Mechanisms of Temporal Perceptual Learning

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Dissertation

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CHAPTER ONE

Our perceptual system is capable of remarkable change throughout life. Consider for example, the image below. Without prior exposure, this picture might just appear to be random black and white patterns on a page; but once the Dalmatian dog has been spotted (hint: it is sniffing at the ground, facing away from the viewer), it remains intact every time we see this picture:

Such a long-term improvement in perceptual ability for otherwise indistinguishable stimuli is known as *perceptual learning*, a process through which an otherwise anatomically stable system can retain functional plasticity throughout the lifetime. Perceptual learning serves an important demonstration of cognitive flexibility in restructuring learned information, and can be an important tool in understanding how the adult nervous system changes beyond the critical period (Fahle, Poggio, & Kellman, 2002).

Over the last 20 years, an emerging body of research begins to expand the scope of perceptual learning research. As William James wrote, “Like other senses, too, our sense of time is sharpened by practice" (James, 1890). Analogous to the Dalmatian example, our capacity to perceive time can be similarly improved through experience (Bueti & Buonomano, 2014). This type of learning is critical in sustaining long-term changes in temporal behavior (Janzen et al., 2014), and offers a unique window into the neural mechanisms of perceptual learning for non-sensory percepts.

The purpose of this dissertation is to elucidate the functional architecture of temporal perceptual learning (TPL). I will begin by providing an overview of empirical progress and remaining challenges in timing research, as well as predominant models that have guided our understanding in the field. Next, I will discuss how these models account for the improvements associated with perceptual training, followed by a description of more general frameworks borrowed from the visual perceptual learning (VPL) literature. Finally, I conclude with predictions based on this framework, and an outline of studies that would further test my hypothesis. Taken together, this dissertation aims to promote an understanding of perceptual learning as a universal characteristic of the nervous system, unified across multiple different modalities within the brain.

Models of Time Perception

Much like space, time constitutes an omnipresent dimension of life – from the milliseconds-to-seconds scale necessary for perception and action, to the organization of days and years that make up the narrative of our lives. So pervasive and elusive is our sense of time, that it has been deemed the "primordial context" (Gibbon et al., 1997). Although the psychological investigation of time is still in its infancy, the field as a whole has fundamentally shaped our understanding for a myriad of cognitive and sensorimotor behaviors from speech comprehension, to movement planning, to memory processes (Buonomano & Mauk, 2004; Meck, 2005; Paton & Buonomano, 2018).

One of the key features of timing behavior is the *scalar property* (in humans: Allan & Gibbon, 1991; Rakitin et al., 1998; Wearden, 2003; in nonhumans: Gibbon, 1977; Gibbon et al., 1988; Gibbon, Church, & Meck, 1984). The scalar property refers to changes in the timing accuracy and variability as a function of the magnitude of an interval, wherein *mean accuracy* varies linearly and accurately with elapsed time, the *coefficient of variation* remains constant. The latter principle, known as *scalar variance*, is a key demonstration of Weber's Law in time perception (Allan, 1979; Gibbon, 1977), and the foundation for one of the most popular and predominant classes of models in timing research.

Dedicated Timing

In its simplest formulation, dedicated timing models such as the Scalar Expectancy Theory (SET) assumes that judgments about time relies on the output of an internal, dedicated, "clock-like" mechanism, often described as consisting of a pacemaker, working memory, and decision module (Creelman, 1962; Gibbon, 1977; Gibbon, Church, & Meck, 1984; Treisman, 1963, 2013). The SET is an information-processing model of time perception and posits the existence of several distinct components (Figure 1). At the onset of a to-be-timed interval, a gate is switched open, and the pacemaker begins emitting pulses at a consistent rate according to a Poisson distribution. These pulses are gated through an active attention mechanism (Meck, 1983; Zakay & Block, 1996) into a temporary accumulator store. Upon termination of the interval, the switch is closed, and the total number of pulses collected during this time becomes encoded into short-term working memory. If a temporal judgment is required, the number of pulses in working memory is compared with long-term reference memory and if what is encoded in working memory exceeds what is expected from reference memory, one response is emitted; conversely the opposite response is emitted if the number of pulses in working memory is less than what is expected from reference memory.

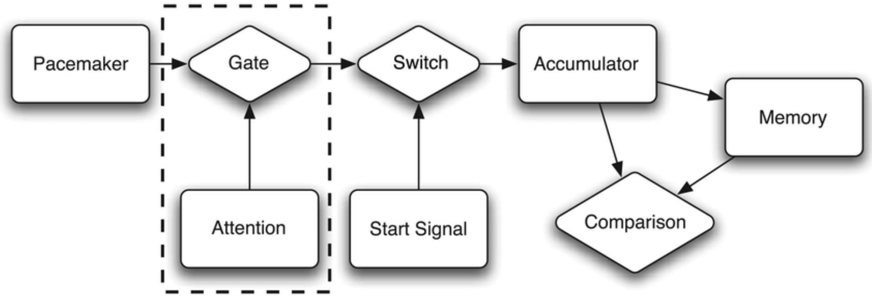

Figure 1. *Components of the internal clock as described by the Scalar Expectancy Theory (Gibbon et al., 1977) with the addition of an attentional gate (Zakay & Block, 1996).*

Throughout history, dedicated timing models have provided a flexible template for interpreting timing behaviors across a wide range of timescales and populations (Allman et al., 2014; Allman & Meck, 2012; Buhusi & Meck, 2005; Droit-Volet, Meck, & Penney, 2007; Lustig & Meck, 2001; Meck, 1996). For instance, research using single-cell recording techniques in nonhuman subjects have found that increases in the rate of the pacemaker component as a result of greater levels of physiological arousal (Angrilli et al., 1997; Droit-Volet & Meck, 2007), signal modality (Droit-Volet, Meck, & Penney, 2007; Goodfellow, 2006; Penney, Gibbon, & Meck, 2000), or pharmacological interventions (Haber & Knutson, 2010; Meck, 1983, 2006) can lead to greater number of pulses in the accumulator by the end of an interval. This in turn results in a subjective overestimation about an interval’s length, as confirmed by research in psychiatric populations (Allman & Meck, 2012; Meck, 2005). Similarly, a faulty attention gate or short-term memory module might alter how many pulses are remembered at the offset of an interval, which in turn contributes to a number distinctive timing deficits in the aging population (Lustig & Meck, 2001, 2011; Xu & Church, 2017). And finally, any inherent or reward-driven biases in the decision module of SET can produce drastic shifts in interval timing behavior and time-based decision making (Gibbon et al., 1988; Kacelnik, Brunner, & Gibbon, 1990; Meck, Doyère, & Gruart, 2012). Taken together, the behavioral outcomes of altering one or many components of the internal clock have been well-confirmed by empirical evidence, making SET one of the most influential and enduring theories in timing research.

