

attentional tasks (Kastner & Ungerleider, 2000; Shipp, 2004; Yantis & Serences, 2003, Green & Bavelier, 2006, 2008). Specifically, the leading theory posited that enhancement from video game training mainly targeted attentional networks and improved behavioral performance by fueling selective attention. However, additional research has offered alternative explanations. Improvements in visual acuity and detecting smaller letters in noise (Green & Bavelier 2007) along with better detection abilities of low contrast Gabor's (Li et al., 2009) would suggest that attention is not the only system being affected by frequent gaming. Is frequent video game training solely an attentional beneficiary? Or does this form of activity really offer "multidimensional" effects as suggested by previous literature? Results from more resent literature suggested interesting conclusions that could be marked by enhanced perceptual learning in a frequent gaming population.

When viewing frequent video gaming from the perspective of perceptual leaning research, it is important to consider all facets that could contribute to an enhanced ability to learn new visual features. Firstly, one major factor of frequent video game playing is the sense of excitability and arousal generated within the player, compared to normal, repetitive psychophysical tasks (Hebert et al., 2005; Przybylski, Ryan, & Rigby, 2009; Segal & Dietz, 1991). Video games are widely considered as a fun and engaging activity for many people which lends credit to the idea that motivational factors may play a role in the behavioral performance change on visual and attentional tasks we see in a frequent gaming population. Not unlike being in a boring college class, engaging and stimulating material

often offers greater degrees of potential learning than simpler repetitive tasks (Vygotsky, 1978). Following this school of thought, video games are often dynamic and increase in task difficulty as the game progresses, which has been shown to facilitate learning (Ahissar & Hochstein, 1997; Linkenhoker & Knudsen, 2002; Sireteanu & Rettenbach, 1995), along with task variability and input (Brady & Kersten, 2003; Kornell & Bjork, 2008). In addition, it is known that video games produce signals in areas of the brain related to cortical plasticity and reward processing (Bao, Chan, & Merzenich, 2001; Koepp et al., 1998). In this sense, we can view frequent video game training as a fun, interactive, dynamic, and rewarding form of behavioral training that would potentially maximize all components that contribute to learning, especially in domains of reward processing and brain plasticity.

Motivation and reward, while important, is not the only causal explanation for learning-related benefits seen through frequent video game playing. Frequent video game playing also elicits perceptual changes such as sharpening, gain enhancement, map expansion, and changes in feedback connectivity that would dynamically interact with visual task demands (Gilbert & Sigman, 2007; Li, Piech, & Gilbert, 2004; Schoups, Vogels, Qian, & Orban, 2001; Yang & Maunsell, 2004). The performance increase seen in visual tasks with gaming populations is likely due to many neural systems improving together at the same time. This would suggest that not only to gamers have the potential ability to acquire new visual tasks quicker, but also have better neural tools to do so. Taking

all these facts together, it is quite possible that frequent video game playing contributes to the enhancement of perceptual learning itself.

Another interesting theory involves the transfer of learning seen in many VPL paradigms. It has been shown that transfer of learning occurs within visual training more readily on easy tasks compared to difficult ones (Ahissar & Hochstein, 1997). However, more recent views attribute task transfer to precision employed on the task rather than the actual task difficulty itself (Jeter, Dosher, Petrov, & Lu, 2009). Considering transfer in perceptual learning is a very plausible route to connecting video game training and enhanced visual abilities to learn. Since video games are often dynamic and increase with difficulty as one progresses through the game, it is possible that the wide range of sensory exposure contributes to learning transfer. Low-precision tasks within video games could be easily acquired and demonstrated in psychophysical trials, along with compiling assorted, transferable skills that amass through the complexity of video game level development. Since transfer is a more basic phenomenon that has been reported with low precision, easier tasks, playing video game frequently could offer the subject with a wide variety of transferable visual skills that accumulate with continued training.

At this point in the literature review, attentional networks, basic visual skills, reward processing, motivation, task ingenuity, and learning transfer have all been considered to play roles in frequent video game training that could offer potential explanations that contribute to enhanced performance in novel environments. While it is still uncertain if research can directly say that frequent

training on a video game would enhance all aspects of VPL, the above line of work is not only indicative of multidimensional benefits, but each finding corresponds with components that drive VPL forward. In terms of mechanisms of VPL, it has been posited that all of these properties contribute to noise reduction and a better perceptual template for frequent gamers when presented with a visual task (Lu & Dosher, 2008). This would suggest that VPL is enhanced through altering the signal to noise ratio in environments as a consequence of frequent video game exposure. Another mechanistic explanation could involve brain connectivity. Frequent video game playing could sharpen a subject's ability to extract statistically task-relevant features from an environment in a dynamic fashion, which would allow for better perceptual templates to be formed when needed. Green & Bavelier described this theory as dynamic resetting of connectivity during visual tasks to best suit the brains needs. More specifically, "…by reshaping neural networks on the fly to extract more accurate statistics from their environment, VGPs may be able to display improvements in a variety of tasks, accounting for the wide transfer of learning discussed above" (Green & Bavelier, 2010). While mechanisms of VPL related to frequent video game exposure are still debated, there seems to be compelling evidence that frequent video game playing can contribute to enhanced perceptual tools that speed up the VPL process.

In the above critique, we have reviewed substantial evidence that suggests that neural components that contribute to VPL are enhanced through frequent video game playing. We have attempted to make a direct connection to the

mechanisms of VPL, although it is still controversial if we can specifically say that *learning itself* is improved with frequent gaming. Visual skills, reward processing, and attention have all been addressed but how can we further speculate that learning itself is modified? In order to do so, all elements of VPL must be considered. Although consolidation is a very significant stage in VPL, it is rarely touched on in video game research. Since we have studied many aspects of VPL that video games benefit, we can determine that many theories posited suggest that the tools frequent exposure to video games offer are a result of active engagement. What many of these studies leave out is learning consolidation that is necessary to VPL. In the first experiment of this dissertation, frequent video game playing and consolidation is investigated. Results would not only offer another mechanistic explanation for VPL enhancement under frequent gaming, but could possibly be the direct link between gaming and VPL that would definitively say that playing video games can enhance learning itself.

3.3 Frequent Video Game Players Resist Perceptual Interference

3.3.1 Abstract (1758 /2000 characters including spaces)

Playing certain types of video games for a long time can improve a wide range of mental processes, from visual acuity to cognitive control. Frequent gamers have also displayed generalized improvements in perceptual learning. In the Texture Discrimination Task (TDT), a widely used perceptual learning paradigm, participants report the orientation of a target embedded in a field of lines and demonstrate robust over-night improvement. However, changing the orientation

of the background lines midway through TDT training interferes with overnight improvements in overall performance on TDT. Interestingly, prior research has suggested that this effect will not occur if a one-hour break is allowed in between the changes. These results have suggested that after training is over, it may take some time for learning to become stabilized and resilient against interference. Here, we tested whether frequent gamers have faster stabilization of perceptual learning compared to non-gamers and examined the effect of daily video game playing on interference of training of TDT with one background orientation on perceptual learning of TDT with a different background orientation. As a result, we found that non-gamers showed overnight performance improvement only on one background orientation, replicating previous results with the interference in TDT. In contrast, frequent gamers demonstrated overnight improvements in performance with both background orientations, suggesting that they are better able to overcome interference in perceptual learning. This resistance to interference suggests that video game playing not only enhances the amplitude and speed of perceptual learning but also leads to faster and/or more robust stabilization of perceptual learning.

3.3.2 Introduction

Every day, more of our society is exposed to rapid video stimulation and virtual environments, ranging from television and movies to interactive games requiring active and vigilant participation. The frequency of exposure is becoming more prevalent in today's youth as well as among the general population, raising

questions of how such activity affects our brain. In the past decade, studies have been conducted examining the differences in visual skill and function with frequent gamers compared to non-gamers. There exists a plethora of viable evidence suggesting differences caused by frequent exposure to video games. This study focuses on the lasting effects of video game exposure and how this activity could influence visual learning.

Earlier studies produced robust effects concerning the effect of frequent video game playing on visual skills and attentional abilities. It has been shown that frequent gamers have enhanced abilities in a variety of visual and attentional skills in comparison to non-gamers. Subjects who frequently played action video games were proficient in processing multiple distractors, quickly identifying visual targets, stretching visual attention over a wide eccentricity range, and resisting the "attentional blink" effect (Green & Bavelier, 2003). These findings suggest that frequent gamers have enhanced attentional resources unlike their non-gamer counterparts. In addition, these finding have been repeatedly confirmed (Boot et al., 2008; Boot & Simons, 2012; Cain et al., 2012; Cain et al., 2014; Dye et al., 2009a; Dye et al., 2009b).

Importantly, frequent video gaming seems to affect visual plasticity (Green et al., 2010) where performance improvement trends seen with frequent video game playing resemble typical aspects of Visual Perceptual Learning (VPL). VPL is defined as long-term enhanced performance as a result of visual experience (Sasaki et al., 2010). Frequent gamers have demonstrated trends in performance change similar to the core principles of VPL, such as higher contrast

sensitivity (Li et al., 2009) and better spatial resolution 9Green & Bavelier, 2007). Thus, frequent video gaming could be considered to be a type of visual perceptual learning (VPL). However, little is known about how video gaming affects temporal dynamics in visual plasticity (Green et al., 2010). In case of VPL, there is an important time course dynamics such as consolidation (Karni et al., 1994; Mednick et al., 2002; Mednick et al., 2003; Stickgold, 2005; Stickgold & Walker, 2005a; Stickgold & Walker 2005b; Yotsumoto et al., 2009). Consolidation here refers to a progressive post-acquisition stabilization of long-term learning as well as to the learning phase(s) during which such presumed stabilization takes place (Dudai, 2003; Dudai, 2004; Stickgold & Walker, 2005a). It has been suggested that at least one hour is necessary for newly encoded perceptual learning to be stabilized so that it is not disrupted or interfered with training of another type of perceptual learning. For example, performance improvement in a task can be interfered with following a similar task if the second task takes place within an hour of the first (Seitz & Watanabe, 2005; Yotsumoto et al., 2009). This effect however, can be described in two modes of interference: anterograde and retrograde. Anterograde interference refers to when performance improvement on the second task is disrupted, whereas retrograde refers to disrupted performance on the first task (Yotsumoto et al., 2009).

If frequent gamers have an enhanced capacity and speed in lower visual processing accompanied with more attentional resources, they may show little interference in learning two similar tasks within a short time window. To address this question, we conducted an interference paradigm that we have developed

earlier (Yotsumoto et al., 2009) in a Texture Discrimination Task (TDT) (Karni & Sagi, 1991; Yotsumoto et al., 2009). We have found that such an interference effect was not observed with a frequent gamer when trainings of two types of perceptual learning were conducted with no time interval between them. In contrast, these results were not seen in a non-gaming population. Thus, the present results suggest that video game playing not only enhances the capacity and speed of perceptual learning but *also* leads to faster and/or more robust stabilization of perceptual learning.

3.3.3 Materials and Methods

3.3.3.1 Participants

Participants were recruited from the Brown University campus using flier and email contact. All participants who volunteered had normal to corrected vision and were aged between 18-25 years old (mean 19.94, ± 0.45 SEM). This study collected 9 frequent gamers (2 female and 7 males) and 9 non-gamers (8 females and 1 male). The gamers had a mean age of 20.33 (± 0.55 SEM) and the non-gamers had a mean age of 19.56 (± 0.73 SEM). The institutional review board of Brown University approved this study. Subjects gave their written informed consent for their participation after the purpose of procedure of the study was thoroughly described.

Frequent gamers and non-gamers were classified according to a survey inquiring about video game playing habits utilizing questions from similar studies (Green & Bavelier, 2003; Green & Bavelier, 2007; Green et al., 2010). Frequent

gamers were classified as those who participated in action video game playing (as defined by previous research (Green & Bavelier, 2003) at least 5 hours a week for a period of 6 months or more continuously (mean 5.64 hours/week, ± 1.88 SE). Non-gamers were classified as those who played less than 1 hour a week in a given 6-month period (mean 0.32 hours/week ± 0.11 SEM). Most frequent gamers and non-gamers were very polarized where frequent gamers played actively and continuously while non-gamers typically did not play any form of video game at all ($t(8)=2.76$, $p=0.02$).

3.3.3.2 Procedures

In the present study, subjects were given a modified version of the TDT paradigm, used in the Yotsumoto and colleagues (2009) study, where subjects were trained on two different TDT backgrounds in immediate succession. This training produced an interference effect where the training from each background interfered with the training from the other. This notion refers back to the concept of consolidation, where a performance improvement would be seen in this paradigm if an hour of rest were allowed in between learning the two backgrounds.

TDT has been originally developed by Karni and Sagi (Karni & Sagi, 1991) and can be manipulated to form both task-relevant and task-irrelevant signals that impact perceptual training (Figure 3.6). The primary goal for the subject is to discriminate an orientation (by responding either with H or V keys for horizontal or vertical) of a target array of oblique lines imbedded in a series of

background horizontal or vertical line segments. The target can be presented in any of the four visual quadrants in the subject's periphery and is referred to as the peripheral orientation task. For the present study specifically, all subjects were trained in the lower left visual quadrant. An additional task is employed as well in order to hold fixation and attention in the center of the stimulus, where subjects are required to report the presence of an L or T at the fixation cross by pressing the corresponding keys. This task is known as the fixation task. TDT can be varied in difficulty through changing the length of Stimulus-to-mask Onset Asynchrony (SOA), which is the time elapsed between the presentation onset of the stimulus and the onset of the mask. If the mask appears more closely following stimulus presentation (small SOA), the task becomes more difficult. After the presentation of the mask, subjects first enter their response to the fixation task followed by their response to the peripheral orientation task.

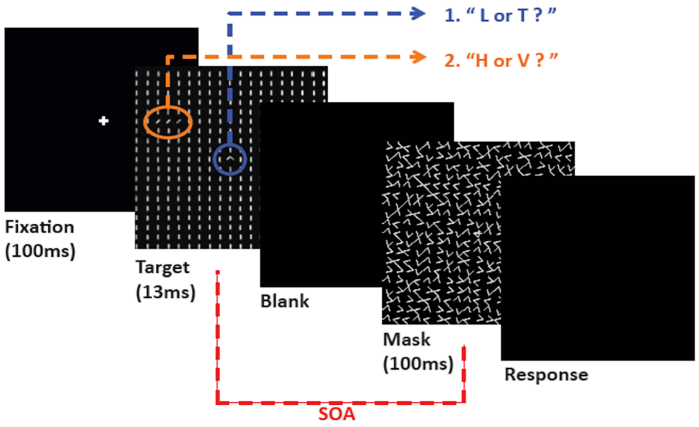


Figure 3.6: The texture discrimination task (TDT) stimulus. An adapted version of the standard TDT used frequently in VPL experimentation. The first target is highlighted in blue where subjects report either the presence of an L or T, which is designed to hold fixation. This is referred to as the fixation task. The second target (peripheral orientation task) is highlighted in orange and requires the subject to respond with an H or V depending if the targets orientation was horizontal or vertical. The peripheral orientation task is the primary measure of performance in the experiment. Note that the blue and

orange circles are provided just for illustrative purposes. They did not appear in the actual experiment. The shorter the SOA, the more difficult the task becomes.

The experiment in the present study consisted of two sessions, which spanned for 2 consecutive days. Each session was 24 hours apart and localized to the afternoon in order to avoid any form of circadian effect. One session was divided into 2 parts. The first half of the first session consisted of either all vertical or all horizontal background lines and the second half of the first session consisted of the opposite orientation for the background (Figure 3.7). For example, if one subject performed the first half of session 1 with a horizontal background, then their second half would be a vertical background stimulus. The second session (24 hours later) contained the same stimuli parameters as the first session. This procedure was counterbalanced across subject to ensure that the actual stimuli themselves were not confounding the results. The purpose of changing the background line orientation within a session is to cause interference in learning (Yotsumoto et al., 2009), where if this had not occurred one would normally see improvement. The core idea behind this involves the concept of learning consolidation, where not enough time is allowed between different background training for learning to be solidified within the brain's memory systems (Sasaki et al., 2010).

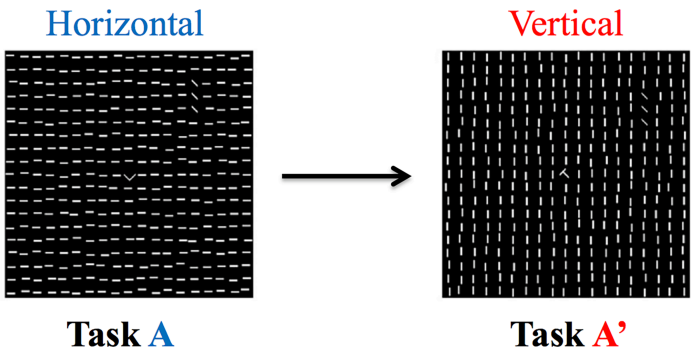


Figure 3.7: TDT background line orientation changes. An example of using TDT to create the interference in learning Subjects were trained on one background (either horizontal or vertical) and then trained on the opposite background with no resting period in between. Previous research suggests that the immediate switch in background stimulus disrupts learning of one or both backgrounds (Yotsumoto et al., 2009).

Both frequent gamers and non-gamers were trained with the same number of trials and blocks. In each session, there were 7 blocks, in each of which was conducted with a single SOA with 39 trials. Thus, there were 7 SOAs used and the total number of trials was 273. The SOAs were 180ms, 160ms, 140ms, 120ms, 100ms, 80ms, 60ms, and presented in this order. Throughout the training, the target was presented at a consistent quadrant of the visual field for each subject.

3.3.4 Results

For analysis, our results have been divided into two separate performance measures, considering both techniques from prior literature (Yotsumoto et al., 2009). The first measure was the 75% threshold SOA, which was computed as follows. First, we obtained the correct response ratio for the peripheral orientation task computed for each SOA and then fitted this data to a logistic psychometric function. This psychometric curve allows us to easily see performance trends across each SOA and define the threshold for each respective session. The

threshold is the point on the psychometric curve that corresponds to the SOA that subjects were able to achieve 75% correct response rate. As noted in our methods, shorter SOAs indicated that the task was more difficult. Thus, the SOA on the curve where subjects had a 75% threshold was the most difficult SOA subjects could handle before dropping below optimal performance rate. If the threshold becomes shorter after training, this indicates that the subject learned the task. The second measure was a simple percent correct for each SOA, which was supplementary to the first threshold measure. While these two measures are correlated, the sensitive aspects may be different.

First, Figure 3.8A shows the 75% threshold for each session of the 2-day training in both frequent gamers and non-gamers. In order to confirm learning of the task, a 2x2x2 repeated measures mixed-design ANOVA was conducted on this data, using day, background, and group as factors. The ANOVA revealed a significant main effect of day for both frequent gamers and non-gamers ($F(1,17)=12.840$, $p=0.002$), suggesting overall performance improvement. Additionally, the main effect of background was also significant ($F(1,17)=4.811$, $0=0.043$) suggesting different trends in performance on each background. The interaction between day, background, and group however, was not significant ($F(1,17)=0.736$, $p=0.404$), as well as the overall group difference examined through the ANOVA ($F(1,17)=1.430$, $p=0.249$). Since different trends in performance on each background were suggested through the analyses, we examined the percent change of the threshold data per background across day 1 and day 2 (Figure 3.8B). The frequent gamers showed average improvement

(10%) for the first background, whereas the non-gamers showed little to no average improvement. This suggests that the retrograde interference occurred with non-gamers, whereas no interference occurred with frequent gamers.