Despite its usefulness, dedicated timing theories such as the SET encounter a number of challenges related to the localization of the internal clock within a biological system. A number of serious attempts have been made at isolating components of the SET within cortico-striatal circuits in both humans and nonhuman animals (Bueti & Macaluso, 2011; Coull, Cheng, & Meck, 2011; Meck, Penney, & Pouthas, 2008) which resulted in the proposal of many putative regions for the interval clock, including: the cerebellum (Ivry, 1997; Spencer & Ivry, 2013), basal ganglia (Harrington, Haaland, & Hermanowicz, 1998), supplementary motor area (Halsband et al., 1993; Macar, Vidal, & Casini, 1999), and primary sensory areas (Johnston, Arnold, & Nishida, 2006; Ramnani & Passingham, 2001). Despite their efforts, there is still very little consensus about a possible neurobiological instantiation of such an internal timer (Buhusi & Meck, 2005; Buonomano & Mauk, 2004). Perhaps more importantly, a number of the fundamental assumptions of the SET have been challenged (Staddon & Higa, 1999; Staddon, 2005), which necessitated a number of ad hoc assumptions, including the introduction of additional clocks (Buhusi & Meck, 2009; Ivry & Richardson, 2002). As a result of the increasing complexity brought forth by these additions, dedicated timing models have largely fallen out of favor in support of a more parsimonious view on timing.

Intrinsic Timing

In contrast to dedicated timing models, intrinsic timing models consider temporal judgments to be an inherent property of neuronal computations, and correspondingly encoded within the neural networks across diverse areas of the brain (Bruno & Cicchini, 2016; Buonomano & Laje, 2011; Buonomano & Mauk, 2004; Duran & Sandamirskaya, 2018; Goel & Buonomano, 2014, 2016; Paton & Buonomano, 2018; Rouchitsas & Vatakis, 2014). These networks are hypothesized to be modality-specific (Karmarkar & Buonomano, 2007), or extend across multiple brain areas (Buonomano & Merzenich, 1995; Yin et al., 2016). The important distinction is that judgments about time, according to intrinsic timing models, reflect the output of different patterns of neural activation rather than a centralized clock mechanism common across all modalities.

One of the most notable characterizations of an intrinsic timing process is described by Matell & Meck (2004) in their striatal beat-frequency (SBF) model (Figure 2). According to SBF, time is encoded by the coincidental activation of striatal medium spiny neurons in the dorsal striatum by neural oscillators. At the onset of an interval, different neural ensembles become "reset" through dopaminergic inputs from the ventral tegmental area (Gu, van Rijn, & Meck, 2015). Since neurons naturally oscillate at different base frequencies, the amount of elapsed time becomes encoded in the differential activation of neural populations at the offset of an interval. Analogous to the decision module in SET, when the firing potential of a group of neurons with different periodicities exceed that of individual neurons, a temporal comparison can be made by reading off the pattern of activation at the start and end of an interval. Over time, a strengthening in the striatal spiny neuron synapses with temporally selective oscillators result in "coincidence detectors" for specific durations (Allman, Penney, & Meck, 2016).

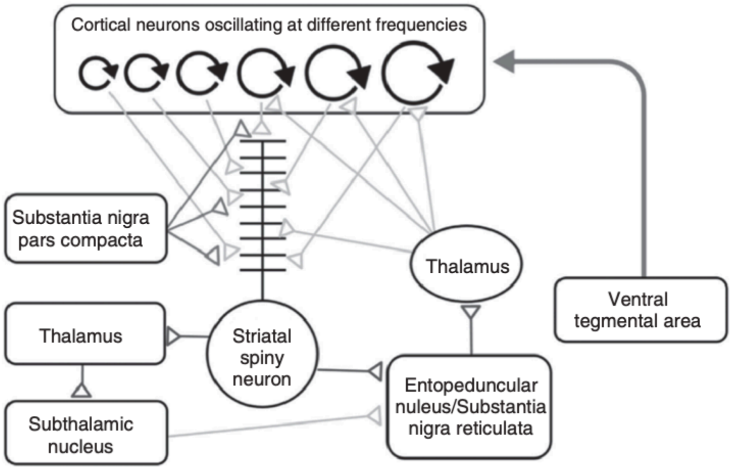

Figure 2. *Depiction of the Striatal Beat Frequency model as described by Matell & Meck (2000, 2004). Figure adapted from Kononowicz, Rijn & Meck (2016).*

One of the major advantages that the SBF have over dedicated timing models such as the SET is the ability to reconcile a number of behavioral observations with corresponding neurobiological mechanisms within the brain (Coull, Cheng, & Meck, 2011; Merchant, Harrington, & Meck, 2013). For example, neurophysiological evidence from single-cell recording of nonhuman primates have demonstrated the existence of duration-selective neuronal responses in the prefrontal cortex. These neurons showed significant adaptation effects in response to visual timing performance which was not observed in the midbrain regions (Mayo & Sommer, 2013). This indicates that activity in the prefrontal cortex can be “read out” to inform the accuracy of temporal judgments as predicted by the SBF model. In addition, Parker et al. (2014) found a temporally selective burst of power in the theta band (4Hz) in the medial frontal cortex in association with the onset of a temporal interval. Following administration of a dopamine receptor antagonist, the increase in theta activity became much weaker and timing precision was also reduced behaviorally. Their results provide a neurophysiological basis for the role of dopamine signaling in resetting a timed interval, as posited by SBF. Lastly, a number of *in vivo* experiments conducted within the last decade using single-cell recording methods in nonhuman animals have also revealed temporal properties in intrinsic computations of local neural networks (Goel & Buonomano, 2014), which further validates the feasibility of SBF in biological systems.

Although intrinsic models are neurally plausible, one of its outstanding challenges is the observation that training-related improvements in time perception are often cross-modal. For instance, a number of temporal learning studies, which will be discussed in more detail in the last section of this chapter, have pointed out that perceptual training using a subsecond auditory interval can improve discrimination performance in an untrained sensory modality (Bratzke, Seifried, & Ulrich, 2012; Grondin & Ulrich, 2011; Nagarajan et al., 1998). These generalization patterns indicate the existence of a centralized or at least partially shared timing mechanism within the brain which allow for the full benefits of training to be shared between a trained and untrained modality. Even taking into account the possibility of an auditory processing advantage in these studies (Kanai et al., 2011; Penney, Gibbon, & Meck, 2000), it remains difficult to reconcile how improvements in a separate neural circuitry can be realized if time is encoded locally within the cells of the sensory cortex.

Interim Summary

Whether our perception of time relies on a centralized, dedicated system or a distributed, intrinsic system remains one of the most important controversies in timing research because its resolution serves to constrain theories about timing as well as the neural structures involved in its perception. The purpose of this section was to introduce the two predominant classes of models in timing research. These models differ in their predictions about how time is encoded and processed by the brain, as well as the neurobiological basis of temporal behavior. Whereas dedicated timing theories posit the existence of a centralized timing mechanism, which can account for a myriad of observable timing (dys)functions, there is currently very little evidence in support of the existence of such a timer within the brain. On the other hand, intrinsic timing models distribute temporal processing across diverse areas of the brain, but suffer when it comes to explanations about cross-modal transfer in temporal learning.

With these considerations, characteristics of temporal learning as well as the extent to which this learning can be generalized to unlearned conditions can offer key insights into the mechanisms of temporal processing in the brain (Ivry & Schlerf, 2008). In the following section, I will review the corpus of literature dedicated to perceptual learning, as well as predominant models that emerge from key empirical findings. While the majority of the works cited are derived from the visual pathway, its relevance to time perception and TPL are discussed in more detail in the last section of this chapter.

Models of Perceptual Learning

Historically, the capacity for improving on our perceptual abilities is thought to be restricted to a critical period during postnatal development. In the seminal work of Wiesel and Hubel, young kittens deprived of all sensory inputs to one of their eyes showed extensive cellular atrophy which led to permanent impairments in visual processing later into adulthood. However, visual behavior was normal when the same monocular deprivation technique was applied following the critical period (Wiesel & Hubel, 1963). Based on their research, it was generally accepted that adequate exposure to visual input during this critical developmental period is necessary for perceptual learning in the brain.

With further research over the last 50 years, we now understand that enhancements in our perceptual abilities can be preserved well into adulthood through a process called perceptual learning (Maniglia & Seitz, 2018; Watanabe & Sasaki, 2015). With extensive training regimes, it is observed that individuals can significantly improve their ability to discriminate orientation (Fiorentini & Berardi, 1980; Ramachandran & Braddick, 1973; Schoups, Vogels, & Orban, 1995), motion direction (Karlene Ball & Sekuler, 1987; Vaina, Sundareswaran, & Harris, 1995), luminance contrast (Fiorentini & Berardi, 1980; Sowden, Rose, & Davies, 2002; Yu, Klein, & Levi, 2004), among many others, with many of these effects persisting over multiple months or even years after training (Ball & Sekuler, 1982; Karni & Sagi, 1993; Sagi & Tanne, 1994).

Despite the rapid accumulation of research, several key questions remain about the mechanisms of perceptual learning. For instance, there is considerable debate over the locus of plasticity, as well as the neural structures involved in learning. Whereas some theories speculate that perceptual learning relies on changes in early visual areas (EVA), including the primary visual cortex (V1), others have reported learning-related enhancements in non-sensory areas of the brain. Relatedly, it is unclear how bottom-up and top-down modulators influence learning, and how changes in neuronal functioning map onto the behavioral effects observed with training. In the following section, I will provide a systematic review of empirical work under three general frameworks, and highlight emergent themes and ongoing controversies in the field.

Early-stage Models

According to early-stage models such as the visual cortical plasticity theory described by Karni & Sagi (1991), plasticity takes place in the local processing of individual neurons of the V1 (Adab & Vogels, 2011; Adini et al., 2004; Alain et al., 2007; Choi & Watanabe, 2012; Dill &

Fahle, 1997; Fahle, 2005; Poggio, Fahle, & Edelman, 1992; Schoups, Vogels, & Orban, 1995; Schwartz, Maquet, & Frith, 2002). This is motivated by the observation that VPL is highly specific to the low-level features of a training stimulus, which resembles the receptive field characteristics of neurons in the V1 (Ahissar & Hochstein, 1997; Fahle & Edelman, 1993; Fiorentini & Berardi, 1980).

One of the classic demonstrations of specificity in VPL comes from a study by Schoups et al. (2001) where monkeys were trained to identify the orientation of a small orientation grating. After an extensive training period, the tuning curves of V1 neurons which selectively coded the trained orientation were significantly steeper than the tuning curves for untrained orientations. This sharpening in neuronal response suggests that perceptual training induced a selective and local change to a trained feature, which is not generalizable to untrained orientations. In humans, VPL is also accompanied by significant increases in the contrast sensitivity (Hua et al., 2010) and BOLD signal response of V1 neurons (Schwartz, Maquet, & Frith, 2002; Walker et al., 2005; Yotsumoto, Watanabe, & Sasaki, 2008) wherein a minute 3° shift in visual angle was effective in ablating VPL completely (Karni & Sagi, 1991). Taken together, these feature- and retinal-specific improvements are consistent with the hypothesis that VPL involves a long-term change in processing efficiency at low-level stages of the information processing hierarchy.

Consistent with early-stage models of VPL, research in TPL also provide support for spatio-temporally local changes in cortical activity. For instance, neuroimaging studies note an increase in the BOLD signal (Bueti et al., 2012) and evoked magnetic field potentials (van Wassenhove & Nagarajan, 2007) of primary sensory areas that corresponded to the sensory modality of a trained interval. These neuronal changes are interpreted as reflecting bottom-up modulation in TPL, wherein plasticity of the sensory area can elicit immediate and profound changes in temporal behavior over time. While it remains unclear from these studies whether these changes in response amplitude is necessarily indicative of plasticity in these areas or simply its involvement during the learning process, it does highlight the possibility that the mechanism of change for TPL, similar to what is proposed for VPL, might involve refinements in local circuitry, or the downstream processing of these circuits on temporal representation.

Limitations of the Early-stage model

One of the major limitations of the early-stage model is the inability to account for the persistence of learning over time. In Yotsumoto et al.'s (2008) study, VPL on a visual discrimination task was dissociable from its associated neural changes when subjects were re-tested following a two-week retention period. Their results suggest that VPL cannot rely solely on plasticity at low-level stages of visual processing since activity of the V1 had returned to pre-training baseline while behavioral performance was maintained over the two-week period. If plasticity was restricted to the V1, we would expect performance to mirror the activation patterns in the EVAs, and not differ significantly from pretest levels.

In addition to Yotsumoto's (2008) findings, single unit recording studies from the primate cortex also reveal enhancements in tuning functions of V1 cells which was not associated with neuronal recruitment or an improvement in visual representation necessary for behavioral change (Schoups et al., 2001). These observations suggest that plasticity within the V1 is insufficient to account for the wide-range of behavioral improvements observed with training, and that VPL must also involve late-stage changes from higher-order cortical areas beyond the V1.