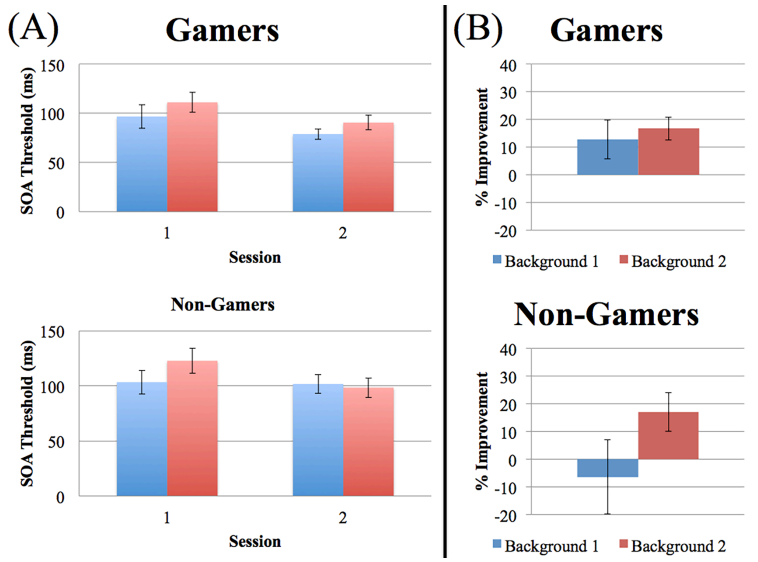


Figure 3.8: The threshold SOA for both frequent gamers and non-gamers (A). The first background trained is highlighted in blue, whereas the second background trained is highlighted in red. The threshold percent improvement across day 1 and day 2 for both frequent gamers and non-gamers (B). The first trained background is colored in blue whereas the second trained background is colored in red. The frequent gamers and non-gamers differed on background 1 performance change, while not much difference is seen in background 2. Results are shown in standard error.

Next, Figure 3.9 shows the percent correct at each SOA for frequent gamers and non-gamers. Since the effect of retrograde interference should be evident at the performance at background 1, a 2x2 repeated measures ANOVA was conducted on the percent correct data at each presented SOA (Figure 3.9) for background 1 with factors day and group yielding a significant group difference ($F(1,6)=10.145$, $p=0.008$). In order to confirm the effect was specific to background 1, another 2x2 repeated measures ANOVA was conducted on the percent correct data at each presented SOA (Figure 3.9) for background 2 with

factors day and group. This ANOVA however, did not reveal any significant group difference significant (F(1,6)=0.378, p=0.550), suggesting that the presence of retrograde interference with the non-gamers.

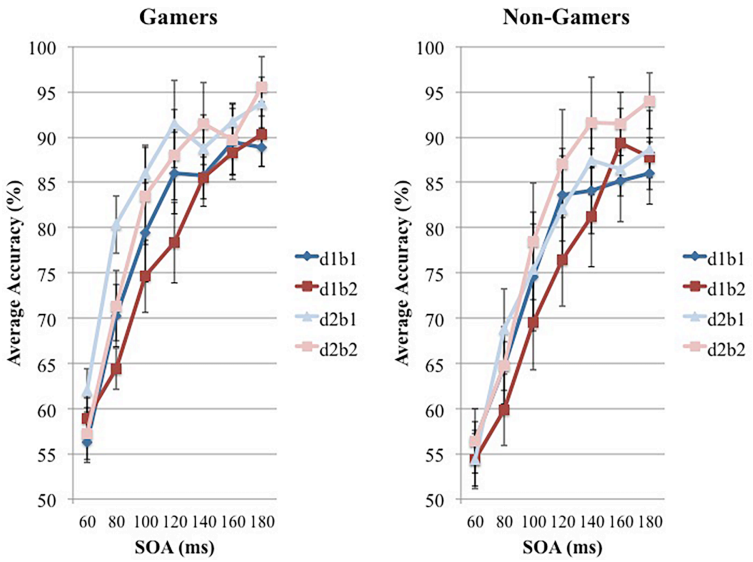


Figure 3.9: The percent correct for each SOA for both frequent gamers and non-gamers. The blue and light-blue lines represent background 1 whereas the red and light-red lines represent background 2. Darker lines are day 1 and lighter lines are day 2. "d1b1" for example, corresponds to day 1 background 1, and "d1b2" corresponds to day 1 background 2, and so forth. Results are shown in standard error.

3.3.5 Discussion

The results from the present study suggest that frequent gamers are more resistant to the interference effect seen in a typical population tested on the modified TDT paradigm (Yotsumoto et al., 2009). Specifically, the non-gamers showed a strong example of retrograde interference, where after learning the second task (background 2), performance improvement on the first task was disrupted. The frequent gamers however, demonstrated this effect to a far lesser degree and produced a positive increase in SOA threshold from day 1 to day 2

with both backgrounds, instead of just the second background as the non-gamers did.

In addition to the retrograde interference findings, an observable difference between performance consistencies can be identified between the frequent gamers and non-gamers. Typically, the frequent gamers exhibited quicker acquisition of the task during training and produced results with less variability than the non-gamers (Figure 3.9). This finding however, would be expected due to previous literature (Green & Bavelier, 2003; Green & Bavelier, 2007; Li et al., 2009), suggesting the enhanced visual abilities of a frequent gaming population, thus denoting more accurate and homogeneous results.

It is important to note the limitations of this study. Specifically, the small number of subjects in each group limits statistical power and could have perhaps concealed additional trends in the data. However, given the significance reached with the current analyses however, the frequent gamers' resistance to interference may be stronger than originally thought. Additionally, identifying frequent gamers and non-gamers could include some confounding factors. In our study, the frequency in gaming was limited to the past 6 month. Thus, even in the non-gamers in our study, many of them reported playing at least one video game in their life. Also, some reported spending brief periods of time playing video games in their childhood or early adulthood, but not enough to classify them as gamers according to the criteria defined by our questionnaires. It is possible that these people may have experienced changes in visual ability due to brief exposure, since prior research demonstrated enhanced performance on useful-field-of-view,

attentional blink, and enumeration tasks after only 10 days of video game training with a non-gaming population (Green & Bavelier, 2003). For this reason, we attempted to polarize our subjects by current time spent in gaming as much as possible by measuring gaming activity in the past 6 months in order to establish the largest group difference in gaming experience. Our significant group difference suggests a high degree of polarization between groups ($t(8)=2.76$, $p=0.02$). The effect of gaming more than 6 months ago on visual processing may be a future study.

Additionally, our efforts with data collection revealed that many frequent gamers happen to be male, thus making it difficult to balance the gender ratio in our participant pool. We attempted to diversify our data collection as much as possible considering this finding, but were only able to a limited extent. Upon investigation however, we could not find any literature supporting sex differences in perceptual learning with interference designs, although there is a recent study that showed the sex difference in the interaction of type of perceptual learning and sleep content (McDevitt et al., 2014). Also, recent data collected in our lab for another project on interference with TDT revealed no statistical difference in behavioral performance trends across males and females (Tamaki et al., 2014).

Since this study was conducted over a 24-hour period, we must also consider the confounding factors brought upon by the time subjects spent not in the laboratory, specifically related to sleep. Although encouraged to get a full night's sleep, it is quite possible that some subjects did not follow instructions and may have been sleep-deprived for the second session. In addition to feeling

groggy during testing, such lack of sleep could have left subjects with less time to experience sleep-dependent memory consolidation, which is thought to contribute significantly to storing the information from the TDT training they received the previous day (Sasaki et al., 2010). Specifically, this would result in a disruption of normal sleep architecture possibly allowing for less efficient consolidation, which could lead to less than optimal task performance (Stickgold, 2005). Current research however, suggests that performance improvement on TDT can be seen even after only 90 minutes of sleep (Mednick et al., 2003), in which case lack of sleep may not be as confounding as originally thought. It is important to note that this research examined typical TDT paradigms, which did not include methods for inducing the interference effect thought to disrupt consolidation. Thus, it is difficult to conclude that subjects would respond to post-sleep interference TDT testing in a similar manner to post-sleep typical TDT testing. These confounding factors most likely did not occur however, since the results from the statistics showed a strong trend in overall learning with both frequent gamers and non-gamers, which most likely would have been less pronounced had our subjects been sleep-deprived.

With regards to our interest in the role of frequent gaming in learning consolidation, our results allow us to speculate on how frequent gamers may have different solidifying mechanisms operating during sleep and wakefulness. It may be possible that the vast amount of visual training frequent gamers receive over the years could help contribute to honing consolidation mechanisms in the brain, especially for visually developed skills. Essentially, this would mean that over the

24-hour period of time between the experimental sessions, more efficient consolidation mechanisms could have been operating in the frequent gamers compared to the non-gamers, resulting in better overall learning. This could suggest that on top of enhanced perceptual abilities, frequent gaming could help sharpen the mechanisms that allow for the consolidation of visual skills. A new model could be proposed offering insight into how frequent gaming affects not only how we deal with presented information, but also how we retain this information as well.

3.4 Mechanisms and Reward-Based Training

The above experiment documents the novel concept that frequent video game playing might be modifying not only perceptual frameworks and visual skills but may also enhance offline consolidative mechanisms that are directly correlated with the general learning process. Up until this point, we have considered how frequent video game playing enhances attention, lower-level visual skill, and temporal processing. These however, are active skills that could contribute to the above finding that frequent video game players acquire TDT quicker. How do we explain the finding with consolidative interference? The conclusions dictate that there could be some offline mechanism responsible for the enhanced learning patter the frequent video gamers demonstrated.

A promising and often recognized aspect of video games is their rewarding nature. While frequent video game playing sharpens visual skills and attentional control, a significant driving factor is the motivation provided for

engaging in the activity (Bao, Chan, & Merzenich, 2001; Koepp et al., 1998). Research has suggested that reinforcement signals in VPL tasks can drive plasticity even at subliminal levels (Seitz et al., 2009). Additionally, the presence of reinforcement signals contributes not only to task-irrelevant learning but also to task-relevant learning (Seitz & Watanabe, 2005). In combination with findings that VPL is enhanced with the presence of feedback (internal reward) compared to no feedback (Herzog & Fahle, 1997), it is reasonable to say that reward and reinforcement signals play a significant role in the enhancement of VPL. With regards to frequent video game playing, a possible link between enhanced offline consolidative mechanisms and frequent video game playing could involve reward processing, where just recently a link between memory consolidation and reward has been established in general learning (Gruber et al., 2016).

While there are many areas in which frequent video game playing could strengthen VPL, including perceptual framework modification or attentional enhancements, a promising link between the offline consolidative mechanisms of VPL and enhancement through video game playing could be understood under reward processing during sleep, which recently has been shown to interact with each other (Igloi et al., 2015). It may be possible that during video game training changes to attentional networks and lower-level visual areas facilitate better performance and task adaptability. However, the consolidative portion of VPL also seems to be enhanced with a frequent video game playing population, which may be due to the rewarding nature of video games. Since the presence of reward has been shown to facilitate VPL, and research has shown that reward processing

occurs during sleep consolidation (Igloi et al., 2015), by targeting reward processing and its role in sleep consolidation specifically, it may be possible to isolate interacting consolidative mechanisms during sleep that lead to VPL enhancement.

Chapter 4

4. Reward and Dopamine

In order to learn more about the sleep consolidation of VPL and how reward is involved we must first explore the research contributing to the classification of various dopaminergic systems and pathways. Understanding the basic elements of how and when dopamine pathways are most functionally active lends clues to how learning (and therefore offline consolidation) may be integrative with such processes. It is important to note that many anatomic studies outlined below are performed on rats or macaques, and therefore should not be considered as a definite representation of reward processing in humans. We can however, use this information as a guide to specific methodology as well as provide a solid knowledge-based foundation for exploring human reward consolidation.

4.1 General Overview

The mesolimbic dopaminergic (ML-DA) spans from the ventral tegmental area (VTA) of the midbrain and projects to various structures such as the nucleus accumbens (NAcc) in addition to the prefrontal cortex (PFC) (Alcaro et al., 2007) (Figure 4.1). The primary behavioral benefit is the promotion of adapted, goal-directed behaviors regulated by dopamine release and other ML-DA activity (Haber and Knutson, 2010; Schultz, 1998). In literature, two significant projections form the ML-DA system have been identified, known as the nigrostriatal pathway and the mesolimbic pathway (Stahl, 2013):

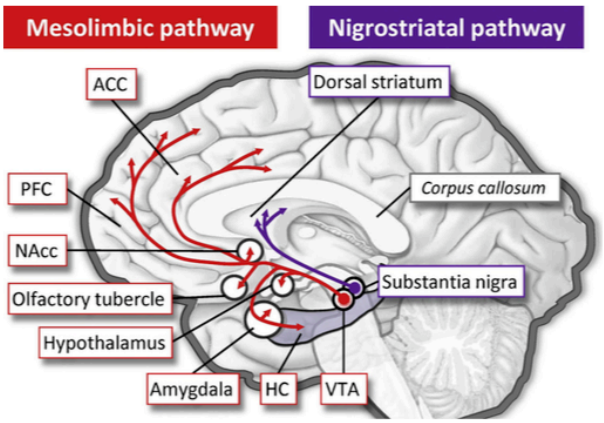


Figure 4.1: Overview schematic of the ML-DA system (Perogamvros and Schwartz, 2012)

As seen in Figure 4.1, the nigrostriatal pathway is believed to project from the substantia nigra (SN) to the dorsal striatum (caudate and putamen). It is believed that this pathway is essential for the modulation of cognitive and behavioral habits (Perogamvros and Schwartz, 2012). The mesolimbic pathway, on the other hand, originates in the VTA and projects to the lateral hypothalamus (LH), NAcc, ventral striatum (VS), amygdala, hippocampal complex (HC), PFC, and the anterior cingulate cortex (ACC) (Perogamvros and Schwartz, 2012). This system is thought to be implicated in motivated behaviors, reward processing, emotional processing, and learning (Adcock et al., 2006; Alcaro et al., 2007; Ikemoto, 2007).

In addition to the defined pathways above, the ML-DA system is believed to uphold unique properties for processing reward and reward-based behavior, as well as serving as the central hub for the development and monitoring of motivated behavior in all mammals (Perogamvros and Schwartz, 2012). Researchers have noted that there are two types of signals that can be

distinguished within the ML-DA system. The first signal is a phasic signal, described as a bursting activity of dopamine concentration lasting up to 2 seconds. This signal originates in mesolimbic pathways, such as NAcc, resulting in burst firing of one or more VTA neurons (Ikemoto, 2007). The second signal is defined as a tonic signal, which is described as a rather slow change in dopamine concentration in the aforementioned regions, believed to last from 10s of seconds to hours to days, suggesting a critical role in the stabilization of affective states involved with motivated behaviors (Ikemoto, 2007). These two types of signals may provide insight into the time-course of learning rewarded behavior.

Furthermore, it is believed that the VTA, as well as the NAcc, constitutes the core of reward processing, even though other brain regions as well as neurotransmitters such as glutamate and GABA are recruited for reward-based behavioral processing (Higgins and Fletcher, 2003; Hikosaka et al., 2008; Ikemoto, 2010; Vlachou and Markou, 2010). Considering the evidence above, researchers interested in the ML-DA pathway have attempted to develop a framework describing the mechanisms of reward processing. Most recent models typically describe a transfer of information from ventral to dorsolateral cortico-basal ganglia circuits during processing, which is thought to transform basic reward responses and unconditioned responding (mesolimbic pathway) into action planning and associative learning (nigrostriatal pathway) (Haber and Knutson, 2010; Ikemoto, 2007). Therefore, we can think of the reward response in two sequences: an immediate response to rewarded presentation and then a lasting response stabilizing and integrating habit-forming behavior based on the initial

response from reward contact. With this "duality" of processing in mind, as well as considering the phasic vs. tonic firing activity of the reward processing neural correlates, a theory was developed in an attempt to unify reward processing under both wakeful and sleep conditions. This was known as the Reward Activation Model (RAM) proposed by Perogamvros and Schwartz in 2012.

4.2 Reward Activation Model (RAM)

The Reward Activation Model (RAM) described by Perogamvros and Schwartz is an attempt to unify a vast body of evidence regarding how rewarded memories associated with the ML-DA system are processed in the brain during both wakefulness and sleep. This theory was put forth based on research performed on animals and anatomical studies observing the activity of dopamine through the time course of reward-based learning and memory acquisition. To date, this model provides valuable speculations into how the ML-DA system may be contributing to the solidification of specific memories during sleep. With this model in mind, we can predict what may happen in human reward-based memory consolidation and even draw conclusions for future quantifiable projects investigating the role of dopamine in sleep consolidation of VPL.

From a broader perspective, the RAM aims to provide research with two distinct features (although more suppositions are offered) of reward-based memory consolidation based on the authors' hypotheses. The RAM first proposes that the temporally sensitive activation of the ML-DA system contributes to memory consolidation mechanisms by prioritizing information based on high

emotional or motivational (rewarding) relevance. The second property of the RAM argues that the ML-DA system participates in these consolidation mechanisms through the modulation of REM-related cortical structures, although proposing importance of additional sleep architecture. In essence, the RAM offers concrete animal evidence on the connection between reward-based memories and offline consolidation that differs from consolidation of regular memories or skills.

The significant characteristics of the RAM are based upon the idea of functional feedback loops from various ML-DA structures (Lisman and Grace, 2005). The gating of relevant motivational/rewarding information is thought to be modulated by activation of the VTA and hippocampal structures. Based on prior research, the activation of the VTA and HC (as well as areas such as the PCC) is believed to be rooted in exposure to novel stimuli. This idea came from research with rats where novelty-seeking behavior was decreased due to the intra-hippocampal infusion of tetrodotoxin (Legault and Wise, 2001) as well as several human studies demonstrating significant activation of the amygdala, VTA, and HC due to exposure to novel situations or objects (Bunzek et al., 2012; Guitart-Masip et al., 2010; Krebs et al., 2011). Perogamvros and Schwartz propose that the HC can activate VTA dopamine cells through a pathway involving the activation of NAcc, which in turn would inhibit the ventral pallidum (VP) leading to the disinhibition of dopamine cells (Floresco et al., 2003). This pathway (HC → VTA) can be thought of as the first part of a two-stage feedback loop that generates dopamine release due to relevant stimuli exposure, referred to as the downward arc of the hippocampal-VTA loop (Lisman and Grace, 2005). This

downward arc is believed to modulate dopamine levels in the VTA and is thought to be related to motivational salience. The upward arc, on the other hand, describes the dopaminergic input from the VTA to the HC (VTA → HC). The increased concentration of dopamine through phasic activation of the VTA activates several pathways, including the loop back to the HC, which is thought to be involved in synaptic plasticity and long-term potentiation (Adcock et al., 2006). Figure 4.2 describes the division between the downward and upward dopamine pathways that may be involved with consolidation of reward/motivational-based memoires during sleep. This theory is further supported by anatomical activation of structures related to the RAM that not only correspond with various sleep stages, but temporally correlate with them, as well (Bandyopadhya et al., 2006; Lansink et al., 2008; Lisman and Grace, 2005; Omelchenko and Sesack, 2006; Pennartz et al., 2011; Saper et al., 2005).