Late-stage Models

In contrast to early-stage models of VPL, late-stage models emphasize training-induced plasticity in cortical connectivity and selective reweighting of decisional processes beyond the V1 (Ahissar & Hochstein, 1993; Chen et al., 2015; Dosher et al., 2013; Dosher & Lu, 2002; Kahnt et al., 2011; Lewis et al., 2009; Liu, Lu, & Dosher, 2010; Petrov, Dosher, & Lu, 2005; Shadlen & Newsome, 2001; Sotiropoulos, Seitz, & Seriès, 2011). Late-stage changes might involve enhancements in external noise reduction mechanisms, thereby increasing signal-to-noise ratio, or improvements in decision and response bias.

In a series of primate studies (Law & Gold, 2008; Law & Gold, 2009), training on a motion discrimination task elicited changes in the lateral intraparietal area – a decision-making unit of the monkey brain (Britten et al., 1996), rather than the middle temporal area, which is the primary sensory unit for representing motion (Maunsell & Van Essen, 1983). These findings suggest that perceptual learning also involve changes in how sensory information is interpreted in forming a behavioral choice, and that low-level learning by itself is insufficient to account for the behavioral improvements observed with practice (Ahissar et al., 2009; Ahissar & Hochstein, 2004; Hochstein & Ahissar, 2002).

In one influential model of perceptual learning derived from the Reverse Hierarchy Theory (RHT), perception is achieved through a top-down process whereby information at the highest level of the visual processing hierarchy is engaged first, followed by lower-level enhancements in basic stimulus features (Ahissar & Hochstein, 1993, 1997; Fahle, Poggio, & Kellman, 2002). RHT proposes that explicit perception beings at higher-order cortices such as the V5 or MT, then proceeds in a downward fashion to engage lower areas via feedback connections (Hochstein & Ahissar, 2002). For example, in a standard “pop-out” feature search paradigm, higher-order cortical activity is necessary to obtain an initial and rapid gist of the visual scene, which begins with large, spread-attention receptive fields of high-level vision. Following this first approximation about the visual feature, the low-level representation systems are activated to confirm and veridically-bind the visual features. Therefore, late-stage models assumes VPL to involve top-down modulating factors which engage higher-order cognitive functions such as attention (Baldassarre et al., 2012) and decision-weighting (Dosher & Lu, 2010) on sensory representation.

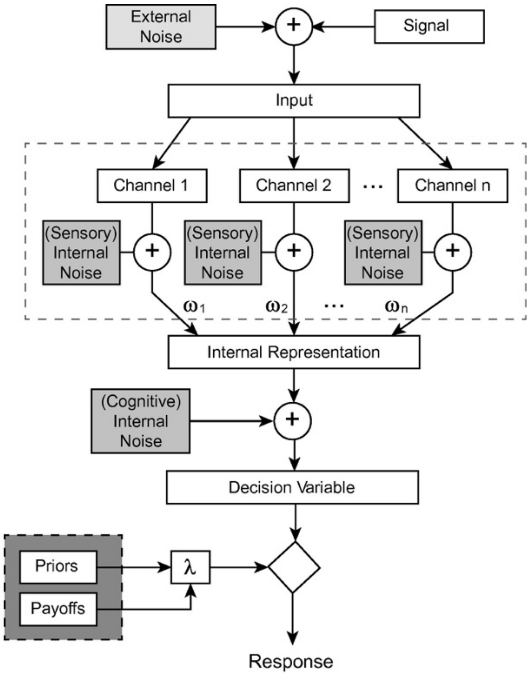

Figure 3. Schematic representation of a perceptual decision model by Amitay et al. (2014). Perceptual learning reflects the reduction in sources of internal (sensory) and external (cognitive) noise.

Another perspective of late-stage models is an improvement in the readout of V1 signals through response reweighting or receptor arrangement along a centralized circuity (Dosher & Lu, 2010; Petrov, Dosher, & Lu, 2005; Poggio, Fahle, & Edelman, 1992). In this view, reweighting of higher-level location-independent representations are operating in parallel with improvements in lower-level location-dependent representations. Predictions of learning specificity and transfer therefore relies on the learned reweighting of location-independent representations (Dosher et al., 2013). In contrast to low-stage models, the locus of learning in late-stage models is proposed to reside in higher-order cognitive/decision areas of the brain, beyond the V1.

Limitations of the Late-stage model

One of the challenges to late-stage models is the inability to account for low-level changes in neuronal response which can take effect after only a few trials or a single exposure to a high-intensity stimulus (Beste & Dinse, 2013). This type of rapid learning cannot be attributable to changes in higher-order cortical areas because there is insufficient time to establish any task-based learning relative to the behavioral improvements observed immediately following training.

In addition, the discovery of task-irrelevant VPL suggests that VPL can take place without conscious perceived effort, which cannot be explained if late-stage mechanisms are the primary driving force behind learning. While it is intuitive that conscious perception of a stimulus would be necessary to elicit VPL, many studies have found that the mere exposure to a subthreshold motion stimulus can induce learning of the motion direction with a supra-threshold coherence (Watanabe, Nã̃ez, & Sasaki, 2001).

The precise mechanisms underlying task-relevant and -irrelevant VPL is an ongoing investigation. One major difference is that task relevant VPL only occurs for supra-threshold stimuli, indicating the involvement of cognitive control mechanisms and sustained attention. On the other hand, task irrelevant VPL can take place for sub-threshold stimuli that bypasses the attentional filter. This hypothesis suggests that attention plays an opposite role in learning wherein increased attention during a task serves to *enhance* task-relevant stimuli while *suppressing* task-irrelevant learning (Watanabe & Sasaki, 2015). In many cases where a stimulus is not suppressed effectively, task-irrelevant learning is reported (Leclercq & Seitz, 2012; Seitz & Watanabe, 2003; Seitz & Watanabe, 2005; Tsushima et al., 2008; Zhang & Kourtzi, 2010). Taken together, these studies suggest that perceptual learning can take place without conscious awareness for a visual feature, which would be necessitated by late-stage learning models.

Hybrid Models

To reconcile the opposing views of early-stage and late-stage models, a number of recent "hybrid" models have been described which predicts the involvement of multiple stages of learning (Chen et al., 2015; Dosher et al., 2013; Harris et al., 2012; Shibata et al., 2014; Watanabe & Sasaki, 2015). In this view, VPL relies on changes in both sensory and cortical stages of perceptual processing, and that successful VPL involves optimizing the interactions between low-level (stimulus-driven) and high-level (task-driven) mechanisms within the brain. Whereas lower-level mechanisms might be primarily engaged during the encoding stage of learning, higher-level mechanisms is necessary to support the retention of learning after initial improvements on a visual task is plateaued (Shibata et al., 2016; Yotsumoto, Watanabe, & Sasaki, 2008).

Several lines of evidence support this view. In a recent fMRI study by Shibata et al. (2016), participants were trained on a motion detection task while BOLD activity was obtained during the pretest and posttest sessions using fMRI. During each test session, participants either performed the trained motion detection task (active-test), or passively view a motion display (passive-test). Their results revealed a significant increase in V3A in response to the trained motion direction irrespective of task (active or passive). In contrast, activity in the V1 and IPS showed significant changes only in association with the trained active task in combination with the trained direction (Shibata et al., 2016). These results suggest that V1 and IPS may underlie task-dependent, high-level learning, whereas the V3A may be involved in the learning of a specific visual feature only. In addition, the degree of neural selectivity observed in these cortical areas also persists over time, paralleling the behavioral improvement associated with VPL (Chen et al., 2015).

Consistent with the results of Shibata et al. (2016), a recent neuroimaging study by Bueti et al. (2012) illustrate a similar neurophysiological dissociation in TPL. Participants were trained using a visual interval over five days. In comparing the performance before and after training, greater activation was observed bilaterally in the V1 for the trained visual interval, and in A1 for the auditory generalization test. However, in both types of tests, the researchers noted greater activation in the left posterior insular and the IPC. Since activation of the insular was amodal, one interpretation of their results is that the insular may be responsible for encoding stimulus-specific information (i.e., the trained interval) while the IPC was more active for the auditory test, suggesting its role in the intermodal transfer of TPL. More broadly, this suggests that the IPC may be viewed as a proxy for late-stage change while the primary sensory areas (A1 and V1) represent early-stage changes, analogous to what is predicted by hybrid models in VPL.

Interim Summary

The field of perceptual learning has undergone remarkable growth in the last 50 years. Understanding the mechanisms of perceptual learning not only informs us about experience-induced changes in sensory processing, but also how the adult brain maintains plasticity long after the critical period. The purpose of this chapter was to highlight emergent themes and models in VPL including specificity and generalization of learning and the involvement of sensory-stage and cognitive-stage brain areas. A two-stage model provides a comprehensive framework for divergent findings among these themes. In the following section, I will integrate the models of time perception and perceptual learning, and outline ways in which the emerging field of TPL can both inform and be informed by our understanding of plasticity in the perceptual system.

Temporal Perceptual Learning

Similar to other forms of perceptual and motor learning, the capacity for timing can be improved with practice (Bueti et al., 2012; Buonomano, Bramen, & Khodadadifar, 2009; Karmarkar & Buonomano, 2003; Meegan, Aslin, & Jacobs, 2000; Nagarajan et al., 1998; Rouchitsas & Vatakis, 2014; van Wassenhove & Nagarajan, 2007; Westheimer, 1999a; Wright et al., 1997; Wright, Wilson, & Sabin, 2010). Even though the study of TPL is very much in its infancy, it is becoming an increasingly important tool in understanding the mechanisms of perceptual learning. To date, there exists a growing foundation of research examining the neural changes that take place with TPL.

In a standard TPL experiment, two intervals are presented in either the auditory or visual modality (Figure 3). On each trial, participants must indicate which of the two intervals was longer using a response key on the keyboard. One of the two intervals – the "standard" – is always the same length on every trial (e.g., 100ms). The other interval – the "comparison" – varies adaptively depending on the participant's performance. This is typically achieved using an adaptive 3:1 staircase procedure. Using such a design, discrimination ability typically improves with training, as revealed through a performance change between the first day of training (pretest) and last day (posttest).

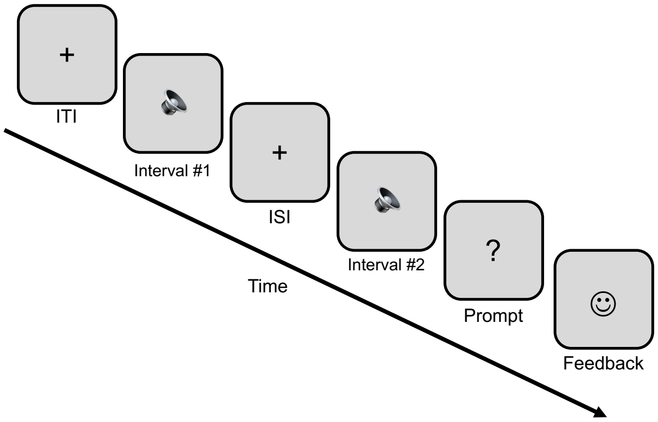

Figure 4. *A two-interval temporal discrimination procedure with feedback. Each trial begins with an intertrial interval (ITI) followed by the first interval. After an interstimulus interval (ISI) around 1000ms, a second interval is presented. Participants must indicate which of the two intervals was shorter.*

In one of the earliest demonstrations of TPL, participants were trained using an auditory temporal discrimination task over ten days. During pretest and posttest sessions, discrimination thresholds were obtained at five different interval conditions: 50ms, 100ms, 200ms, 300ms at 1kHz and 100ms at 4kHz. During training, all participants only practiced the 100ms at 1kHz condition. Following practice, Wright et al. noted a significant improvement in discrimination performance for the trained interval (100ms) at both the trained (1kHz) and untrained (4 kHz) frequencies (Figure 4). In contrast, no improvements were observed in the conditions with either a shorter or longer interval than the trained condition (Wright et al., 1997).

The results of Wright et al.'s (1997) study, confirmed later by numerous replication studies, highlight two hallmark characteristics of TPL. The first is *interval specificity*, which refers to the specificity of learning to a trained interval, and correspondingly the lack of generalization towards untrained intervals differing by as little as 50ms from the trained interval condition (Lapid, Ulrich, & Rammsayer, 2009a). The second feature of TPL is that improvements in temporal discrimination can transfer across different stimulus dimensions and sensory modalities which differ from the trained condition. For instance, training using a somatosensory stimulus on the left hand of an individual can produce a significant improvement on the opposite (untrained) hand if the interval length is identical (Nagarajan et al., 1998). And similarly, training in one modality (e.g., vision) have been shown to improve performance in an untrained modality (Bratzke, Seifried, & Ulrich, 2012; Bueti et al., 2012; Grondin & Ulrich, 2011; Nagarajan et al., 1998), as well from empty to filled intervals (Karmarkar & Buonomano, 2003), and from sensory to motor tasks (Meegan, Aslin, & Jacobs, 2000). However, it should be noted that the generalization patterns between visual and auditory modalities is not always bidirectional.