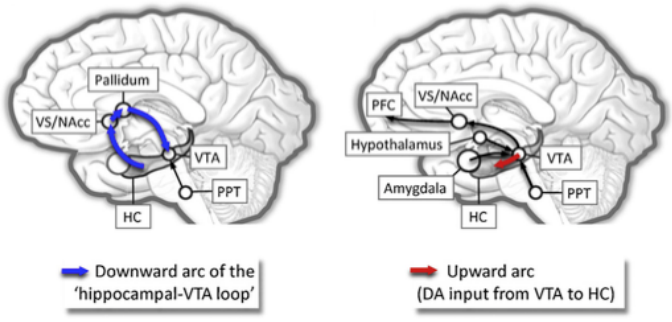


Figure 4.2: Neural activation upward and downward arcs in the ML-DA system. The downward Arc (HC → VTA): the HC activates VTA dopamine cells via a pathway involving the NAcc. The NAcc then inhibits the VP leading to the disinhibition of dopamine cells. This increases the population activity of dopaminergic neurons by a large magnitude. Upward Arc (VTA → HC): this is thought to be related to synaptic plasticity and learning by enhancing long-term potentiation. Increased levels of dopamine promote the feedback loop and are thought to strengthen connections between these key areas of the reward system (Perogamvros and Schwartz, 2012)

The description above may provide a mechanistically sound proposal for the RAM and how dopamine may be involved in reward-based memory consolidation, although much more information regarding sleep variables is needed. Perogamvros and Schwartz offer several pieces of evidence connecting their RAM with basic sleep architecture, such as sleep stage variation modulated by the VTA, ultimately concluding with a cyclic model of dopamine release and sleep-stage conversion emphasizing different parts of sleep architecture necessary to consolidation. It is important to note at this stage Perogamvros and Schwartz have based most of their research off of the *learning-consolidation model*, where reactivation and replay of specific cortical structures based on information learned during wakefulness is emphasized. In the RAM, not only is functional replay a significant factor, but sleep stage variation as well, suggesting possible explanations through the dual-process hypothesis or the sequential hypothesis (Deikelmann and Born, 2010; Maquet, 2001; Stickgold, 2005).

Perogamvros and Schwartz propose that during the SWS portion of a regular sleep cycle, processing of reward-based memories would involve the activity of the downward arc of the HC-VTA loop. Coordinated activation of the HC and VS during this sleep stage is thought to be related to the tonic release of dopamine from the VTA, suggesting a possible mechanism contributing to sleep consolidation of memory-reward associations (Lansink et al., 2009; Floresco et al., 2003). This evidence is further supported by studies conducted on rats where the activation of VS reward-related neurons during SWS was found to be highly selective for memories that require high storage priority, such as motivational or

rewarded memories (Lansink et al., 2008). Activity from the VTA however, is not specifically confined to NREM sleep, but rather follows a cyclic nature mirroring the downward and then upward arc of the RAM. In addition to the activity observed during SWS, the RAM supports findings of phasic dopamine bursting activity in the VTA during REM sleep indicative of off-line replay of recent memory traces (Dahan et al., 2007; Lena et al., 2005; Louie and Wilson, 2001; Peigneux et al., 2003; Walker and van der Helm, 2009). It is thought that the phasic activation of the VTA during REM sleep may be contributing to LTP and memory formation in the HC through the upward arc of the RAM (Adcock et al., 2006; Lisman and Grace, 2005), especially considering evidence demonstrating that LTP in the HC is dependent on dopamine release itself (Bach et al., 1999; Li et al., 2003). This, together with evidence suggesting that the VTA is necessary for the transition into REM sleep to begin with by projecting directly to the sublaterodorsal nucleus (SLD) of the pons – a key structure in REM generation (Boissard et al., 2002; Clement et al., 2011; Fort et al., 2009), leads Perogamvros and Schwartz to the conclusion that VTA activity and loop functionality of the RAM are heavily involved with not only sleep consolidation, but can define the sleep architecture itself based on dopaminergic regulation. Figure 4.3 represents Perogamvros and Schwartz's view of the RAM feedback loop with respect to REM generation and sleep cycle alternation.

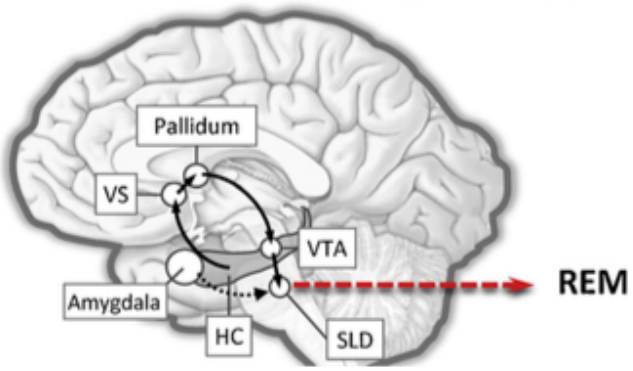


Figure 4.3: The RAM and sleep cycle involvement. Tonic dopamine release response induced by the downward arc of the hippocampal-VTA loop leads to the activation of the VTA at the end of a NREM cycle. The VTA then provides phasic bursting activity that creates a hyperdopaminergic state and projects to the hippocampus (LTP) and also to the SLD, thought to be involved in initiating the onset of a REM period. This process is thought to be a key factor in sleep consolidation (Perogamvros and Schwartz, 2012).

4.3 Additional Research and Speculations

The RAM proposed by Perogamvros and Schwartz offers key insights into the mechanistic approach to sleep consolidation of rewarded skills in animal subjects. From this research, and additional evidence, we can speculate how dopamine regulation may guide preferential memories based on their favorable properties for survival. As mentioned above however, this idea of dopamine involvement in neural consolidation is widely examined in animal methodology but has very little human evidence to support behavioral learning trends mediated by reward-based memories, especially with regard to VPL or other forms of learning. Specifically, if we wish to uncover how reward-based visual plasticity occurs during sleep with humans, future studies involving imaging techniques and electrophysical approaches are needed to dissociate learning from reward-based learning. Current research on humans predominantly involves few motor studies, examining retention and consolidation through either anticipatory reward or

incentivizing payment. Review of this literature as well as additional imaging research suggests learning trends that could mirror some aspects of Perogamvros and Schwartz's RAM as well as new directions for uncovering the mechanisms of offline consolidation for VPL of reward-based memories.

4.3.1 Reward and Motor Learning

If we wish to explore the link between reward-based memories and the sleep consolidation of VPL, we can look to neighboring projects investigating the role of reward on consolidation in different modalities. Motor learning studies, while few, have demonstrated such effects. In particular, a study conducted in 2009 found that behavioral overnight improvements in performance on a finger-tapping task were heightened by the presence of an anticipatory reward (Fischer and Born, 2009). Specifically, this study utilized an interference paradigm, where training on two similar but slightly different motor tasks in immediate succession results in diminished performance gains, possibly reflective of offline consolidation properties (Brashers-Krug et al., 1996; Korman et al., 2003; Shadmehr and Brashers-Krug, 1997). It is believed however, that due to the temporal sensitivity of consolidating these motor memories, that a good amount of time in between learning these competing motor tasks is needed in order to diminish the interference effect. Specifically, sleep is believed to be the key factor in solidifying and making motor memories resistant to interference (Fischer et al., 2002; Korman et al., 2007; Maquet

et al., 2003; Walker et al., 2003). This effect is similar to VPL, where prior studies using the texture discrimination task found interference properties when changing the task-irrelevant portion of the stimulus (Yotsumoto et al., 2009a).

In Jan Born's study, emphasis of reward on one particular motor sequence (meaning, subjects received higher compensation for performance on one of the two learned sequences) was used to demonstrate anticipatory reward effects on the behavioral performance trends from the initial training to testing the following session. Born set up a 12-hour interval design, where the first session was either at 10am or 10pm, then followed by a second session 12 hours later, effectively creating wake and sleep conditions for the subjects. Primary findings suggested that the presence of a reward on one of the finger-tapping sequences increased performance of not just that sequence, but on both sequences learned, in a sense diminishing the interference effect. The wake group also saw significant performance improvements during the second session, although not nearly as great as the group that underwent sleep-dependent conditions. These results suggest that reward modulation of motor learning during sleep promotes selective enhancement of such memories and even enhances all relative memories to the rewarded task.

In Born's study, we see a clear difference in performance between sleep and wake groups, as well as between rewarded and unrewarded groups. This interaction in behavioral data suggests reward is actively

modulating motor systems during sleep, specifically. Additional studies on motor learning have found similar trends, noting that an offline retention period is critical to see behavioral performance changes in a positive direction. One specific study published in Current Biology, demonstrated the time-course framework of offline motor consolidation with respect to rewarding, neutral, and punishing conditions (Abe et al., 2011). In this experiment, researchers measured performance on subjects who were trained on the isometric pinch force task, where, using a monitor for display, the goal is to keep a red dot on top of a target by using pinching motions. With training, subjects show improvements over time similar to other motor paradigms. The researchers measured performance after initial training 6 hours, 24 hours, and then 30 days later respectively in order to quantify the time-course for task learning. Three conditions were used: one neutral (control), one with increased payment depending on performance (reward), and one with punishment, where money was subtracted based on error rate. Figure 4.4 depicts the results, illustrating the significant potential of involving reward systems in learning environments. Essentially, this study shows that apart from other forms of learning, reward modulation seems to be the most prominent mechanism involved with generating brain plasticity.

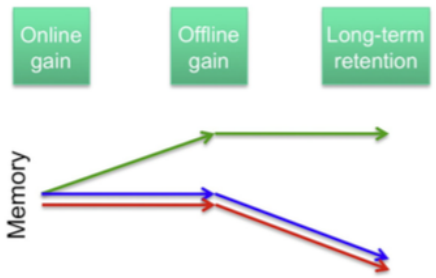


Figure 4.4: Time course in motor learning. The green bar represents the rewarded condition, whereas the blue and red represent neutral and punishment conditions. The y-axis denotes memory or rather, performance indicative of the memory's strength (Abe et al., 2011).

4.3.2 Reward and VPL

So far, the collection of reviewed literature along with speculative assumptions based on relative research has granted evidence supporting reward-modulated mechanisms during sleep consolidation. We have reviewed the reward system in detail, as well as the corresponding mechanisms that contribute to plasticity and lasting behavior through the exposure of motivational stimuli. While mostly shown in animals, these findings are not considered far-fetched when discussing human learning. Behavioral studies with human participants show similar trends in data that that we might expect considering the anatomical and electrophysical/imaging data on rats and primates. The understanding of reward-modulated sleep consolidation in humans however, is quite limited (as discussed above) and confined mostly to the motor domain. Recently however, studies in vision science have taken on the notion that reward may play an essential reward in visual plasticity and learning. Research on

reward-modulation of VPL during sleep consolidation however, remains unclear.

If we backtrack to our primate resources, we can find valuable clues that hint at the selective activation of the visual system in correspondence with reward-related areas that could drive plasticity. A study published in Neuron in 2013 does just this (Arsenault et al., 2013). The dopaminergic modulatory system has been found to be a potential candidate for distributing reward-based information to the visual cortex (Tan, 2009). It is believed that the reward system within the midbrain dopaminergic complex exhibits phasic prediction error response signaling the difference between outcome and expectation (Bromberg-Martin et al., 2010; Shultz et al., 1997), meaning reward value. In addition, prediction error signals originating in this reward hub are believed to be relayed through a wide network of connections (Lidow et al., 1991) resulting in increased dopamine release (Gonon, 1988; Zhang et al., 2009), activity modulation (Pessiglione et al., 2006), and plasticity (Surmeier et al., 2010) at projection destinations. Along with this evidence, a recent fMRI study (Vickery et al., 2011) demonstrated that reward information could span to most relevantly tested brain regions. With this in mind, modulatory reward signals could projection to the visual cortex during visual learning. Abe and colleagues demonstrated direct activation and decreased activation of the primate visual cortex corresponding to the presence of a juice reward on a visual cue-pairing stimulus. The essential findings demonstrate a

relationship between the dopaminergic activity in the midbrain reward hub and the projection sites (including the visual cortex) where modification may be taking place.

Abe and colleagues provide a solid foundation for investigating the neuromodulatory effects of dopamine on active visual sites with respect to plasticity. Their research however, only scratches the surface of how full time course consolidation may be involved. A prominent study back in 2009 examined the effects of reward on VPL, demonstrating key elements that link the visual system and reward networks together (Seitz et al., 2009). In this experiment, the researchers approached the controversy view of bottom-up vs. top-down processing guiding VPL through a novel method. Human subjects were hooked up to a water system with a tube that was placed in their mouth delivering water during specific phases of the training. The actual training itself however, consisted of passively viewing Gabor patches though only one eye. Presentation of dynamic noise in the other eye aimed to, in essence, make the Gabor orientations subliminal to the subject. The idea was to train subjects on orientation sensitivity without conscious action or repetition seen in common VPL experiments (Sasaki et al., 2009). Instead, a specific Gabor orientation was paired with a water-release from the apparatus. Thus, every time the subject was exposed to a predefined orientation, water was delivered from the tube into their mouths. Subjects were water-deprived to ensure a rewarding element behind the water consumption. The results (and method

representation) are displayed in Figure 4.5, where subjects showed increased sensitivity to the "trained" orientation even though they had no conscious recollection of being trained on that orientation. The conclusions show that diffuse reward signals, spanning to the early visual cortex, were sufficient to induce VPL. This is a direct connection between reward-modulatory systems and VPL.

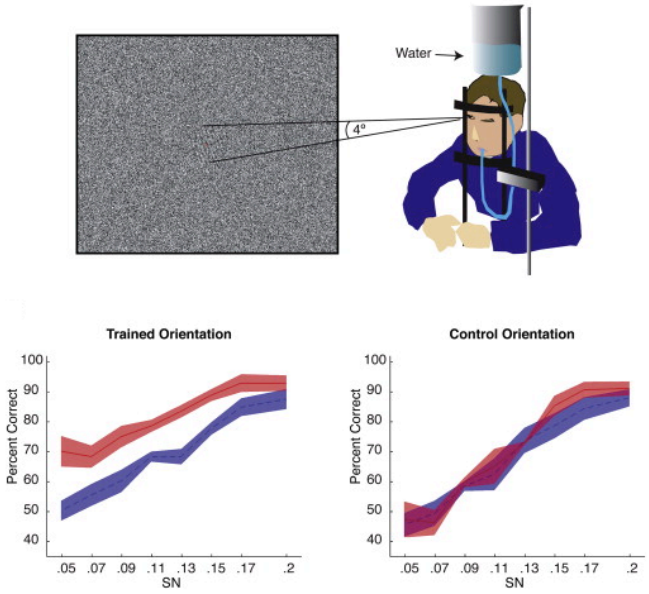


Figure 4.5: Rewards evoke learning of unconsciously processed visual stimuli in adult humans. A basic representation of the water apparatus and stimuli used in the experiment. The two graphs represent data collected from the trained orientation (red) and the untrained orientation (blue) (Seitz et al., 2009).

Reviewing the literature and contributions made to explore the mechanisms for reward-modulation and learning have revealed important findings in discovering how reward may interact with the sleep consolidation of VPL. Extensive animal research as well as human behavioral studies illustrated interactions between on-site brain activation and reward signal midbrain origins.

While this body of research provided offers many explanations to possible mechanistic frameworks for reward and learning, VPL and the reward-based interaction with sleep consolidation still remain largely unclear.

Chapter 5

5. Sleep Consolidation of Rewarded Visual Perceptual Learning

In this chapter, two experiments are laid out addressing sleep consolidation in reward-driven VPL. As discussed above, mechanisms have been found in animal studies that suggest reward processing occurs during sleep and is related to plastic functions in the brain. Additionally, behavioral studies with humans have illustrated that reward and sleep consolidation may interact with each other through motor learning. Given the research showing the effect of reward processing in VPL, it is necessary to examine how this process occurs in order to uncover possible methods to enhance VPL.

5.1 Reward Reactivates and Facilitates Visual Perceptual Learning During REM Sleep

5.1.1 Abstract

[Words: 298/300]

Visual perceptual learning (VPL) is defined as a long-term performance improvement on a perceptual task as a result of perceptual experience. It has been found that sleep strengthens and consolidates VPL. In parallel to the effect of sleep, reinforcement given through external primary reward (such as water) has been found to facilitate VPL. However, it remains unclear whether sleep and reward independently influence VPL or whether they interact with each other. Our previous research has found a significant interaction between reward and sleep in performance improvement on a visual task, suggesting that the effect of

reward on VPL is enhanced during sleep. Here, we investigated the neural mechanism of the interaction of reward and sleep on VPL of the texture discrimination task (TDT). Twenty-two participants were trained and tested on TDT before and after a nap during which brain activity was monitored with polysomnography. During training, half of the participants received auditory feedback and water as a reward through a tube for a correct response (reward group), while the other half only received auditory feedback for a correct response (no-reward group). First, we replicated the previous results that performance improvement after a nap was significantly larger for the reward group than for the no-reward group. Second, the reward group showed significantly longer REM sleep periods than the no-reward group. Third, during REM sleep, the reward group showed both significantly higher alpha activity at the fronto-central regions that are involved in the brain's reward system and significantly lower theta activity at the untrained side of the visual cortex, in comparison to the no-reward group. Finally, these neural modulations by reward were highly correlated with performance improvements. These results suggest that reward given during training allows the reward system to reactivate and interacts with visual processing during subsequent REM sleep.

5.1.2 Introduction

Visual perceptual learning (VPL) is defined as a long-term performance improvement on a perceptual task as a result of perceptual experience (Dosher & Lu, 1998; Dosher & Lu, 1999; Sagi, 2011; Sasaki et al., 2010). It has been found

that sleep strengthens and consolidates VPL (Karni et al., 2004; Mednick et al., 2003; Yotsumoto et al., 2009). In parallel to the effect of sleep, reinforcement given through external primary reward (such as water) has been found to facilitate VPL (Seitz et al., 2009). However, it remains unclear whether sleep and reward independently influence VPL or whether they interact with each other.

In the past 20 years, sleep's effect on VPL has been critically studied. It has been found that both NREM and REM sleep play significant roles in the consolidation of VPL (Karni et al., 2004; Stickgold et al., 2001; Yotsumoto et al., 2009). That is to say, without sleep after visual training, VPL is abolished and performance improvement is not seen. The benefits from sleep are not specific to an overnight's rest however, and even a short 90-minute nap during daytime has been shown to consolidate VPL (Mednick et al., 2003).

In addition to sleep's effect, research has also shown that reward given during training has been found to enhance VPL (Kim et al., 2015; Seitz et al., 2009). Together, these findings suggest that sleep and reward are significant factors in facilitating VPL. However, to our knowledge, the relationship between sleep and reward and how they influence VPL is largely not understood. In previous studies that have shown the effect of reward on VPL, all subjects have slept after rewarded training (Seitz et al., 2009). This poses a problem. In these reward studies, we cannot ignore the possibility that sleep may have influenced the primary findings. It is quite possible that the effect from reward may be dependent on sleep, or that there may be entirely independent processes. For example, in the study conducted by Seitz and colleagues in 2009, the

experimental design consisted of daily training sessions lasting over a week long. Subjects were trained on a subliminal Gabor orientation paired with water reward. The results showed improved performance on the orientation trained over several days. This study, along with others, include multiple days of training, which leaves the open question of whether sleep is influencing the performance improvement.

Thus, the purpose of the present study is to dissociate the effects of sleep and reward on VPL. For the present study, we proposed two predictions. First, sleep may not necessary for reward to be effective on VPL. This would mean that the effects of sleep and reward on VPL should be independent and show no interaction. Second, sleep may be interacting with reward on VPL. This would propose the novel theory that suggests that the effect of reward on VPL training is present only after a period of sleep and not during a period of wakefulness.

Our results from the present two experiments demonstrate both behavioral and electrophysical evidence that there is indeed an interaction reward processing of VPL tasks during sleep. Our first experiment compared subjects who received rewarded VPL training with subjects who received regular VPL training, both over a 12 hour period of either pure wakefulness or both wakefulness and sleep. The findings suggested a strong behavioral performance improvement specifically in the group that was allowed to sleep and was trained with a reward paired with the VPL task. Our second experiment replicated the previous results that performance improvement after a short nap was significantly larger for rewarded subjects than for the no-reward subjects. Additionally, the rewarded subjects

showed significantly longer REM sleep periods than the no-reward subjects, and finally, during REM sleep, the rewarded subjects showed both significantly higher alpha activity at the fronto-central regions that are involved in the brain's reward system and significantly lower theta activity at the untrained side of the visual cortex, in comparison to the no-reward subjects. These neural modulations by reward were highly correlated with performance improvements and ultimately suggest that reward given during training allows the reward system to reactivate and interact with visual processing during subsequent REM sleep.

5.1.3 Experiment 1

5.1.3.1 Method and Design

5.1.3.1.1 Participants

Participants were recruited from the Brown University campus using flier and email contact. All participants who volunteered had normal to corrected vision and were aged between 18-25 years old. This study collected a total of 47 participants (27 female). The institutional review board of Brown University approved this study. Subjects gave their written informed consent for their participation after the purpose of the study was thoroughly described. All subjects were given a screening document to identify individuals that could safely refrain from eating or drinking 5 hours prior to the experiment. Subjects were compensated at $10 per hour for their time spent in the laboratory and subjects who did not meet the screening criteria were excluded from the study. Additionally, frequent video game players were excluded in order to account for

prior research suggesting gaming influence on visual perceptual learning (VPL) tasks (Berard et al., 2015; Green & Bavelier, 2003; Green & Bavelier, 2007; Green et al., 2010).

5.1.3.1.2 Apparatus

The stimuli were presented using Psychophysics Toolbox (Brainard, 1997 and Pelli, 1997) for MATLAB® (The MathWorks, Natick, MA) on a Macintosh G5 computer. The stimuli appeared on a 19″ CRT monitor with a resolution of 1024 by 768 pixels and a refresh rate of 85 Hz. The viewing distance was 25 cm. A chin rest was used to maintain the participants' head position. The participants used a computer keyboard to make responses. Water was delivered using a ValveLink®8.2 system made by Automate Scientific, Inc.

5.1.3.1.3 Stimuli

Subjects were given a modified version of the Texture Discrimination Task (TDT) (Yotusmoto et al., 2009; Karni & Sagi 1991) paradigm (Figure 5.1).

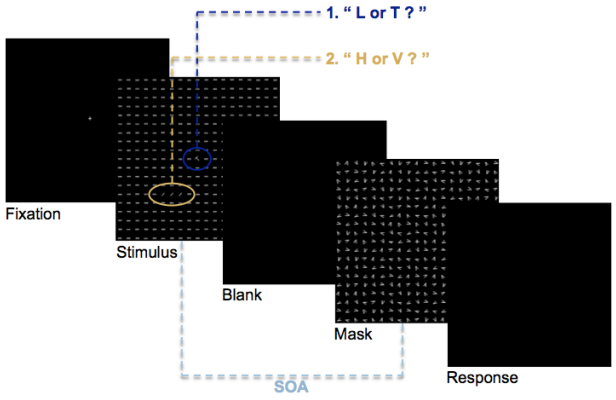


Figure 5.1: The texture discrimination task (TDT) stimulus. The first target is highlighted in blue where subjects report either the presence of an L or T, which is designed to hold fixation. This is referred to as the fixation task. The second target

(peripheral orientation task) is highlighted in orange and requires the subject to respond with an H or V depending if the targets orientation was horizontal or vertical. The peripheral orientation task is the primary measure of performance in the experiment. Note that the blue and orange circles and lines are provided just for illustrative purposes. They did not appear in the actual experiment. All conditions in the experiment were given auditory feedback for both targets. The shorter the Stimulus-to-mask Onset Asynchrony (SOA), the more difficult the task becomes.

For the present study specifically, all subjects were trained in the lower left visual quadrant. TDT was varied in difficulty through changing the length of Stimulus-to-mask Onset Asynchrony (SOA), which is the time elapsed between the presentation onset of the stimulus and the onset of the mask. After the presentation of the mask, subjects first entered their response to the fixation task followed by their response to the peripheral orientation task.

The size of the TDT stimulus was a 14°-by-14° visual angle. The position of each line segment in the background display moved slightly, by 0–0.05° between trials. The general stimulus was composed of whitish/gray lines 0.43°-by-0.07° (32 cd/m^2) that were presented against a black background (0.5 cd/m^2). The position of the peripheral orientation task varied slightly between each trial, but was consistently presented within the lower left quadrant within a 3°–5° visual angle from the center of the display.

5.1.3.1.4 Design

The experiment in the present study consisted of two sessions: a training session and a testing session. Each session (first training then testing) was 12 hours apart and began either at 9-10pm or 9-10am depending on group assignment. There were four groups in total each consisting of 12 subjects (Figures 5.2). Two groups began their training session at 9-10pm and the testing

session again in the morning at 9-10am. Of these two groups, one received a water-delivered reward during the task upon correct response to the TDT peripheral orientation task, whereas the other group did not. The remaining two groups went through the same procedure, except they began their training session at 9-10am instead of at night, and began the testing session at 9-10pm. This ensured two separate populations where one served as the sleep group and the other as the wake group. The sleep and wake populations had two subgroups consisting of either a reward or no reward condition as stated above. Subjects in the reward groups were asked to refrain from eating or drinking for 4-5 hours prior to the sessions. Due to an unexpected period of daytime napping, which could confound the results, one subject had to be excluded from the wake/reward group, leaving the total sample for the study at 47 participants.

Before beginning the experiment, a practice TDT block was given in order to ensure all subjects could see the stimuli and adequately handle the task itself. In the practice block, the upper right quadrant was used for the peripheral orientation task. The upper right quadrant was used for practice (compared to the lower left quadrant for the actual experiment) in order to ensure that all subjects began testing at the same level of experience. Previous research (Karni & Sagi, 1991) suggests that location specificity takes place in TDT, which posits that training in one quadrant would not transfer performance to another quadrant. Since most subjects were given a different amount of trials for practice, depending on how easy the task initially was for them, the lower left quadrant was used in the actual experiment. All subjects revived the same number of trials in the lower left visual

quadrant. In both practice and the real experiment, auditory feedback was provided for the center fixation task to facilitate subjects' fixation and additionally, the same feedback was provided for the peripheral orientation task..

Once the experiment began, subjects were given the same number of TDT trials and blocks for both training and testing sessions. In each of the training and testing sessions, there were 2 subsequent sets of 8 blocks, in each of which was conducted with a single SOA with 39 trials. Thus, there were 8 SOAs used for the first half of the sessions followed by an identical set of 8 SOAs for the second half of the sessions. The total number of trials was 624, which resulted in about 1 hour for each session. The SOAs were 400ms, 180ms, 160ms, 140ms, 120ms, 100ms, 80ms, and 60ms, and presented in this order for each half of both of the sessions. The 400ms SOA was presented at the beginning of each half as a practice round in order to allow subjects to acclimate better to the task. Subjects only in the reward groups received a droplet of water along with the auditory feedback provided for the peripheral orientation task. Water was delivered through a tube subjects held in their mouth for the duration of the experiment. Subjects in the no-reward groups were not equipped with the feeding tube nor were they given water upon correct response for the peripheral orientation task (Figure 5.2).

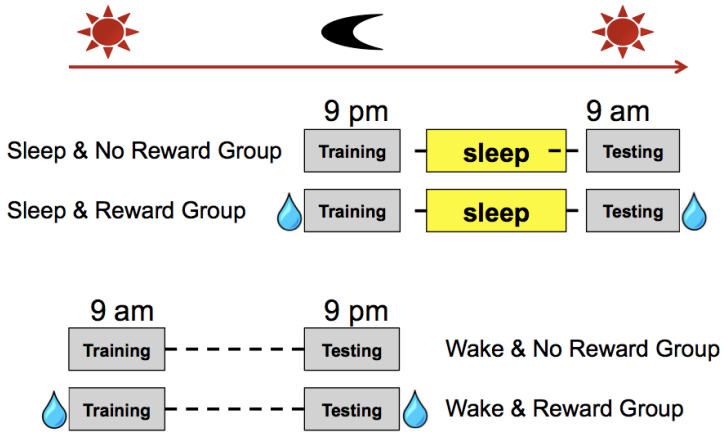


Figure 5.2: Sleep and reward experiment 1 design. Subjects in the reward groups were trained on TDT coupled with a water delivery system. The first group (wake group) began the training session in the morning and then the testing session12 hours later. The second group (sleep group) began the training session in the evening and the testing session 12 hours later in the morning. Subjects in the no reward groups were given TDT without the aforementioned water delivery system. The first group (wake group) began the training session in the morning and the testing session12 hours later. The second group (sleep group) began the training session in the evening and the testing session 12 hours later in the morning.

All subjects were asked to keep their regular sleep habits and refrain from daytime napping for the duration of the experiment. Subjects that did not follow these instructions were excluded from data analysis. Additionally, all subjects in the study were asked to abstain from any caffeine consumption during the day of the experiment.

5.1.3.1.5 Performance Measurement

In order to measure behavioral performance change for the TDT sessions, the 75% threshold SOA for each of training and testing session was computed as follows. First, we obtained the correct response ratio for the peripheral orientation task computed for each SOA and then fitted this data to a logistic psychometric function (Yotsumoto et al., 2009) This psychometric curve allows us to easily see

performance trends across each SOA and define the threshold for each respective session. The threshold is the point on the psychometric curve that corresponds to the SOA that subjects were able to achieve 75% correct response rate (Figure 5.3). As noted in our methods, shorter SOAs indicated that the task was more difficult. Thus, the SOA on the curve where subjects had a 75% threshold was the most difficult SOA subjects could handle before dropping below optimal performance rate. If the threshold becomes shorter after training, this indicates that the subject learned the task.

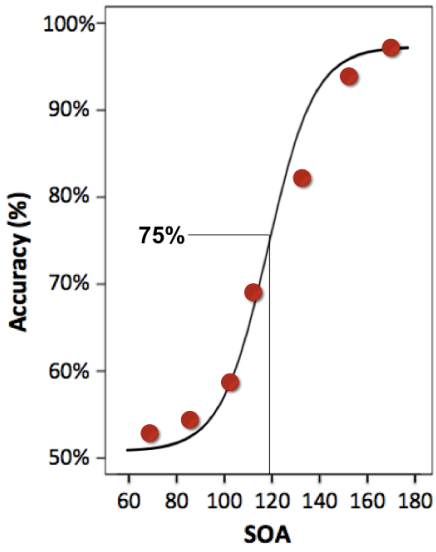


Figure 5.3: TDT performance threshold. In total, 7 different SOA's were used during the experiment, each ranging from 180ms to 60ms. SOA presentation became more difficult as subjects progressed through the training. For the results, subjects performed with roughly 90-100% accuracy at the higher SOA, but then dropped off as they advanced through the session and approached more difficult SOA's such as 80 or 60ms. In order to find the optimal performance threshold defined for the session, a logistic function was fitted to the data. The point on the curve that corresponded to the SOA in which 75% accuracy was achieved represented the subject's optimal performance known as the performance threshold.

5.1.3.2 Results

For our analysis, we measured the SOA thresholds at the training and testing sessions for each of the 4 groups. The difference between the training

session threshold SOA and the testing session threshold SOA divided by the training session SOA multiplied by 100 was defined as the TDT threshold change (Figure 5.3). The greater the TDT threshold change, the larger the performance improvement. We measured the TDT threshold change in the 4 groups with whether or not subjects slept as a factor, as well as whether or not they received the water reward. A 2x2 ANOVA was applied to examine the effect sleep and reward on VPL (Figure 5.4). A significant main effect of sleep ($F(1,43)=22.545$, $p<0.001$) and a significant main effect of reward was found ($F(1,43)=5.207$, $p<0.05$), as well as a significant interaction between sleep and reward factors ($F(1,43)=4.207$, $p<0.05$). Additionally, a significant simple main effect of sleep was observed for the reward groups ($F(1,43)=23.116$, $p<0.001$), along with a significant simple main effect of reward on the sleep groups ($F(1,43)=9.388$, $p<0.005$). A marginally significant simple main effect of sleep was also found for the no reward groups ($F(1,43)=3.637$, $p=0.06$). There was no significant difference in the wake groups between reward and no-reward conditions ($F(1,43)=0.027$, $p=0.87$).

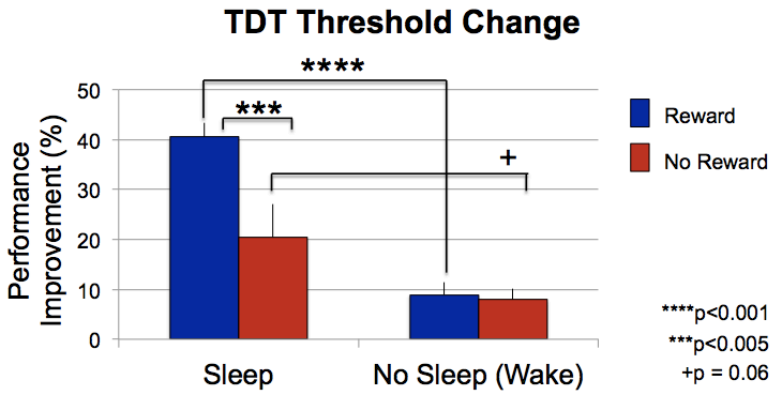


Figure 5.4: Experiment 1 TDT threshold change across sessions. In order to assess performance improvement, TDT threshold change was compared between the training and testing sessions by subtracting testing session SOA thresholds from training session SOA thresholds and then dividing by training session SOA thresholds. This value was then multiplied to obtain our TDT threshold change in percentage.

In order to rule out the possibility of circadian influence on performance, we compared thresholds for the training sessions for each of the 4 groups. Additionally, this calculation was made in order to address circadian influences that could have had impact on the data due to different timing for the training sessions across groups. No significant difference was observed in starting thresholds between all four groups (Figure 5.5).

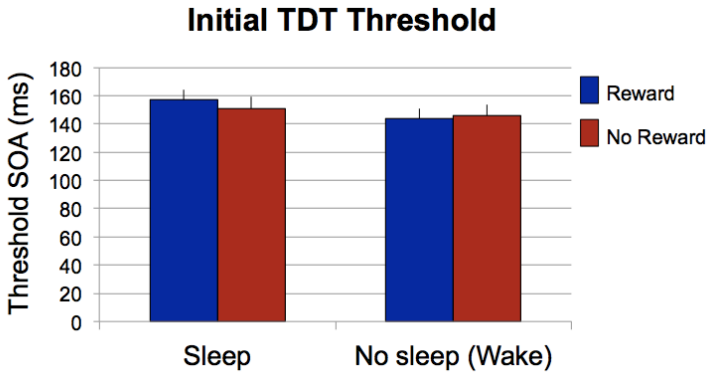


Figure 5.5: Initial TDT threshold on the first session. Thresholds of the training sessions for each of the 4 groups were compared in order to ensure that performance change was not due to initial group differences or circadian factors.

5.1.4 Experiment 2

5.1.4.1 Method and Design

5.1.4.1.1 Participants

Participants were recruited from the Brown University campus using flier and email contact. All participants who volunteered had normal to corrected

vision and were aged between 18-25 years old. This study collected a total of 22 participants (12 females). The institutional review board of Brown University approved this study. Subjects gave their written informed consent for their participation after the purpose of procedure of the study was thoroughly described. All subjects were given a screening document to identify individuals that could safely refrain from eating or drinking 5 hours prior to the experiment. Additionally, subjects were administered the Sleep-Wake habits Questionnaire and the Munich Chrono-Type Questionnaire. Subjects were required to have a regular sleep schedule of approximately 7-8 hours of sleep ranging from an 11pm to 12am bedtime, as well as meet other criteria specified in the questionnaires. Subjects who deviated from their normal sleep schedule for more than a 2-hours during a weeklong period prior to the experiment were excluded from the study. Subjects were compensated at $25 per hour for their time spent in the laboratory and subjects who did not meet the screening criteria were excluded from the study. Additionally, frequent video game players were excluded in order to account for prior research suggesting gaming influence on VPL tasks (Berard et al., 2015; Green & Bavelier, 2003; Green & Bavelier, 2007; Green et al., 2010).

5.1.4.1.2 Apparatus

The apparatus used in Experiment 2 was identical to that of Experiment 1, except with the addition of polysomnography (PSG). Brain activity during sleep was recorded and analyzed using a 64-channel electroencephalogram (EEG), electrooculogram (EOG), and electromyogram (EMG) from BrainVision LLC®

software and equipment. The visual stimuli were presented using Psychophysics Toolbox (Brainard, 1997 and Pelli, 1997) for MATLAB® (The MathWorks, Natick, MA) on a Macintosh G5 computer. The stimuli appeared on a 19″ CRT monitor with a resolution of 1024 by 768 pixels and a refresh rate of 85 Hz. The viewing distance was 25 cm. A chin rest was used to maintain the participants' head position. The participants used a computer keyboard to make responses. Water was delivered using a ValveLink®8.2 system made by Automate Scientific, Inc.

5.1.4.1.3 Stimuli

Subjects were given a modified version of the TDT paradigm (Figure 5.1). For the present study, all subjects were trained in the lower left visual quadrant. TDT was varied in difficulty through changing the length of SOA. After the presentation of the stimulus, subjects first entered their response to the fixation task followed by their response to the peripheral orientation task.

The size of the TDT stimulus was a 14°-by-14° visual angle. The position of each line segment in the background display moved slightly, by 0–0.05° between trials. The general stimulus was composed of whitish/gray lines 0.43°-by-0.07° (32 cd/m^2) that were presented against a black background (0.5 cd/m^2). The position of the peripheral orientation task varied slightly between each trial, but was consistently presented within the lower left quadrant within a 3°–5° visual angle from the center of the display.

5.1.4.1.4 Design

The experimental design in Experiment 2 was improved upon from Experiment 1 in order to ensure that performance changes more accurately measured the effect from sleep and reward presence on TDT threshold change among the subject groups. The same water-feeder was used for the reward group subjects as well as the same computer display and MATLAB code to ensure uniformity. All subjects were first given a training session, where there were 2 subsequent sets of 8 blocks, in each of which was conducted with a single SOA with 39 trials. Thus, there were 8 SOAs used for the first half of the training session followed by an identical set of 8 SOAs for the second half of the training session. The total number of trials was 624, which resulted in about 1 hour for the training session. The SOAs were 400ms, 180ms, 160ms, 140ms, 120ms, 100ms, 80ms, and 60ms, and presented in this order for each half of the training session. The 400ms SOA was presented at the beginning of each half as a practice round in order to allow subjects to acclimate better to the task. The testing session was identical to the training session, except that each block contained only 5 trials instead of 39. This resulted in a total of 80 trials or about 10 minutes for the testing session. Throughout the training and testing, the target was presented at a consistent quadrant of the visual field for each subject.