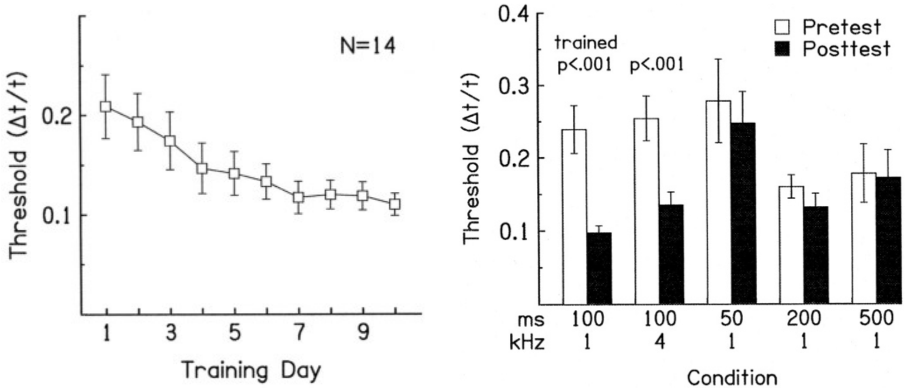

Figure 5. *Experimental results of Wright et al. (1997). (a) Average reduction in discrimination threshold for the trained interval at the trained frequency across training days and (b) generalization patterns for all conditions tested. Significant learning effects were observed for the trained duration at both the trained and untrained interval pitch.*

Conditions of learning specificity and generalization reveal an interesting narrative about what is being changed in the process of temporal learning. On the one hand, interval specificity indicates a selective enhancement in our internal representations of the trained interval. This is likely achieved through duration-tuning mechanisms in the brain rather than an overall improvement in timing ability. Preliminary support for this comes from a series of imaging studies by Hayashi and colleagues (Hayashi et al., 2013, 2015, 2018; Protopapa et al., 2018) demonstrating interval-specific reductions in neural activity following exposure to a temporal stimulus. Based on their results, Hayashi et al. proposed the existence of a general time-keeping mechanism in the parietal lobe which selectively responds to a trained duration across a wide range of interval values. More generally, the finding of interval specificity in TPL is consistent with an intrinsic timing hypothesis because an improvement in the internal clock or centralized timer would lead to a systematic improvement across all intervals tested (i.e., a "sharpening" of the internal clock).

On the other hand, learning generalization to nontemporal dimensions of a trained task suggests that TPL may be *insensitive* to certain sensory-level characteristics. For instance, learning might involve an enhancement in the neural circuitry that is tuned to the temporal aspects of a stimulus, but not the input modality in which the stimulus is encoded. In contrast to the condition of interval specificity, generalizability of learning suggests that TPL may involve improvements in a centralized and modular timing mechanism, whereby training enhances the encoding and response to a trained interval, regardless of input modality or task.

In order to reconcile these conflicting perspectives, one possibility is that different mechanisms might be involved in the learning and generalization of temporal intervals. This dissociation would suggest that qualities of specificity and generalization can occur in parallel, without the need for overlapping resources. In one such investigation, Wright et al. (2010) compared the time-course of specificity and generalization in TPL using an auditory discrimination task. Participants were trained for either two, four, or ten days. Following training, all of the participants showed an improvement in temporal discrimination for the trained interval. However, only participants in the four- and ten-day groups showed improvements for the untrained pitch, suggesting a partial dissociation between the mechanisms underlying learning specificity and generalization with an "early" emergence of specificity for the trained interval, followed by a "late" transfer of learning to an untrained condition (Wright, Wilson, & Sabin, 2010).

Corroborating with Wright et al.'s (2010) suggestion of a dissociation between the mechanisms of specificity and generalization, two recent neurophysiological studies reveal the involvement of different brain areas during different stages of learning. In the first study, sustained activation of the basal ganglia and IPC accompanied early stages of learning in a temporal discrimination task while the right dorsolateral prefrontal cortex was activated later, suggesting its general involvement in decision-making and temporal comparison functions (Rao, Mayer, & Harrington, 2001). These findings highlight a potential difference in the time-course of activation for various brain areas that accompany the different stages of temporal processing at a behavioral level. In the second study, participants were trained on a 200ms visual interval, while generalization conditions were assessed in the auditory modality using both the trained (200ms) and untrained (100ms and 400ms) interval conditions. Following training, Bueti et al. (2012) observed an increase in the hemodynamic response of EVAs in response to the trained interval, in contrast, generalization within the untrained modality was associated with activity of the left inferior parietal cortex (IPC). This dissociation suggests that learning-related changes in BOLD activity can be distinct from the neural circuitry underlying its generalization, and that structural and functional changes are likely taking place at both modality-specific and modality-independent areas of the brain in support of TPL.

Remaining Challenges

Despite the growing interest in TPL, a number of fundamental questions remain about the neurophysiological mechanisms supporting this learning. These questions stem in a large part, due to the lack of understanding for: (1) the *locus of plasticity* in the temporal processing hierarchy which supports the observed behavioral improvements in temporal discrimination, and (b) the interaction between sensory and non-sensory cortical areas during learning.

Based on the corpus of literature reviewed thus far, it can be noted that VPL and TPL share a number of crucial similarities in both behavior and neural mechanism. These similarities suggest that the same theoretical models from VPL can be applied to our understanding of TPL, which additionally promotes the development of a unifying model of perceptual learning across both fields. In the following section, we apply the two-stage model of perceptual learning to TPL, and outline specific predictions based on this framework, as well as a summary of studies that would test these hypotheses.

Question Statement & Rationale

The main question addressed in this dissertation is whether changes in low-level processes alone are sufficient for improving temporal discrimination performance. The term “low-level” refers to stimulus-specific or featural-level processes that likely relies on the sensory stage of information processing. This is contrasted with “high-level” mechanisms which refer to learning of task-specific and often rule-based strategies which involve higher-order or cognitive cortices of the brain. Similar to the dual-stage model proposed by Watanabe & Sasaki (2015), we predict that TPL can be appropriately described through a two-stage process, involving both sensory and non-sensory changes. Whereas TPL is traditionally thought to only involve changes in temporal representation, we propose that high-level processes must also be involved in improving time. Consistent with this framework, three hypotheses are tested.

The first hypothesis is that TPL enhances the featural representation of a temporal stimulus, and is encoded locally in the sensory cortices of the brain. Similar to a sharpening in the tuning curves of V1 neurons in VPL, this hypothesis posits a sharpening in temporal resolution for a trained interval during low-level stages of temporal processing, relying on neuroplastic changes in the sensory areas only. This is referred to as the low-level hypothesis.