Subjects in the reward group were asked to refrain from eating or drinking for 4-5 hours prior to the training session. Additionally, all subjects in the study were asked to abstain from any caffeine consumption during the day of the

experiment. Subjects were instructed to maintain regular sleep habits in accordance with the screening process, which occurred prior to experimentation.

For experiment 2, a nap design was employed on our participants in a similar fashion to previous studies investigating VPL and sleep-dependent influences (Mednick et al., 2003). Using a nap design allows for a wide variety of flexible options including the ability to control for the subject's length of sleep, sleep stage inclusion, as well as control for circadian factors and possible confounds that can occur outside the laboratory (Figure 5.6).

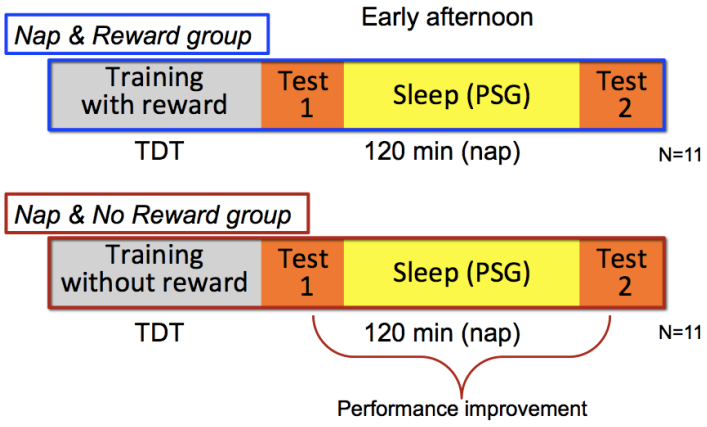


Figure 5.6: Sleep and reward experiment 2 design. The entire experiment was conducted over a 5-hour period beginning at 12:00pm. All subjects slept in the sleep chamber from 2:00pm to 4:00pm. Short pre-nap and post-nap test sessions were used to measure performance improvement on TDT. This behavioral data was correlated with sleep architecture properties obtained with PSG.

Subjects were asked to arrive at the laboratory at 0:00pm order to prepare for PSG application (Figure 5.6). All subjects were held to the same timeframe in order to account for possible circadian effects. After a 1-hour period of TDT training and a short 10-minute TDT test session, subjects were allowed to rest for a period of approximately 30 minutes while PSG electrodes were applied.

These electrodes included a 64-channel electroencephalogram (EEG) cap used to measure surface cortical activity, an electrooculogram (EOG) for eye movement, and electromyogram (EMG) measuring muscle tension. The 120-minute nap began at around 2pm for all subjects. The second 10-minute TDT test session was conducted at approximately 4:30pm, once subjects were awake and unequipped with the PSG electrodes.

Subjects were split into two groups: a reward group that received a water reward during a correct response to the peripheral orientation task training and a no-reward group that underwent the same training but without the water reward.

5.1.4.1.5 Sleep Scoring

Sleep stages were scored according to the American Associated of Sleep Medicine (AASM) criteria for sleep.

5.1.4.1.6 Performance Measurement

In order to measure behavioral performance change for the TDT sessions, the 75% threshold SOA for each of training and testing sessions was computed as follows. First, we obtained the correct response ratio for the peripheral orientation task computed for each SOA and then fitted this data to a logistic psychometric function. This psychometric curve allows us to easily see performance trends across each SOA and define the threshold for each respective session. The threshold is the point on the psychometric curve that corresponds to the SOA that

subjects were able to achieve 75% correct response rate (Figure 5.3). As noted in our methods, shorter SOAs indicated that the task was more difficult. Thus, the SOA on the curve where subjects had a 75% threshold was the most difficult SOA subjects could handle before dropping below optimal performance rate. If the threshold becomes shorter after training, this indicates that the subject learned the task.

Brain activity obtained from PSG was analyzed using BrainVision LLC® software. Scalp EEG channels were re-referenced from Fz to TP 10 and TP 9 to more accurately measure spontaneous oscillation activity. A 30 Hz high-pass filter was applied to the data before scoring in order to reduce noise. Data was recorded and sampled at 500 Hz, and FFT analysis was performed in order to extract oscillation power measured in μV^2.

5.1.4.2 Results

5.1.4.2.1 TDT Performance Improvement

Behavioral performance change was assessed along with sleep architecture. Both subjects in the reward ($t(11)=9.743$, $p<0.001$) and no-reward ($t(11)=3.003$, $p=0.013$) groups demonstrated performance improvement on TDT between the first and second tests sessions. A significant difference in performance improvement between the reward and no-reward groups was also observed ($F(1,20)=11.461$, $p=0.003$) (Figure 5.7).

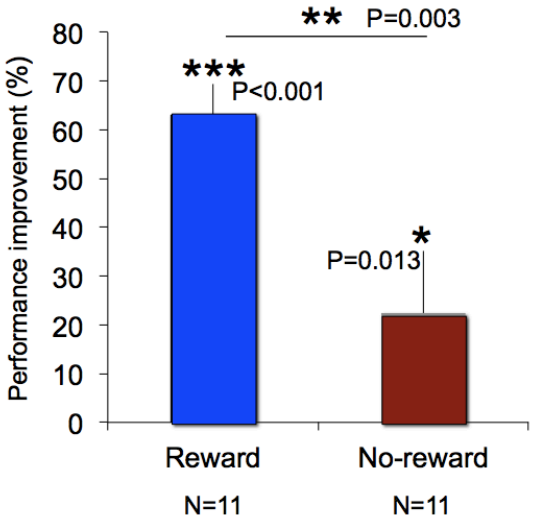


Figure 5.7: Experiment 2 TDT threshold change. SOA thresholds for the two test sessions were achieved in the same fashion as in Experiment 1. Both reward and no-reward groups were statistically tested against baseline and as well as against each other.

5.1.4.2.2 REM Sleep Duration

Along with the behavioral results, a significant difference in average time spent in REM sleep during the nap (Figure 5.8) was noted between the reward and no-reward subjects ($t(22)=3.012$, $p=0.007$).

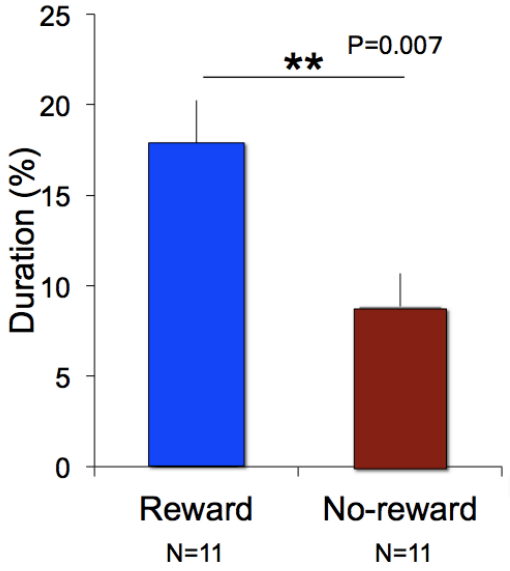


Figure 5.8: REM sleep duration. For the duration of the 120-minute napping period, PSG was applied and brain activity was monitored. One area of interest is sleep architecture over the nap, which includes length of time spent in varies sleep stages. Previous research has indicated NREM and REM sleep can play an important role in facilitating visual perceptual learning (Sasaki et al., 2010). Here we found significant difference in the time spent in REM sleep during the napping portion between subject groups.

A significant correlation was found between TDT performance improvement and time spent in REM sleep during the nap (r=0.70, n=22, p=0.0003) (Figure 5.9).

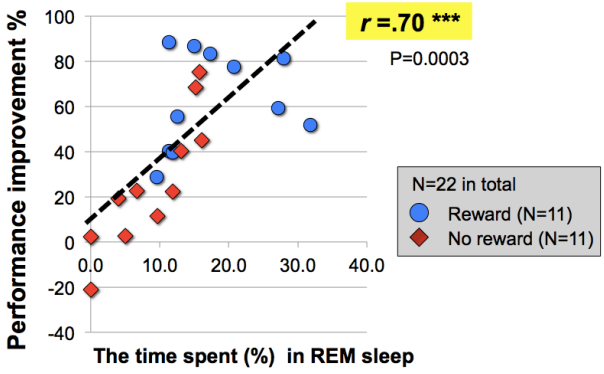
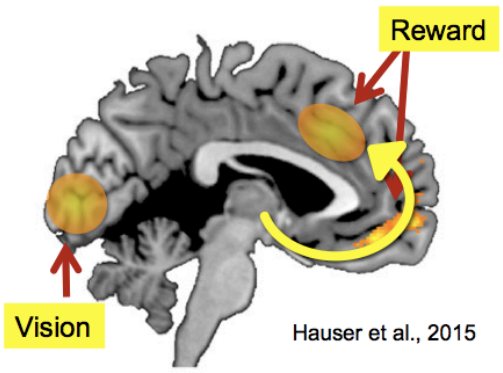


Figure 5.9: TDT performance and REM sleep correlation. In order to connect the behavioral performance improvement difference with the sleep architecture difference seen between the reward and no reward groups, a correlation was found where length of time spent in REM correlated with a larger TDT threshold change.

5.1.4.2.3 REM Sleep Spontaneous Oscillations

In addition to behavioral performance and REM sleep quantity, spontaneous oscillations measured during the REM periods in were examined. During REM sleep, alpha (10-12 Hz) and theta (5-9 Hz) bands are major spontaneous oscillations that occur in humans. Fronto-central and occipital EEG channels were specifically investigated (Figure 5.10). Fronto-central EEG channels were selected due to prior literature indicating that there is a reward

system that forms a neural arc that originates from the striatum to medial prefrontal areas. Additionally, recent studies indicate that reward processing in the medial prefrontal area will appear in the front-central EEG channels. Thus, fronto-central channels were chosen as an indication of reward processing. For visual processing, we selected the trained and untrained hemisphere of the occipital EEG channels. The trained hemisphere was contralateral to the target presentation in the subject's visual field, and the untrained hemisphere was ipsilateral to the target presentation in the subject's visual field. A frequency analysis was conducted in order to obtain the mean power for 30 sec for these 6 measures during REM sleep.



Region	Oscillation	
Fronto-central	Alpha	Theta
Occipital (trained)	Alpha	Theta
Occipital (untrained)	Alpha	Theta

Figure 5.10: Visual and reward brain areas. Regions of interest for the present study include the occipital trained and untrained hemisphere as well as the fronto-central electrode channels that indicate reward-processing activity. Alpha and theta bands were chosen based on unique and specialized occurrence during REM sleep (CITE)

A MANOVA was applied on the 6 oscillations to yield significant effect of alpha and theta power between the reward and no-reward groups (Pillais'

Trace = 0.613, F(6,13) = 3.437, p = 0.029), where the effect size ≒ 0.613, and 37.6% of the variance accounted for. Additionally, a series of one-way ANOVA on each of the 6 oscillations was performed demonstrating a significant effect on the fronto-central alpha band (F(1,18) = 4.759, p = 0.043) and the occipital untrained hemisphere theta band (F(1,18) = 6.773, p = 0.018) (Figure 5.11). The fronto-central alpha power and the occipital theta power at the untrained side were significantly and negatively correlated (r=-0.61, n=20, p=0.004) (Figure 5.12). In addition to this, a significant negative correlation between untrained occipital theta and TDT performance improvement was found (r=-0.57, n=20, p=0.009) (Figure 5.13).

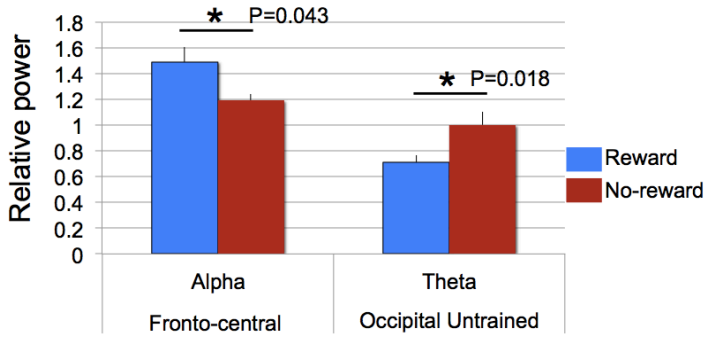


Figure 5.11: EEG power density. Brain oscillation power (μV^2) was obtained for the fronto-central and occipital trained/untrained hemispheres. Oscillation power is thought to reflect changes in brain processing during sleep that could reflect plasticity (CITE). Significant differences in both alpha and theta bands were found between the fronto-central and occipital untrained hemispheres respectively, between the reward and no reward groups.

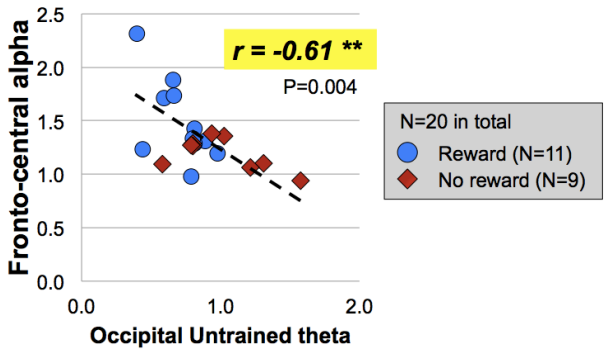


Figure 5.12: Alpha and theta band correlation. A significant negative correlation was found between fronto-central alpha power and the occipital untrained hemisphere's theta power. This could suggest a suppression mechanism occurring in the untrained visual hemisphere that corresponds to more reward processing occurring as a result of reward-driven VPL.

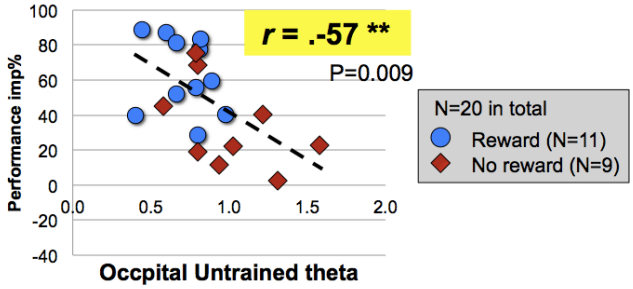


Figure 5.13: TDT performance and suppression of the visual cortex. A correlation was found between greater TDT threshold change and lower untrained occipital theta power. Along with Figure 12, this could suggest a suppressing mechanism occurring as a result of better performance change across the two testing sessions of the experiment.

5.1.5 Discussion

The results from this project suggest a significant interaction between rewarded VPL processing and sleep consolidation. In Experiment 2, performance improvement was best seen when subjects were allowed to sleep and received reward paired with TDT training. This finding was further examined under Experiment 3 using electrophysical methodology over a period of napping. Behavioral results from Experiment 1 were replicated in Experiment 3, which

correlated with significantly different sleep architecture involving REM sleep duration and spontaneous brain wave oscillation properties between the reward and no-reward groups. From this data, we conclude that rewarded training facilitates VPL and is reactivated specifically during REM sleep.

Alpha and theta bands are considered to be major spontaneous oscillations in the human brain, appearing prominently during REM sleep (Klimesch et al., 1999; Finelli et al., 2000; Nishida et al., 2009). Our findings suggested interesting activity during REM sleep, where specifically, alpha and theta bands were found to have significant differences between the reward and no reward groups in Experiment 3. For the analysis, fronto-central and occipital EEG channels were selected. These specific were selected because previous research indicated that there is a reward system that forms a neural arc that originates from the striatum to medial prefrontal areas (Hauser et al., 2015). This research indicated that reward processing in the medial prefrontal area would appear in the front-central EEG channels, which therefore led to the conclusion that these channels could be representative of reward processing activation. For visual processing, the trained and untrained hemispheres of the occipital EEG channels were selected (Yotsumoto et al., 2009). The trained hemisphere was contralateral to the visual field with the target presentation, and the untrained hemisphere was ipsi-lateral to the visual field containing the target presentation. In TDT, the target is surrounded by the background orientation that needs to be segregated by the target. The untrained hemisphere thus corresponded to the background region.

Frequency analysis was conducted to obtain the mean power for 30 sec for these 6 measures during REM sleep.

These results suggest that reward given at training seems to modulate post-training sleep content leading to performance improvement. Especially, rewarded training makes REM sleep longer, and enhances the fronto-central alpha power and suppresses the theta power at the untrained occipital site. We speculate that the reward at training stimulated the dopaminergic neural circuits, a part of the midbrain-prefrontal reward processing system, which led to a status preferable for maintenance of REM sleep. Perhaps, during REM sleep, the reward system is reactivated and is shown as an increase in activation of the fronto-central alpha power. The reactivated reward system then sends suppressive signals to the visual cortex, especially to the untrained hemisphere, shown as decreased theta power during REM sleep (Kim et al., 2015; Sasaki et al., 2010; Seitz & Watanabe, 2005). The reduced theta activity was in a robust negative correlation with performance improvement. It is possible that reducing noise in the untrained hemisphere would contribute to performance improvement.

It is important however, to note the limitations of this study. In Experiment 2, all subjects were scheduled under a 12-hour design where the majority of time was not spent in the laboratory. This means it is quite possible that in all 47 subjects, there could have been strong variability in what activities they engaged in when not in the laboratory. Regular sleep habits were asked to be maintained as well as abstaining from daytime napping. It may be possible that

some subjects slept better or longer than others or may have engaged in various daytime activities that could have influenced consolidation.

Since reward was given on both the training and testing session in the reward groups in Experiment 2, there could have been influence in initial task performance. Figure 5.5 denotes the initial thresholds, which do not support this confounding factor, but still should not be ruled out. Additionally, only the reward groups were required to fast before the training and testing sessions, which could have influenced performance throughout the task.

Experiment 3 was more tightly controlled than Experiment 2, where the entirety of the procedure took place in the laboratory. However, it should be noted that similar confounding factors existed just as in Experiment 2. Only subjects in the reward group were required to fast, although each group was allowed to have a snack before the napping period. Our data suggests equal numbers of subjects in each group that chose to eat before the nap. Regardless, the presence of food during the experiment could have influenced the nap (Willie et al., 2001; Crispim et al., 2007).

One primary difference between Experiment 2 and Experiment 3 is that during Experiment 2, subjects were not given TDT paired with reward during the two testing sessions. This means that during the final retest in which performance improvement was assessed, subjects in the reward groups were given TDT with reward in the first experiment but not in the second. The behavioral data suggests no strong difference although performance improvement is slightly lower in Experiment 3. This is expected however, since subjects were allowed less time

between testing sessions to consolidate the training compared to Experiment 2 where subjects had 12 hours.

Chapter 6

6. Summary and Cumulative Discussion

The primary aim of this dissertation involved investigating the mechanisms of VPL and how these systems can be targeted for enhancement. Aspects of consolidation, reward processing, and unique behavioral training methods such as playing video games were examined and tested in order identify key elements of these factors that contribute to facilitating VPL.