Evidence in support of the low-level hypothesis is the consistent observation of learning specificity to a trained temporal interval, with no generalization to untrained intervals (Bueti et al., 2012; Hayashi et al., 2018; Karmarkar & Buonomano, 2003; Nagarajan et al., 1998; van Wassenhove & Nagarajan, 2007; Wright, Wilson, & Sabin, 2010). Evidence of interval-specificity suggests that the mechanisms underlying TPL is temporally-specific (Bueti, Bahrami, & Walsh, 2008; Hayashi et al., 2015; Protopapa et al., 2018), possibly relying on duration-selective tuning mechanisms in the brain (Ivry & Richardson, 2002; Matell & Meck, 2004).

The second hypothesis is that TPL changes the set of response strategies associated with the temporal task, and likely engages non-sensory areas of the brain. According to this hypothesis, TPL does not necessarily involve enhancements in temporal perception *per se*, but rather improvements in our ability to respond in a given task. Accordingly, these mechanisms would engage non-sensory areas of the brain, and lead to task-specific improvements in temporal discrimination, similar to what is proposed in late-stage models of VPL. This is referred to as the high-level hypothesis.

In contrast to the low-level hypothesis, the high-level hypothesis posits that improvements in temporal discrimination reflects changes in the way we respond to a temporal stimulus within a given task. Learning is therefore the result of an optimization of decision processes specific to a trained task and therefore, learning specificity does not necessarily reflect any changes in the representation of the stimulus itself. This possibility has been extensively discussed in VPL (Maniglia & Seitz, 2018) but could be applied to TPL as well (Meegan, Aslin, & Jacobs, 2000; Nagarajan et al., 1998; Wright, Wilson, & Sabin, 2010).

Preliminary support for the high-level hypothesis in TPL comes from a growing number of studies that have collectively demonstrated the involvement of the parietal cortex in a number of different temporal tasks (Hayashi et al., 2013, 2015, 2018). In one such study, Hayashi et al.

(2015) reported duration-selective reductions in neural activation of the IPC when a temporal interval is repeated presented to the participant. This reduction in neuronal activity occurred regardless of task-relevancy for the adapted duration and generalized across a broad range of trained durations, which indicates the existence of a modality-independent representational system for temporal information. Moreover, the frontoparietal network, and in particular the IPC, contains duration-tuning mechanisms necessary for the kind of temporal selectivity often observed in temporal learning (Hayashi et al., 2015, 2018; Karmarkar & Buonomano, 2003; Meegan, Aslin, & Jacobs, 2000; Nagarajan et al., 1998; Wright et al., 1997; Wright, Wilson, & Sabin, 2010).

Finally, we consider the possibility that neuroplastic changes can occur between sensory and non-sensory areas of the brain and these changes directly relate to the behavioral effects of TPL over time. These three hypotheses, and their associated predictions, are summarized below:

Question: what is the locus of change in TPL?				
	Stage of information processing	**Possible brain areas involved**	**What is improved?**	**Predictions**
H1	early-stage	only sensory (e.g., V1, A1)	representation of temporal interval	Learning is interval specific, task independent, generalization to unlearned conditions if the feature (temporal interval) is identical
H2	late-stage	only nonsensory/higher areas (e.g., IPC)	task-processing strategies	Learning is interval specific, task dependent, generalization to unlearned conditions only if task parameters and processing strategies are identical
H3	both	interaction between sensory and nonsensory areas	A combination of task-related and interval-specific improvements, possibly in weighting structures and interactions between low-level and high-level processes	Learning is interval specific, task dependent, generalization to unlearned conditions only if optimal weighting structures are identical

In our first study, we provide behavioral evidence in support of high-level learning using psychophysics. We found that: (1) learning is sensitive to statistical regularities in the training stimulus and (2) learning is specific to the response strategies used in a given task. The predictions of these studies are inconsistent with a low-level hypothesis. Next, we explored the locus of this change using proton magnetic resonance spectroscopy, ^{1}H-MRS (Stagg et al., 2009) in a sensory-related and cognitive brain area. We found that: (1) TPL was associated with metabolic changes in the IPC (a higher-order decision area) and not the A1 (a lower-order sensory area) and (2) this change was especially prominent during initial stages of learning, and returned to baseline after a few sessions of training. Taken together, these results support the involvement of late-stage processes beyond what is predicted by the low-level hypothesis; demonstrating the inability for early-stage models to fully account for all aspects of temporal learning behavior.

In summary, the current dissertation work investigates the locus of plasticity in TPL using a combination of psychophysics and neuroimaging techniques. If sustained, this research will be the first step in understanding the neurochemical processes involved in TPL, establishing a critical link between perceptual learning in the visual and temporal domains. In extension, our work continues to recognize time perception not as a unitary phenomenon distinct from our other senses, but a universal characteristic of the sensory system.

CHAPTER TWO

Our ability to estimate and remember the passage of time plays an important role in our daily activities and as such, having an accurate model of time perception is essential to understanding the mechanisms across a wide range of temporal and nontemporal behaviors. One of the central questions underlying these improvements concern the locus of this learning: what is being changed when we learn to time? On the one hand, TPL might reflect a refinement in the sensory representations of a trained interval (low-level hypothesis), on the other hand, TPL might involve changes in task-specific behavior which in turn lead to better performance on a trained task (high-level hypothesis). We refer to this dichotomy between low-level (i.e., learning to sense) and high-level hypotheses (i.e., learning to respond) as the "locus of learning" problem, and we aim to address this question in the present set of experiments by investigating the effects of stimulus and task structure on TPL.

Evidence of low-level changes in temporal processing following perceptual training is the observation that performance improvements are often bound to the trained interval and does not generalize to other untrained intervals (i.e., interval-specificity). In an early study by Wright and colleagues (1997), discrimination training with a 100ms auditory interval was found to significantly improve performance post-training, but the same amount of practice did not improve performance in any neighboring (e.g., 50ms, 200ms, 500ms) conditions. Interval-specificity suggests that the mechanisms underlying learning is largely temporally specific, which hints at the existence of duration-selective tuning mechanisms in the brain (Bueti, Bahrami, & Walsh, 2008; Hayashi et al., 2015; Protopapa et al., 2018). Interval-specificity is an important characteristic of TPL and has been widely reported across the literature (Bueti et al., 2012; Hayashi et al., 2018; Nagarajan et al., 1998; van Wassenhove & Nagarajan, 2007; Wright, Wilson, & Sabin, 2010) with a few exceptions (Lapid, Ulrich, & Rammsayer, 2009b).