In the first experiment, frequent video game playing was found to be beneficial for VPL consolidation, specifically with regard to stabilization during both wakeful and sleep aspects of consolidation. Since reward and motivation are integrated factors in most action video games, in order to explain the findings behind experiment 1, reward-driven VPL was investigated under consolidative mechanisms in experiment 2. The results yielded a significant interaction between reward and sleep during VPL, suggesting that in order for there to be an effect of reward on VPL, a period of sleep was needed. The next stage involved identifying the mechanisms behind this interaction, where in experiment 3, polysomnography was used to uncover the specific sleep architecture associated with reward processing. The findings suggested that, when subjects are trained with rewarded stimuli in VPL (compared to simple repeated exposure), reward processing is reactivated during subsequent REM sleep periods, which modulates the visual processing to aid in consolidative mechanisms. We observed the most performance improvement on VPL tasks when subjects were motivated with a reward and allowed to undergo a period of post-training sleep. These performance

effects were emphasized when sleep and reward were paired together, suggesting that these conditions are integral to maximizing VPL enhancement.

With the findings from this dissertation, we can continue exploring VPL enhancement with the knowledge that reward and sleep consolidation are heavily involved with encouraging visual plasticity. Continued research in this direction includes imaging experiments to fully uncover the mechanisms of reward-based VPL consolidation that we investigated using electrophysical techniques. Not only will this future line of research clarify the mechanisms of VPL enhancement, but it will also lend conclusions to the debated field of sleep consolidation, as well as ongoing discussion regarding the mechanisms of diffuse reward signals in the brain that are related to visual plasticity.

Neuroimaging methods could be employed to measure activation within the visual cortex and midbrain. Combined with our solid platform of data that has been collected using PSG, we could further develop and hone our hypotheses for neural activations in response to reward-based consolidation of VPL. Correlated BOLD activity between the visual cortex and midbrain reward system reflected in the Reward Activation Model could suggest more concrete evidence of communication between the two areas that are specific to reward-based VPL in humans. In addition to measuring activation, a new cutting-edge MRI technique could be utilized to measure excitatory and inhibitory changes in various parts of the brain. This is known as Magnetic Resonance Spectroscopy (MRS) (Cousijn et al., 2014; Hu et al., 2013; Stagg et al., 2009; Jocham et al., 2012) and primarily investigates the changes in glutamate and GABA to speculate on plastic or

inhibitory states of specific brain regions, such as the visual cortex. Since research on the reward system in rats has found that reward-based learning may depend not only on dopamine release but also could be related to glutamate and GABA activity (Higgins and Fletcher, 2003; Hikosaka et al., 2008; Ikemoto, 2010; Vlachou and Markou, 2010), we could employ MRS at specific time intervals after or before training to gauge the plastic state of the visual cortex and possibly deeper brain areas involved with reward processing. Not only would this research tell us more about excitatory/inhibitory changes in the brain that contribute to visual plasticity, but it may as well also provide information on how dopamine release and reward-based learning is intertwined with the time-course visual plasticity as well.

Another area of interest that contributes to the consolidation of visual plasticity includes interference paradigms (Yotsumoto et al., 2009a; Fischer and Born, 2009). The mechanism of interference in VPL was covered in experiment 1. With the current design and specification, we can use reward as a tool to probe the stability of interfering memories including characteristics of consolidation and reconsolidation. According to Fischer and Born, diffuse reward signals would boost learning of all relevant information, including interfering information. Using MRI as well as electrophysical data, interference paradigms with reward and VPL could be used to further understand how consolidation functions (as well as explain the results from experiment 1) and work towards developing a unified mechanism of reward-based VPL sleep consolidation.

Additionally, an interesting by-product of this research could involve information critical to the discussion of sleep consolidation itself. Since this field is still debated, the knowledge of reward systems and VPL can be used as tools for arguing specific aspects of consolidation models. Below, future possible experimentation based on our current work is outlined.

The first direction would be to examine the dual process hypothesis and the sequential hypothesis through data already collected. Since the collected subjects are set up in a paradigm designed to achieve one full sleep cycle, we can look at the amount of time spent in each sleep stage as well whether the presence of REM sleep statistically affects the data (since some subjects show REM periods within a 90 minute sleep session, whereas others do not). We can compare the subjects who achieved a REM period during the nap with the subjects who did not and look at TDT behavioral performance improvement to see if REM played a significant role in learning. Since TDT is a procedural task, according to past literature, we would expect to see only improvement with subjects who achieved a period of REM sleep (Marshall et al., 2004; Born et al., 2006; Rasch et al., 2007). Past studies with nap experiments have even reported that TDT performance improvement is only seen after a 90-minute nap with REM and SWS present together (Mednick et al., 2003). Our results have suggested learning without a REM period, however more subjects would be needed to make this a statistical significance. If we do find behavioral improvement without the presence of a REM period, this would suggest new evidence not only counter prior findings with nap studies but would provide additional evidence against the

dual process hypothesis, since this hypothesis would posit that REM is needed to consolidate procedural (TDT) tasks. If, on the other hand, behavioral improvement were seen only with REM, then this would offer support for either the dual process hypothesis or the sequential hypothesis and would conform to prior findings (Mednick et al., 2003). Parsing out the sequential hypothesis compared to the dual process hypothesis could be investigated using SOREMPs (Sleep Onset REM Periods), in order to achieve a napping period with REM and no SWS (Bishop et al., 1996) to see if TDT behavioral performance still increased without the presence of SWS.

One of the most easily approachable hypotheses of the learning consolidation model with our current data set would be the spontaneous oscillation hypothesis. In this hypothesis, the essential idea is that looking simply at sleep stages such as SWS and REM sleep are too broad and too crude to identify the specific mechanisms of sleep-dependent learning and consolidation (Diekelmann et al., 2009). For example, studies have found the relevance of sleep spindle activity across both REM and SWS periods ranging from improvements in verbal memory to motor learning (Gais et al., 2002; Nishida & Walker, 2007; Morin et al., 2008; Tamaki et al., 2008a, 2009). In addition, the presence of SWA and theta activity across REM and SWS periods was found to be involved with performance improvement on various tasks (Born et al., 2006; Poe et al., 2000). Given the evidence, it would seem that other frequencies such as sleep spindles and theta frequencies could play a role in sleep-dependent learning and consolidation irrespective of which sleep stage they occur. Since full PSG data on

subjects has already been collected in the present studies, additional analysis of different frequency bands across the entire nap period could reveal interesting trends in those who experience performance improvement compared to a novel interference group. Analysis of frequency bands confined to specific sleep stages could also reveal interesting evidence supporting or countering this hypothesis. In addition to examining SWA, theta, and spindle frequencies, future analyses are being prepared to investigate *all* possible frequency bands emerging during the nap for both the learning and interference conditions. This would include examining lighter stages of sleep with spontaneous alpha fluctuations and perhaps even beta frequencies. Essentially, with our available data and refined nap paradigm (including a new interference group), a full range of oscillatory frequencies can be investigated to see trends in the learning condition compared to the interference condition.

In conclusion, this dissertation aims to provide a solid framework for the progression of reward-processing, consolidation, and VPL enhancement. Additionally, current projects and future directions outline a series of possible experiments that can be used to uncover the mechanisms of reward-based VPL consolidation. Not only would this research contribute to the enhancement of VPL, but it can also be used to support or challenge pieces of evidence debated today in the field of visual plasticity.

References

Abe, M., Schambra, H., Wassermann, E. M., Luckenbaugh, D., Schweighofer, N., & Cohen, L. G. (2011). Reward improves long-term retention of a motor memory through induction of offline memory gains. *Current Biology*, *21*(7), 557-562.

Adcock, R. A., Thangavel, A., Whitfield-Gabrieli, S., Knutson, B., & Gabrieli, J. D. (2006). Reward-motivated learning: mesolimbic activation precedes memory formation. *Neuron*, *50*(3), 507-517.

Agnew, H. W., Webb, W. B., & Williams, R. L. (1966). THE FIRST NIGHT EFFECT: AN EEG STUDYOF SLEEP. *Psychophysiology*, *2*(3), 263-266.

Ahissar, M., & Hochstein, S. (1993). Attentional control of early perceptual learning. *Proceedings of the National Academy of Sciences*, *90*(12), 5718-5722.

Ahissar, M., & Hochstein, S. (1997). Task difficulty and the specificity of perceptual learning. *Nature*, *387*(6631), 401-406.

Ahissar, M., & Hochstein, S. (2004). The reverse hierarchy theory of visual perceptual learning. *Trends in cognitive sciences*, *8*(10), 457-464.

Alcaro, A., Huber, R., & Panksepp, J. (2007). Behavioral functions of the mesolimbic dopaminergic system: an affective neuroethological perspective. *Brain research reviews*, *56*(2), 283-321.

Alvarez, P., & Squire, L. R. (1994). Memory consolidation and the medial temporal lobe: a simple network model. *Proceedings of the National Academy of Sciences*, *91*(15), 7041-7045.

American Academy of Sleep Medicine, & Iber, C. (2007). *The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications*. American Academy of Sleep Medicine.

Arnell, K. & Jolicoeur, P. (1999). The attentional blink across stimulus modalities: evidence for central processing limitation. J. Exp. Psychol. Human Percept. Perform. 25, 630-648

Arsenault, J. T., Nelissen, K., Jarraya, B., & Vanduffel, W. (2013). Dopaminergic reward signals selectively decrease fMRI activity in primate visual cortex. *Neuron*, *77*(6), 1174-1186.

Bach, M. E., Barad, M., Son, H., Zhuo, M., Lu, Y. F., Shih, R., ... & Kandel, E. R. (1999). Age-related defects in spatial memory are correlated with defects

in the late phase of hippocampal long-term potentiation in vitro and are attenuated by drugs that enhance the cAMP signaling pathway. *Proceedings of the national academy of sciences*, *96*(9), 5280-5285.

Ball, K. K., Beard, B. L., Roenker, D. L., Miller, R. L. & Griggs, D. S. (1988). Age and visual search: expanding the useful field of view. J. Optic. Soc. Am. 5, 2210-2219

Ball, K., & Sekuler, R. (1987). Direction-specific improvement in motion discrimination. Vision research, 27(6), 953-965.

Bandyopadhya, R. S., Datta, S., & Saha, S. (2006). Activation of pedunculopontine tegmental protein kinase A: a mechanism for rapid eye movement sleep generation in the freely moving rat. *The Journal of neuroscience*, *26*(35), 8931-8942.

Bao, S., Chan, V. T., & Merzenich, M. M. (2001). Cortical remodelling induced by activity of ventral tegmental dopamine neurons. *Nature*, *412*(6842), 79-83.

Berard, A. V., Cain, M. S., Watanabe, T., & Sasaki, Y. (2015). Frequent video game players resist perceptual interference. PLoS One, 10(3), e0120011. doi:10.1371/journal.pone.0120011

Bishop, C., Rosenthal, L., Helmus, T., Roehrs, T., & Roth, T. (1996). The frequency of multiple sleep onset REM periods among subjects with no excessive daytime sleepiness. *SLEEP-NEW YORK-*, *19*, 727-730.

Boissard, R., Gervasoni, D., Schmidt, M. H., Barbagli, B., Fort, P., & Luppi, P. H. (2002). The rat ponto-medullary network responsible for paradoxical sleep onset and maintenance: a combined microinjection and functional neuroanatomical study. *European Journal of Neuroscience*, *16*(10), 1959-1973.

Boot, W. R., & Simons, D. J. (2012). Advances in video game methods and reporting practices (but still room for improvement): a commentary on Strobach, Frensch, and Schubert (2012). Acta Psychol (Amst), 141(2), 276-277; discussion 278-280. doi:10.1016/j.actpsy.2012.06.011

Boot, W. R., Kramer, A. F., Simons, D. J., Fabiani, M., & Gratton, G. (2008). The effects of video game playing on attention, memory, and executive control. Acta Psychol (Amst), 129(3), 387-398. doi:10.1016/j.actpsy.2008.09.005

Born, A. P., Law, I., Lund, T. E., Rostrup, E., Hanson, L. G., Wildschiødtz, G., ... & Paulson, O. B. (2002). Cortical deactivation induced by visual stimulation in human slow-wave sleep. *Neuroimage*, *17*(3), 1325-1335.

Born, J., Rasch, B., & Gais, S. (2006). Sleep to remember. *The Neuroscientist*, *12*(5), 410-424.

Brady, M. J., & Kersten, D. (2003). Bootstrapped learning of novel objects. *Journal of Vision*, *3*(6), 2-2.

Brainard, D. H. (1997). The psychophysics toolbox. *Spatial vision*, *10*, 433-436.

Brashers-Krug, T., Shadmehr, R., & Bizzi, E. (1996). Consolidation in human motor memory. *Nature*, *382*(6588), 252-255.

Breton, J., & Robertson, E. M. (2014). Flipping the switch: mechanisms that regulate memory consolidation. *Trends in cognitive sciences*, *18*(12), 629-634.

Broadbent, D. & Broadbent, M. (1987). From detection to identification: response to multiple targets in rapid serial visual presentation. Percept. Psychophys. 42, 105-113

Bromberg-Martin, E. S., Matsumoto, M., & Hikosaka, O. (2010). Dopamine in motivational control: rewarding, aversive, and alerting. *Neuron*, *68*(5), 815-834.

Bunzeck, N., Doeller, C. F., Dolan, R. J., & Duzel, E. (2012). Contextual interaction between novelty and reward processing within the mesolimbic system. *Human brain mapping*, *33*(6), 1309-1324.

Cain, M. S., Landau, A. N., & Shimamura, A. P. (2012). Action video game experience reduces the cost of switching tasks. Atten Percept Psychophys, 74(4), 641-647. doi:10.3758/s13414-012-0284-1

Cain, M. S., Prinzmetal, W., Shimamura, A. P., & Landau, A. N. (2014). Improved control of exogenous attention in action video game players. Name: Frontiers in Psychology, 5, 69.

Caithness, G., Osu, R., Bays, P., Chase, H., Klassen, J., Kawato, M., Wolpert, D. M. & Flanagan, J. R. (2004). Failure to consolidate the consolidation theory of learning for sensorimotor adaptation tasks. J. Neurosci. 24 , 8662-8671.

Censor, N., Karni, A., & Sagi, D. (2006). A link between perceptual learning, adaptation and sleep. *Vision research*, *46*(23), 4071-4074.

Chun, M. M. & Potter, M. C. (1995). A two-stage model for multiple target detection in rapid serial visual presentation. J. Exp. Psychol. Human Percept. Perform. 21, 109-127

Clément, O., Sapin, E., Bérod, A., Fort, P., & Luppi, P. H. (2011). Evidence that neurons of the sublaterodorsal tegmental nucleus triggering paradoxical (REM) sleep are glutamatergic. *Sleep*, *34*(4), 419.

Clemente, C. D., Sterman, M. B., & Wyrwicka, W. (1964). Post-reinforcement EEG synchronization during alimentary behavior. *Electroencephalography and clinical Neurophysiology*, *16*(4), 355-365.

Cohen, M. X., Elger, C. E., & Ranganath, C. (2007). Reward expectation modulates feedback-related negativity and EEG spectra. *Neuroimage*, *35*(2), 968-978.

Cousijn, H., Haegens, S., Wallis, G., Near, J., Stokes, M. G., Harrison, P. J., & Nobre, A. C. (2014). Resting GABA and glutamate concentrations do not predict visual gamma frequency or amplitude. *Proceedings of the National Academy of Sciences*, *111*(25), 9301-9306.

Crispim, C. A., Zalcman, I., Dáttilo, M., Padilha, H. G., Edwards, B., Waterhouse, J., ... & de Mello, M. T. (2007). The influence of sleep and sleep loss upon food intake and metabolism. *Nutrition research reviews*, *20*(02), 195-212.

Czarnecki, A., Birtoli, B., & Ulrich, D. (2007). Cellular mechanisms of burst firing-mediated long-term depression in rat neocortical pyramidal cells. *The Journal of Physiology*, *578*(2), 471-479.

Dahan, L., Astier, B., Vautrelle, N., Urbain, N., Kocsis, B., & Chouvet, G. (2007). Prominent burst firing of dopaminergic neurons in the ventral tegmental area during paradoxical sleep. *Neuropsychopharmacology*, *32*(6), 1232-1241.

Dayan, P., & Balleine, B. W. (2002). Reward, motivation, and reinforcement learning. *Neuron*, *36*(2), 285-298.

Diekelmann, S., Wilhelm, I., & Born, J. (2009). The whats and whens of sleep-dependent memory consolidation. *Sleep medicine reviews*, *13*(5), 309-321.

Dinse, H. R., Ragert, P., Pleger, B., Schwenkreis, P., & Tegenthoff, M. (2003). Pharmacological modulation of perceptual learning and associated cortical reorganization. *Science*, *301*(5629), 91-94.

Donlea, J. M., Ramanan, N., & Shaw, P. J. (2009). Use-dependent plasticity in clock neurons regulates sleep need in Drosophila. *Science*, *324*(5923), 105-108.

Dosher, B. A., & Lu, Z. L. (1998). Perceptual learning reflects external noise filtering and internal noise reduction through channel reweighting. Proceedings of the National Academy of Sciences, 95(23), 13988-13993.

Dosher, B. A., & Lu, Z. L. (1999). Mechanisms of perceptual learning. Vision research, 39(19), 3197-3221.

Dudai, Y. (2002). Memory from A to Z: Keywords, concepts, and beyond. *New York:: Oxford University Press.*

Dudai, Y. (2003). Memory From A to Z: Keywords, Concepts, and Beyond (Book). Choice: Current Reviews for Academic Libraries, 41(1), 127.

Dudai, Y. (2004). The neurobiology of consolidations, or, how stable is the engram? Annu Rev Psychol, 55, 51-86. doi:10.1146/annurev.psych.55.090902.142050

Dye, M. W., Green, C. S., & Bavelier, D. (2009a). The development of attention skills in action video game players. Neuropsychologia, 47(8-9), 1780-1789. doi:10.1016/j.neuropsychologia.2009.02.002

Dye, M. W., Green, C. S., & Bavelier, D. (2009b). Increasing Speed of Processing With Action Video Games. Curr Dir Psychol Sci, 18(6), 321-326. doi:10.1111/j.1467-8721.2009.01660.x

Ellenbogen, J. M., Hu, P. T., Payne, J. D., Titone, D., & Walker, M. P. (2007). Human relational memory requires time and sleep. *Proceedings of the National Academy of Sciences*, *104*(18), 7723-7728.

Ellenbogen, J. M., Hulbert, J. C., Stickgold, R., Dinges, D. F., & Thompson-Schill, S. L. (2006b). Interfering with theories of sleep and memory: sleep, declarative memory, and associative interference. *Current Biology*, *16*(13), 1290-1294.

Ellenbogen, J. M., Payne, J. D., & Stickgold, R. (2006a). The role of sleep in declarative memory consolidation: passive, permissive, active or none?. *Current opinion in neurobiology*, *16*(6), 716-722.

Engel, A. K., Fries, P., & Singer, W. (2001). Dynamic predictions: oscillations and synchrony in top–down processing. *Nature Reviews Neuroscience*, *2*(10), 704-716.

Eriksen, B. A. & Eriksen, C. W. (1974). Effects of noise letters upon the identification of a target letter in nonsearch task. Percept. Psychophys. 16, 143-149

Eschenko, O., Mölle, M., Born, J., & Sara, S. J. (2006). Elevated sleep spindle density after learning or after retrieval in rats. *The Journal of neuroscience*, *26*(50), 12914-12920.

Fahle, M. (2004). Perceptual learning: A case for early selection. *Journal of vision*, *4*(10), 4-4.

Fahle, M., & Poggio, T. (2002). Perceptual learning. MIT Press.

Fahle, M., Edelman, S., & Poggio, T. (1995). Fast perceptual learning in hyperacuity. *Vision research*, *35*(21), 3003-3013.

Fan, J., McCandliss, B. D., Fossella, J., Flombaum, J. I., & Posner, M. I. (2005). The activation of attentional networks. *Neuroimage*, *26*(2), 471-479.

Ficca, G., & Salzarulo, P. (2004). What in sleep is for memory. *Sleep medicine*, *5*(3), 225-230.

Finelli, L. A., Baumann, H., Borbély, A. A., & Achermann, P. (2000). Dual electroencephalogram markers of human sleep homeostasis: correlation between theta activity in waking and slow-wave activity in sleep. *Neuroscience*, *101*(3), 523-529.

Fiorentini, A., & Berardi, N. (1980). Perceptual learning specific for orientation and spatial frequency. Nature.

Fischer, S., & Born, J. (2009). Anticipated reward enhances offline learning during sleep. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *35*(6), 1586.

Fischer, S., Hallschmid, M., Elsner, A. L., & Born, J. (2002). Sleep forms memory for finger skills. *Proceedings of the National Academy of Sciences*, *99*(18), 11987-11991.

Floresco, S. B., West, A. R., Ash, B., Moore, H., & Grace, A. A. (2003). Afferent modulation of dopamine neuron firing differentially regulates tonic and phasic dopamine transmission. *Nature neuroscience*, *6*(9), 968-973.

Fort, P., Bassetti, C. L., & Luppi, P. H. (2009). Alternating vigilance states: new insights regarding neuronal networks and mechanisms. *European Journal of Neuroscience*, *29*(9), 1741-1753.

Frank, M. J., Woroch, B. S., & Curran, T. (2005). Error-related negativity predicts reinforcement learning and conflict biases. *Neuron*, *47*(4), 495-501.

Furmanski, C. S., Schluppeck, D., & Engel, S. A. (2004). Learning strengthens the response of primary visual cortex to simple patterns. *Current Biology*, *14*(7), 573-578.

Gais, S., & Born, J. (2004). Low acetylcholine during slow-wave sleep is critical for declarative memory consolidation. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(7), 2140-2144.

Gais, S., Mölle, M., Helms, K., & Born, J. (2002). Learning-dependent increases in sleep spindle density. *The Journal of Neuroscience*, *22*(15), 6830-6834.

Gais, S., Plihal, W., Wagner, U., & Born, J. (2000). Early sleep triggers memory for early visual discrimination skills. *Nature neuroscience*, *3*(12), 1335-1339.

Gilbert, C. D., & Sigman, M. (2007). Brain states: top-down influences in sensory processing. *Neuron*, *54*(5), 677-696.

Gilbert, C., & Foster, A. (2001). Childhood blindness in the context of VISION 2020: the right to sight. *Bulletin of the World Health Organization*, *79*(3), 227-232.

Gilestro, G. F., Tononi, G., & Cirelli, C. (2009). Widespread changes in synaptic markers as a function of sleep and wakefulness in Drosophila. *Science*, *324*(5923), 109-112.

Giuditta, A., Ambrosini, M. V., Montagnese, P., Mandile, P., Cotugno, M., Zucconi, G. G., & Vescia, S. (1995). The sequential hypothesis of the function of sleep. *Behavioural brain research*, *69*(1), 157-166.

Gonon, F. G. (1988). Nonlinear relationship between impulse flow and dopamine released by rat midbrain dopaminergic neurons as studied by in vivo electrochemistry. *Neuroscience*, *24*(1), 19-28.

Gottfried, J. A., O'Doherty, J., & Dolan, R. J. (2003). Encoding predictive reward value in human amygdala and orbitofrontal cortex. *Science*, *301*(5636), 1104-1107.

Green, C. S., & Bavelier, D. (2003). Action video game modifies visual selective attention. Nature, 423(6939), 534-537. doi:10.1038/nature01647

Green, C. S., & Bavelier, D. (2006). Effect of action video games on the spatial distribution of visuospatial attention. *Journal of experimental psychology: Human perception and performance*, *32*(6), 1465.

Green, C. S., & Bavelier, D. (2007). Action-video-game experience alters the spatial resolution of vision. Psychol Sci, 18(1), 88-94. doi:10.1111/j.1467-9280.2007.01853.x

Green, C. S., & Bavelier, D. (2008). Exercising your brain: a review of human brain plasticity and training-induced learning. *Psychology and aging*, *23*(4), 692.

Green, C. S., Li, R., & Bavelier, D. (2010). Perceptual Learning During Action Video Game Playing. Topics in Cognitive Science, 2(2), 202-216. doi:10.1111/j.1756-8765.2009.01054.x
.

Green, C. S., Pouget, A., & Bavelier, D. (2010). Improved probabilistic inference as a general learning mechanism with action video games. *Current Biology*, *20*(17), 1573-1579.

Gruber, M. J., Ritchey, M., Wang, S. F., Doss, M. K., & Ranganath, C. (2016). Post-learning Hippocampal Dynamics Promote Preferential Retention of Rewarding Events. *Neuron*, *89*(5), 1110-1120.

Guitart-Masip, M., Bunzeck, N., Stephan, K. E., Dolan, R. J., & Düzel, E. (2010). Contextual novelty changes reward representations in the striatum. *The Journal of Neuroscience*, *30*(5), 1721-1726.

Haber, S. N., & Knutson, B. (2010). The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology*, *35*(1), 4-26.

Hallschmid, M., Mölle, M., Fischer, S., & Born, J. (2002). EEG synchronization upon reward in man. *Clinical Neurophysiology*, *113*(7), 1059-1065.

Hasselmo, M. E. (1999). Neuromodulation: acetylcholine and memory consolidation. *Trends in cognitive sciences*, *3*(9), 351-359.

Hauser, T. U., Hunt, L. T., Iannaccone, R., Walitza, S., Brandeis, D., Brem, S., & Dolan, R. J. (2015). Temporally Dissociable Contributions of Human Medial Prefrontal Subregions to Reward-Guided Learning. J Neurosci, 35(32), 11209-11220. doi:10.1523/JNEUROSCI.0560-15.2015

Hébert, S., Béland, R., Dionne-Fournelle, O., Crête, M., & Lupien, S. J. (2005). Physiological stress response to video-game playing: the contribution of built-in music. *Life sciences*, *76*(20), 2371-2380.

Herzog, M. H., & Fahle, M. (1997). The role of feedback in learning a vernier discrimination task. *Vision research*, *37*(15), 2133-2141.

Herzog, M. H., & Fahle, M. (1998). Modeling perceptual learning: Difficulties and how they can be overcome. *Biological cybernetics*, *78*(2), 107-117.

Herzog, M. H., & Fahle, M. (1999). Effects of biased feedback on learning and deciding in a vernier discrimination task. *Vision Research*, *39*(25), 4232-4243.

Higgins, G. A., & Fletcher, P. J. (2003). Serotonin and drug reward: focus on 5-HT 2C receptors. *European journal of pharmacology*, *480*(1), 151-162.

Hikosaka, O., Bromberg-Martin, E., Hong, S., & Matsumoto, M. (2008). New insights on the subcortical representation of reward. *Current opinion in neurobiology*, *18*(2), 203-208.

Hölscher, C., Anwyl, R., & Rowan, M. J. (1997). Stimulation on the positive phase of hippocampal theta rhythm induces long-term potentiation that can be depotentiated by stimulation on the negative phase in area CA1 in vivo. *The Journal of Neuroscience*, *17*(16), 6470-6477.

Hu, Y., Chen, X., Gu, H., & Yang, Y. (2013). Resting-state glutamate and GABA concentrations predict task-induced deactivation in the default mode network. *The Journal of Neuroscience*, *33*(47), 18566-18573.

Huber, R., Ghilardi, M. F., Massimini, M., & Tononi, G. (2004). Local sleep and learning. *Nature*, *430*(6995), 78-81.

Huber, R., Ghilardi, M. F., Massimini, M., Ferrarelli, F., Riedner, B. A., Peterson, M. J., & Tononi, G. (2006). Arm immobilization causes cortical plastic changes and locally decreases sleep slow wave activity. *Nature neuroscience*, *9*(9), 1169-1176.

Huerta, P. T., & Lisman, J. E. (1995). Bidirectional synaptic plasticity induced by a single burst during cholinergic theta oscillation in CA1 in vitro. *Neuron*, *15*(5), 1053-1063.

Igloi, K., Gaggioni, G., Sterpenich, V., & Schwartz, S. (2015). A nap to recap or how reward regulates hippocampal-prefrontal memory networks during daytime sleep in humans. *Elife*, *4*, e07903.

Ikemoto, S. (2007). Dopamine reward circuitry: two projection systems from the ventral midbrain to the nucleus accumbens–olfactory tubercle complex. *Brain research reviews*, *56*(1), 27-78.

Ikemoto, S. (2010). Brain reward circuitry beyond the mesolimbic dopamine system: a neurobiological theory. *Neuroscience & biobehavioral reviews*, *35*(2), 129-150.

Jeter, P. E., Dosher, B. A., Petrov, A., & Lu, Z. L. (2009). Task precision at transfer determines specificity of perceptual learning. *Journal of Vision*, *9*(3), 1-1.

Jocham, G., Hunt, L. T., Near, J., & Behrens, T. E. (2012). A mechanism for value-guided choice based on the excitation-inhibition balance in prefrontal cortex. *Nature neuroscience*, *15*(7), 960-961.

Kami, A., Tanne, D., Rubenstein, B. S., Askenasy, J. J., & Sagi, D. (1994). Dependence on REM sleep of overnight improvement of a perceptual skill. *Science*, *265*(5172), 679-82.

Karni, A., & Bertini, G. (1997). Learning perceptual skills: behavioral probes into adult cortical plasticity. *Current opinion in neurobiology*, *7*(4), 530-535.

Karni, A., & Sagi, D. (1991). Where practice makes perfect in texture discrimination: evidence for primary visual cortex plasticity. *Proceedings of the National Academy of Sciences*, *88*(11), 4966-4970.

Karni, A., Meyer, G., Rey-Hipolito, C., Jezzard, P., Adams, M. M., Turner, R., & Ungerleider, L. G. (1998). The acquisition of skilled motor performance: fast and slow experience-driven changes in primary motor cortex. *Proceedings of the National Academy of Sciences*, *95*(3), 861-868.

Karni, A., Tanne, D., Rubenstein, B. S., Askenasy, J. J., & Sagi, D. (1994). Dependence on REM sleep of overnight improvement of a perceptual skill. *Science*, *265*(5172), 679-682.

Karni, A., Tanne, D., Rubenstein, B. S., Askenasy, J. J., & Sagi, D. (1994). Dependence on REM sleep of overnight improvement of a perceptual skill. Science, 265(5172), 679-682.

Kaufman, E., Lord, M., Reese, T. & Volkman, J. (1949). The discrimination of visual number. Am. J. Psychol. 62, 498-525

Kim, D., Ling, S., & Watanabe, T. (2015). Dual mechanisms governing reward-driven perceptual learning. F1000Res, 4, 764. doi:10.12688/f1000research.6853.1

Klimesch, W. (1999). EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. *Brain research reviews*, *29*(2), 169-195.

Koepp, M. J., Gunn, R. N., Lawrence, A. D., Cunningham, V. J., Dagher, A., Jones, T., ... & Grasby, P. M. (1998). Evidence for striatal dopamine release during a video game. *Nature*, *393*(6682), 266-268.

Korman, M., Doyon, J., Doljansky, J., Carrier, J., Dagan, Y., & Karni, A. (2007). Daytime sleep condenses the time course of motor memory consolidation. *Nature neuroscience*, *10*(9), 1206-1213.

Korman, M., Raz, N., Flash, T., & Karni, A. (2003). Multiple shifts in the representation of a motor sequence during the acquisition of skilled performance. *Proceedings of the National Academy of Sciences*, *100*(21), 12492-12497.

Kornell, N., & Bjork, R. A. (2008). Learning concepts and categories is spacing the "enemy of induction"?. *Psychological science*, *19*(6), 585-592.

Krakauer, J. W., & Shadmehr, R. (2006). Consolidation of motor memory. *Trends in neurosciences*, *29*(1), 58-64.

Krebs, R. M., Heipertz, D., Schuetze, H., & Duzel, E. (2011). Novelty increases the mesolimbic functional connectivity of the substantia nigra/ventral tegmental area (SN/VTA) during reward anticipation: evidence from high-resolution fMRI. *Neuroimage*, *58*(2), 647-655.

Lansink, C. S., Goltstein, P. M., Lankelma, J. V., Joosten, R. N., McNaughton, B. L., & Pennartz, C. M. (2008). Preferential reactivation of motivationally relevant information in the ventral striatum. *The Journal of Neuroscience*, *28*(25), 6372-6382.

Lansink, C. S., Goltstein, P. M., Lankelma, J. V., McNaughton, B. L., & Pennartz, C. M. (2009). Hippocampus leads ventral striatum in replay of place-reward information. *PLoS biology*, *7*(8), e1000173.

Lauwereyns, J., Takikawa, Y., Kawagoe, R., Kobayashi, S., Koizumi, M., Coe, B., ... & Hikosaka, O. (2002). Feature-based anticipation of cues that predict reward in monkey caudate nucleus. *Neuron*, *33*(3), 463-473.

Lavie, N. & Cox, S. (1997). On the efficiency of visual selective attention: efficient visual search leads to inefficient distractor rejection. Psychol. Sci. 8, 395-398

Law, C. T., & Gold, J. I. (2008). Neural correlates of perceptual learning in a sensory-motor, but not a sensory, cortical area. Nature neuroscience, 11(4), 505-513.

Lechner, H. A., Squire, L. R. & Byrne, J. H. (1999). 100 years of consolidation - remembering Müller and Pilzecker. Learn. Mem. 6 , 77-87.

Legault, M., & Wise, R. A. (2001). Novelty-evoked elevations of nucleus accumbens dopamine: dependence on impulse flow from the ventral

subiculum and glutamatergic neurotransmission in the ventral tegmental area. *European Journal of Neuroscience*, *13*(4), 819-828.

Lena, I., Parrot, S., Deschaux, O., Muffat-Joly, S., Sauvinet, V., Renaud, B., ... & Gottesmann, C. (2005). Variations in extracellular levels of dopamine, noradrenaline, glutamate, and aspartate across the sleep–wake cycle in the medial prefrontal cortex and nucleus accumbens of freely moving rats. *Journal of neuroscience research*, *81*(6), 891-899.

Leon, M. I., & Shadlen, M. N. (1999). Effect of expected reward magnitude on the response of neurons in the dorsolateral prefrontal cortex of the macaque. *Neuron*, *24*(2), 415-425.

Li, C. S. R., Padoa-Schioppa, C., & Bizzi, E. (2001). Neuronal correlates of motor performance and motor learning in the primary motor cortex of monkeys adapting to an external force field. *Neuron*, *30*(2), 593-607.

Li, R. W., Ngo, C., Nguyen, J., & Levi, D. M. (2011). Video-game play induces plasticity in the visual system of adults with amblyopia. *PLoS Biol*, *9*(8), e1001135.

Li, R., Polat, U., Makous, W., & Bavelier, D. (2009). Enhancing the contrast sensitivity function through action video game training. Nat Neurosci, 12(5), 549-551. doi:10.1038/nn.2296

Li, S., Cullen, W. K., Anwyl, R., & Rowan, M. J. (2003). Dopamine-dependent facilitation of LTP induction in hippocampal CA1 by exposure to spatial novelty. *Nature neuroscience*, *6*(5), 526-531.

Li, W., Piëch, V., & Gilbert, C. D. (2004). Perceptual learning and top-down influences in primary visual cortex. *Nature neuroscience*, *7*(6), 651-657.

Lidow, M. S., Goldman-Rakic, P. S., Gallager, D. W., & Rakic, P. (1991). Distribution of dopaminergic receptors in the primate cerebral cortex: quantitative autoradiographic analysis using [3 H] raclopride,[3 H] spiperone and [3 H] SCH23390. *Neuroscience*, *40*(3), 657-671.

Linkenhoker, B. A., & Knudsen, E. I. (2002). Incremental training increases the plasticity of the auditory space map in adult barn owls. *Nature*, *419*(6904), 293-296.

Lisman, J. E., & Grace, A. A. (2005). The hippocampal-VTA loop: controlling the entry of information into long-term memory. *Neuron*, *46*(5), 703-713.

Louie, K., & Wilson, M. A. (2001). Temporally structured replay of awake hippocampal ensemble activity during rapid eye movement sleep. *Neuron*, *29*(1), 145-156.

Lu, Z. L., & Dosher, B. A. (2008). Characterizing observers using external noise and observer models: assessing internal representations with external noise. *Psychological review*, *115*(1), 44.

Maquet, P. (2001). The role of sleep in learning and memory. *Science*, *294*(5544), 1048-1052.

Maquet, P., Schwartz, S., Passingham, R., & Frith, C. (2003). Sleep-related consolidation of a visuomotor skill: brain mechanisms as assessed by functional magnetic resonance imaging. *The Journal of Neuroscience*, *23*(4), 1432-1440.

Marco-Pallares, J., Cucurell, D., Cunillera, T., García, R., Andrés-Pueyo, A., Münte, T. F., & Rodríguez-Fornells, A. (2008). Human oscillatory activity associated to reward processing in a gambling task. *Neuropsychologia*, *46*(1), 241-248.

Marshall, L., Helgadóttir, H., Mölle, M., & Born, J. (2006). Boosting slow oscillations during sleep potentiates memory. *Nature*, *444*(7119), 610-613.

Marshall, L., Mölle, M., Hallschmid, M., & Born, J. (2004). Transcranial direct current stimulation during sleep improves declarative memory. *The Journal of neuroscience*, *24*(44), 9985-9992.

McDevitt, E. A., Rokem, A., Silver, M. A., & Mednick, S. C. (2014). Sex differences in sleep-dependent perceptual learning. Vision Res, 99, 172-179. doi:10.1016/j.visres.2013.10.009

McNamara, C. G., Tejero-Cantero, Á., Trouche, S., Campo-Urriza, N., & Dupret, D. (2014). Dopaminergic neurons promote hippocampal reactivation and spatial memory persistence. *Nature neuroscience*.

Mednick, S. C., Nakayama, K., Cantero, J. L., Atienza, M., Levin, A. A., Pathak, N., & Stickgold, R. (2002). The restorative effect of naps on perceptual deterioration. *Nature neuroscience*, *5*(7), 677-681.

Mednick, S., Nakayama, K., & Stickgold, R. (2003). Sleep-dependent learning: a nap is as good as a night. Nat Neurosci, 6(7), 697-698. doi:10.1038/nn1078

Miller, G. (2007). Hunting for meaning after midnight. *Science*, *315*(5817), 1360-1363.

Mitz, A. R. (2005). A liquid-delivery device that provides precise reward control for neurophysiological and behavioral experiments. *Journal of neuroscience methods*, *148*(1), 19-25.

Morin, A., Doyon, J., Dostie, V., Barakat, M., Tahar, A. H., Korman, M., ... & Carrier, J. (2008). Motor sequence learning increases sleep spindles and fast frequencies in post-training sleep. *Sleep*, *31*(8), 1149.

Müller, G. E. & Pilzecker, A. (1900). Experimental contributions to the theory of memory. Z. Psychol. Ergänzungsband 1 , 1-300.

Nieuwenhuis, S., Holroyd, C. B., Mol, N., & Coles, M. G. (2004). Reinforcement-related brain potentials from medial frontal cortex: origins and functional significance. *Neuroscience & Biobehavioral Reviews*, *28*(4), 441-448.

Nishida, M., & Walker, M. P. (2007). Daytime naps, motor memory consolidation and regionally specific sleep spindles. *PLoS One*, *2*(4), e341.

Nishida, M., Pearsall, J., Buckner, R. L., & Walker, M. P. (2009). REM sleep, prefrontal theta, and the consolidation of human emotional memory. *Cerebral Cortex*, *19*(5), 1158-1166.

O'Doherty, J. P., Buchanan, T. W., Seymour, B., & Dolan, R. J. (2006). Predictive neural coding of reward preference involves dissociable responses in human ventral midbrain and ventral striatum. *Neuron*, *49*(1), 157-166.

O'Doherty, J. P., Deichmann, R., Critchley, H. D., & Dolan, R. J. (2002). Neural responses during anticipation of a primary taste reward. *Neuron*, *33*(5), 815-826.

Omelchenko, N., & Sesack, S. R. (2006). Cholinergic axons in the rat ventral tegmental area synapse preferentially onto mesoaccumbens dopamine neurons. *Journal of Comparative Neurology*, *494*(6), 863-875.

Osu, R., Hirai, S., Yoshioka, T. & Kawato, M. (2004). Random presentation enables subjects to adapt to two opposing forces on the hand. Nat. Neurosci. 7 , 111-112.

Pascual-Leone, A. (1999). Transcranial magnetic stimulation: studying the brain--behaviour relationship by induction of 'virtual lesions'. *Philosophical Transactions of the Royal Society of London B: Biological Sciences*, *354*(1387), 1229-1238.

Pavlides, C., Greenstein, Y. J., Grudman, M., & Winson, J. (1988). Long-term potentiation in the dentate gyrus is induced preferentially on the positive phase of θ-rhythm. *Brain research*, *439*(1), 383-387.

Peigneux, P., Laureys, S., Fuchs, S., Destrebecqz, A., Collette, F., Delbeuck, X., ... & Maquet, P. (2003). Learned material content and acquisition level

modulate cerebral reactivation during posttraining rapid-eye-movements sleep. *Neuroimage*, *20*(1), 125-134.

Pelli, D. G. (1997). The VideoToolbox software for visual psychophysics: Transforming numbers into movies. *Spatial vision*, *10*(4), 437-442.

Pennartz, C. M. A., Ito, R., Verschure, P. F. M. J., Battaglia, F. P., & Robbins, T. W. (2011). The hippocampal–striatal axis in learning, prediction and goal-directed behavior. *Trends in neurosciences*, *34*(10), 548-559.

Perogamvros, L., & Schwartz, S. (2012). The roles of the reward system in sleep and dreaming. *Neuroscience & Biobehavioral Reviews*, *36*(8), 1934-1951.

Pessiglione, M., Seymour, B., Flandin, G., Dolan, R. J., & Frith, C. D. (2006). Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. *Nature*, *442*(7106), 1042-1045.

Petersen, S. E., & Posner, M. I. (2012). The attention system of the human brain: 20 years after. *Annual review of neuroscience*, *35*, 73.

Pleger, B., Foerster, A. F., Ragert, P., Dinse, H. R., Schwenkreis, P., Malin, J. P., ... & Tegenthoff, M. (2003). Functional imaging of perceptual learning in human primary and secondary somatosensory cortex. *Neuron*, *40*(3), 643-653.

Plihal, W., & Born, J. (1999). Memory consolidation in human sleep depends on inhibition of glucocorticoid release. *Neuroreport*, *10*(13), 2741-2747.

Poe, G. R., Nitz, D. A., McNaughton, B. L., & Barnes, C. A. (2000). Experience-dependent phase-reversal of hippocampal neuron firing during REM sleep. *Brain research*, *855*(1), 176-180.

Potter, M. C., Chun, M. M., Banks, B. S. & Muckenhoupt, M. (1998). Two attentional deficits in serial target search: the visual attentional blink and an amodal task-switch deficit. J. Exp. Psychol. Human Percept. Perform. 24, 979-992

Proksch, J. & Bavelier, D. (2002). Changes in the spatial distribution of visual attention after early deafness. J. Cogn. Neurosci. 14, 1-5

Przybylski, A. K., Ryan, R. M., & Rigby, C. S. (2009). The motivating role of violence in video games. *Personality and Social Psychology Bulletin*, *35*(2), 243-259.

Rasch, B., Büchel, C., Gais, S., & Born, J. (2007). Odor cues during slow-wave sleep prompt declarative memory consolidation. *Science*, *315*(5817), 1426-1429.

Raymond, J. E., Shapiro, K. L. & Arnell, K. M. (1992). Temporary suppression of visual processing in an RSVP task: an attentional blink? J. Exp. Psychol. Human Percept. Perform. 18, 849-860

Roelfsema, P. R., van Ooyen, A., & Watanabe, T. (2010). Perceptual learning rules based on reinforcers and attention. *Trends in cognitive sciences*, *14*(2), 64-71.

Romei, V., Brodbeck, V., Michel, C., Amedi, A., Pascual-Leone, A., & Thut, G. (2008). Spontaneous fluctuations in posterior α-band EEG activity reflect variability in excitability of human visual areas. *Cerebral cortex*, *18*(9), 2010-2018.

Roth, S. R., Sterman, M. B., & Clemente, C. D. (1967). Comparison of EEG correlates of reinforcement, internal inhibition and sleep. *Electroencephalography and Clinical Neurophysiology*, *23*(6), 509-520.

Sagi, D. (2011). Perceptual learning in Vision Research. Vision Res, 51(13), 1552-1566. doi:10.1016/j.visres.2010.10.019

Sagi, D., & Tanne, D. (1994). Perceptual learning: learning to see. *Current opinion in neurobiology*, *4*(2), 195-199.

Saper, C. B., Scammell, T. E., & Lu, J. (2005). Hypothalamic regulation of sleep and circadian rhythms. *Nature*, *437*(7063), 1257-1263.

Sasaki, Y., Nanez, J. E., & Watanabe, T. (2009). Advances in visual perceptual learning and plasticity. *Nature Reviews Neuroscience*, *11*(1), 53-60.

Sasaki, Y., Nanez, J. E., & Watanabe, T. (2010). Advances in visual perceptual learning and plasticity. Nat Rev Neurosci, 11(1), 53-60. doi:10.1038/nrn2737

Schoups, A. A., Vogels, R., & Orban, G. A. (1995). Human perceptual learning in identifying the oblique orientation: retinotopy, orientation specificity and monocularity. The Journal of physiology, 483(Pt 3), 797.

Schoups, A., Vogels, R., Qian, N., & Orban, G. (2001). Practising orientation identification improves orientation coding in V1 neurons. *Nature*, *412*(6846), 549-553.

Schultz, W. (1998). Predictive reward signal of dopamine neurons. *Journal of neurophysiology*, *80*(1), 1-27.

Schultz, W. (2000). Multiple reward signals in the brain. *Nature reviews neuroscience*, *1*(3), 199-207.

Schultz, W. (2006). Behavioral theories and the neurophysiology of reward. *Annu. Rev. Psychol.*, *57*, 87-115.

Schultz, W., Dayan, P., & Montague, P. R. (1997). A neural substrate of prediction and reward. *Science*, *275*(5306), 1593-1599.

Schultz, W., Tremblay, L., & Hollerman, J. R. (2000). Reward processing in primate orbitofrontal cortex and basal ganglia. *Cerebral Cortex*, *10*(3), 272-283.

Schwartz, S., Maquet, P., & Frith, C. (2002). Neural correlates of perceptual learning: a functional MRI study of visual texture discrimination. *Proceedings of the National Academy of Sciences*, *99*(26), 17137-17142.

Segal, K. R., & Dietz, W. H. (1991). Physiologic responses to playing a video game. *American Journal of Diseases of Children*, *145*(9), 1034-1036.

Seitz, A. R., & Watanabe, T. (2003). Psychophysics: Is subliminal learning really passive?. *Nature*, *422*(6927), 36-36.

Seitz, A. R., Kim, D., & Watanabe, T. (2009). Rewards evoke learning of unconsciously processed visual stimuli in adult humans. Neuron, 61(5), 700-707. doi:10.1016/j.neuron.2009.01.016

Seitz, A. R., Yamagishi, N., Werner, B., Goda, N., Kawato, M., & Watanabe, T. (2005). Task-specific disruption of perceptual learning. *Proceedings of the National Academy of Sciences of the United States of America*, *102*(41), 14895-14900.

Seitz, A., & Watanabe, T. (2005). A unified model for perceptual learning. *Trends in cognitive sciences*, *9*(7), 329-334.

Shadmehr, R. & Brashers-Krug, T. (1997). Functional stages in the formation of human long-term motor memory. J. Neurosci. 17 , 409-419.

Shadmehr, R., & Holcomb, H. H. (1997). Neural correlates of motor memory consolidation. *Science*, *277*(5327), 821-825.

Shi, H. S., Luo, Y. X., Xue, Y. X., Wu, P., Zhu, W. L., Ding, Z. B., & Lu, L. (2011). Effects of sleep deprivation on retrieval and reconsolidation of morphine reward memory in rats. *Pharmacology Biochemistry and Behavior*, *98*(2), 299-303.

Shibata, K., Watanabe, T., Sasaki, Y., & Kawato, M. (2011). Perceptual learning incepted by decoded fMRI neurofeedback without stimulus presentation. *science*, *334*(6061), 1413-1415.

Shipp, S. (2004). The brain circuitry of attention. *Trends in cognitive sciences*, *8*(5), 223-230.

Shiu, L. P., & Pashler, H. (1992). Improvement in line orientation discrimination is retinally local but dependent on cognitive set. *Perception & psychophysics*, *52*(5), 582-588.

Sinton, C. M., Fitch, T. E., & Gershenfeld, H. K. (1999). The effects of leptin on REM sleep and slow wave deltain rats are reversed by food deprivation. Journal of sleep research, 8(3), 197-203.

Sireteanu, R., & Rettenbach, R. (1995). Perceptual learning in visual search: Fast, enduring, but non-specific. *Vision research*, *35*(14), 2037-2043.

Smith, A. T., Singh, K. D., & Greenlee, M. W. (2000). Attentional suppression of activity in the human visual cortex. Neuroreport, 11(2), 271-277.

Snowden, P. T., Davies, I. R., & Roling, P. (2000). Perceptual learning of the detection of features in X-ray images: a functional role for improvements in adults' visual sensitivity?. Journal of Experimental Psychology: Human perception and performance, 26(1), 379.

Spanis, C. W., & Squire, L. R. (1987). Stability of long temporal gradients of retrograde amnesia in mice. Behavioral and neural biology, 48(2), 237-245.

Stagg, C. J., Best, J. G., Stephenson, M. C., O'Shea, J., Wylezinska, M., Kincses, Z. T., ... & Johansen-Berg, H. (2009). Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. *The Journal of neuroscience*, *29*(16), 5202-5206.

Stahl, S. M. (2013). *Stahl's essential psychopharmacology: neuroscientific basis and practical applications*. Cambridge university press.

Sterman, M. B., & Wyrwicka, W. (1967). EEG correlates of sleep: evidence for separate forebrain substrates. *Brain Research*, *6*(1), 143-163.

Stickgold, R. (2005). Sleep-dependent memory consolidation. *Nature*, *437*(7063), 1272-1278.

Stickgold, R., & Walker, M. P. (2005a). Memory consolidation and reconsolidation: what is the role of sleep? Trends Neurosci, 28(8), 408-415. doi:10.1016/j.tins.2005.06.004

Stickgold, R., & Walker, M. P. (2005b). Sleep and memory: the ongoing debate. *Sleep*, *28*(10), 1225-1227.

Stickgold, R., Hobson, J. A., Fosse, R., & Fosse, M. (2001). Sleep, learning, and dreams: off-line memory reprocessing. *Science*, *294*(5544), 1052-1057.

Stickgold, R., James, L., & Hobson, J. A. (2000a). Visual discrimination learning requires sleep after training. *Nature neuroscience*, *3*(12), 1237-1238.

Stickgold, R., Whidbee, D., Schirmer, B., Patel, V., & Hobson, J. A. (2000b). Visual discrimination task improvement: A multi-step process occurring during sleep. *Journal of Cognitive Neuroscience*, *12*(2), 246-254.

Surmeier, D. J., Shen, W., Day, M., Gertler, T., Chan, S., Tian, X., & Plotkin, J. L. (2010). The role of dopamine in modulating the structure and function of striatal circuits. *Progress in brain research*, *183*, 148-167.

Tamaki M, B. A., Watanabe T, Sasaki Y. (2014) Enhanced sigma activity in early visual area during sleep associated with visual perceptual learning. Sleep 2014, Minneapolis.

Tamaki, M., Matsuoka, T., Nittono, H., & Hori, T. (2008). Fast sleep spindle (13–15 Hz) activity correlates with sleep-dependent improvement in visuomotor performance. *Sleep*, *31*(2), 204.

Tamaki, M., Matsuoka, T., Nittono, H., & Hori, T. (2009). Activation of fast sleep spindles at the premotor cortex and parietal areas contributes to motor learning: A study using sLORETA. *Clinical Neurophysiology*, *120*(5), 878-886.

Tan, C. O. (2009). Anticipatory changes in regional cerebral hemodynamics: a new role for dopamine?. *Journal of neurophysiology*, *101*(6), 2738-2740.

Thut, G., Nietzel, A., Brandt, S. A., & Pascual-Leone, A. (2006). α-Band electroencephalographic activity over occipital cortex indexes visuospatial attention bias and predicts visual target detection. *The Journal of neuroscience*, *26*(37), 9494-9502.

Tononi, G. (2004). An information integration theory of consciousness. *BMC neuroscience*, *5*(1), 42.

Tononi, G., & Cirelli, C. (2003). Sleep and synaptic homeostasis: a hypothesis. *Brain research bulletin*, *62*(2), 143-150.

Trick, L. M. & Pylyshyn, Z. W. (1993). What enumeration studies can show us about spatial attention: evidence for limited capacity preattentive processing. J. Exp. Psychol. Human Percept. Perform. 19, 331-351

Tuholski, S. W., Engle, R. W. & Baylis, G. C. (2001). Individual differences in working memory capacity and enumeration. Mem. Cogn. 29, 484-492

Ungerleider, S. K. A. L. G. (2000). Mechanisms of visual attention in the human cortex. *Annual review of neuroscience*, *23*(1), 315-341.

Vaina, L. M., Belliveau, J. W., Des Roziers, E. B., & Zeffiro, T. A. (1998). Neural systems underlying learning and representation of global motion. *Proceedings of the National Academy of Sciences*, *95*(21), 12657-12662.

Vickery, T. J., Chun, M. M., & Lee, D. (2011). Ubiquity and specificity of reinforcement signals throughout the human brain. *Neuron*, *72*(1), 166-177.

Vidal, J. R., Chaumon, M., O'Regan, J. K., & Tallon-Baudry, C. (2006). Visual grouping and the focusing of attention induce gamma-band oscillations at different frequencies in human magnetoencephalogram signals. *Journal of Cognitive Neuroscience*, *18*(11), 1850-1862.

Vlachou, S., & Markou, A. (2010). GABA B receptors in reward processes. *Advances in pharmacology*, *58*, 315-371.

von Stein, A., Chiang, C., & König, P. (2000). Top-down processing mediated by interareal synchronization. *Proceedings of the National Academy of Sciences*, *97*(26), 14748-14753.

Vyazovskiy, V., Borbely, A. A., & Tobler, I. (2000). Fast track: Unilateral vibrissae stimulation during waking induces interhemispheric EEG asymmetry during subsequent sleep in the rat. *Journal of sleep research*, *9*(4), 367-371.

Vygotsky, L. (1978). Interaction between learning and development. *Readings on the development of children*, *23*(3), 34-41.

Walker, M. P. (2009). The role of sleep in cognition and emotion. *Annals of the New York Academy of Sciences*, *1156*(1), 168-197.

Walker, M. P., & Stickgold, R. (2004). Sleep-dependent learning and memory consolidation. *Neuron*, *44*(1), 121-133.

Walker, M. P., & Stickgold, R. (2006). Sleep, memory, and plasticity. *Annu. Rev. Psychol.*, *57*, 139-166.

Walker, M. P., & van Der Helm, E. (2009). Overnight therapy? The role of sleep in emotional brain processing. *Psychological bulletin*, *135*(5), 731.

Walker, M. P., Brakefield, T., Hobson, J. A. & Stickgold, R. (2003) Dissociable stages of human memory consolidation and reconsolidation. Nature 425 , 616-620.

Walker, M. P., Brakefield, T., Morgan, A., Hobson, J. A., & Stickgold, R. (2002). Practice with sleep makes perfect: sleep-dependent motor skill learning. *Neuron*, *35*(1), 205-211.

Watanabe, T., Náñez, J. E., & Sasaki, Y. (2001). Perceptual learning without perception. *Nature*, *413*(6858), 844-848.

Watanabe, T., Náñez, J. E., Koyama, S., Mukai, I., Liederman, J., & Sasaki, Y. (2002). Greater plasticity in lower-level than higher-level visual motion processing in a passive perceptual learning task. *Nature neuroscience*, *5*(10), 1003-1009.

Wiesel, T. N., & Hubel, D. H. (1963). Single-cell responses in striate cortex of kittens deprived of vision in one eye. J Neurophysiol, 26(6), 1003-1017.

Wiesel, T. N., & Hubel, D. H. (1963). Single-cell responses in striate cortex of kittens deprived of vision in one eye. J Neurophysiol, 26(6), 1003-1017.

Willie, J. T., Chemelli, R. M., Sinton, C. M., & Yanagisawa, M. (2001). To eat or to sleep? Orexin in the regulation of feeding and wakefulness. *Annual review of neuroscience*, *24*(1), 429-458.

Yamagishi, N., Callan, D. E., Goda, N., Anderson, S. J., Yoshida, Y., & Kawato, M. (2003). Attentional modulation of oscillatory activity in human visual cortex. *Neuroimage*, *20*(1), 98-113.

Yang, T., & Maunsell, J. H. (2004). The effect of perceptual learning on neuronal responses in monkey visual area V4. *The Journal of Neuroscience*, *24*(7), 1617-1626.

Yantis, S., & Serences, J. T. (2003). Cortical mechanisms of space-based and object-based attentional control. *Current opinion in neurobiology*, *13*(2), 187-193.

Yotsumoto, Y., Chang, L. H., Watanabe, T., & Sasaki, Y. (2009a). Interference and feature specificity in visual perceptual learning. *Vision research*, *49*(21), 2611-2623.

Yotsumoto, Y., Sasaki, Y., Chan, P., Vasios, C. E., Bonmassar, G., Ito, N., ... & Watanabe, T. (2009b). Location-specific cortical activation changes during sleep after training for perceptual learning. *Current Biology*, *19*(15), 1278-1282.

Yotsumoto, Y., Watanabe, T., & Sasaki, Y. (2008). Different dynamics of performance and brain activation in the time course of perceptual learning. *Neuron*, *57*(6), 827-833.

Zhang, L., Doyon, W. M., Clark, J. J., Phillips, P. E., & Dani, J. A. (2009). Controls of tonic and phasic dopamine transmission in the dorsal and ventral striatum. *Molecular pharmacology*, *76*(2), 396-404.