In contrast to the low-level hypothesis, learning can be driven alternatively by changes in the way we respond to a perceptual stimulus, optimizing the high-level decision processes specific to a trained task. In this view, the observation of learning specificity to a trained stimulus does not necessarily reflect any change in the representation of the stimulus itself (Maniglia & Seitz, 2018), suggesting that low-level learning by itself is insufficient to account for the behavioral improvements observed with practice. In a series of primate studies (Law & Gold, 2008; Law & Gold, 2009), perceptual training of a visual motion discrimination task led to changes in the lateral intraparietal area – a decision-making unit, rather than the middle temporal area, which is the primary sensory unit for representing motion. What these findings reveal about the mechanism of perceptual learning is that the brain must also adjust for the optimal stimulus-response weights given the relevant task structure (Ahissar et al., 2009; Ahissar & Hochstein, 2004; Hochstein & Ahissar, 2002) and therefore, learning must involve changes in how sensory information is interpreted to form a behavioral choice.

The purpose of the present study is to provide evidence in support of high-level changes in temporal processing by systematically assessing the roles of stimulus and task structure on TPL. First, we asked whether learning on one timing task is transferrable to an untrained task when the intervals used between the tasks are identical. We hypothesized that if learning occurs at the level of interval representation (low-level), improvements on the trained interval should transfer to an unlearned task so long as the refined interval representation is preserved. On the other hand, if TPL relies on learning of appropriate response strategies (high-level), then we would not expect any generalization for the untrained task since the two tasks do not share a common set of structures and decision rules.

Secondly, we seek to investigate the effect of stimulus uncertainty on TPL. A recent finding on the learning of visual features (i.e., visual perceptual learning; VPL) revealed that improvements in visual discrimination relied on fixed stimulus structure during training (Adini et al., 2004; Kuai et al., 2005; Yu, Klein, & Levi, 2004). In one such study, participants were asked to determine which stimulus pair had the highest contrast. Improvements on the contrast discrimination task was only found for the group which received practice on seven fixed base contrasts but not when they practiced the same contrast pairs in a mixed-by-trial (i.e., differing from trial-to-trial) manner. What this suggests is that the degree of stimulus uncertainty or the ability to discern statistical regularities in training input may influence the type of decision strategy that is adopted by the viewer (Adini et al., 2004). Therefore, if TPL shares similar mechanisms of learning as VPL, we would also expect roving effects to occur when we use fixed vs. random temporal stimuli during training. We predict that stochasticity (that is, higher uncertainty in a prior distribution) would impair TPL if the high-level hypothesis is true, since learning is affected by the decision strategy and sensitivity thresholds within the given task. However, if a low-level hypothesis is true, then TPL should not be affected by roving effects (or changes in stimulus structure) since learning is taking place at the sensory level for the interval.

In summary, the locus of learning problem of TPL addresses the question whether practicing any temporal task primarily improves the representation of an interval (low-level hypothesis), or task-based processing strategies (high-level hypothesis). The present study addresses this dichotomy by investigating effects of stimulus and task structure on temporal learning. If improvements in temporal discrimination can transfer to an unlearned task and this learning is not influenced by varying the distribution of a target stimulus, this will suggest that TPL is not influenced by high-level factors such as task processing and/or memory of a stimulus distribution and therefore will be in accordance with the hypothesis that learning occurs at the level of interval representation (low-level hypothesis). If, on the other hand, transfer of learning is observed for the untrained task and this learning is influenced by knowledge about the distribution of a target stimulus, this will support the hypothesis that TPL involves changes in high-level, task-based processes since the two tasks do not share a common set of structures and decision rules.

Results from our experiments provide evidence in support of high-level changes in temporal discrimination performance, whereby behavioral improvements were dependent on fixed stimulus structure during training and did not generalize under a new set of task structures. Both findings are consistent with current models of perceptual learning and provide grounds for constructing a unifying framework of perceptual learning across modalities.

Methods

Participants. Twenty-nine right-handed adults (16 females; mean age: 23.8 ± 3.9 years) with normal or corrected-to-normal vision and hearing were recruited for participation in our experiment. We justified our sample size using the G*Power software (Faul et al., 2007) with a medium effect size of .40 and a power estimate of .80. A total of 24 subjects were determined to be necessary for significance in a mixed-model ANOVA with this analysis (2 groups, $F_{critical}$ = 1.05, non-centrality parameter = 184.32). Two participants were unable to complete the experiment due to scheduling conflicts, and four more outliers (see *Results*) were excluded from analysis due to abnormally high thresholds during training (>2.5SD from the group mean). For the control experiment, nine new participants were recruited from the same subject population (8 females; mean age: 22.4 ± 2.9 years). Each session was held at the same time each day to avoid possible confounding effects of time of day on temporal processing (Lustig & Meck, 2001). Informed consent was obtained in writing from each subject prior to commencing the study and approved by the institutional review board (IRB) at Brown University.

Stimulus and Apparatus. Participants were seated in a sound-insulated room with dim lighting. All stimuli were generated and presented using MATLAB with Psychophysics Toolbox extensions, version 3.0.14 (Kleiner et al., 2007) and presented on a ViewSonic – VA2226w monitor, measuring 20 x 14 inches, with a refresh rate of 75Hz and a viewing distance of approximately 38cm. Auditory stimuli were presented at 86 dB SPL through noise-cancelling Sennheisser headphones and included a 5ms on and off ramp. All responses were collected using a standard US keyboard.

Procedure. We used a standard pretest-training-posttest design over seven consecutive days (Figure 4a). During the training phase (Days 2 to 6), each participant completed 2400 trials of a single-interval temporal discrimination task. We justified the number of practice trials under the guidance of previous studies which have demonstrated substantial learning effects using ~2500 trials (Meegan et al., 2000; Van Wassenhove & Nagarajan, 2007; Bratzke et al., 2012), and with as little as a single day of training with 900 trials (Westheimer, 1999). At the beginning of each session, participants were presented with a 200ms tone at 1kHz and instructed to categorize subsequent intervals as being either "longer" or "shorter" than the reference. In the training phase, response feedback was provided immediately after every response by the participant. For the RI group, comparison intervals were drawn from a gaussian distribution with a mean of 200ms and minimum and maximum bounds of 158ms and 242ms, respectively. In the FI group, 1 out of 8 predetermined interval values (158, 170, 182, 194, 206, 218, 230, 242ms) were selected at random, with equal probability. Similar to the RI group, the mean and range of these intervals were 200ms and 158ms to 242ms, respectively.

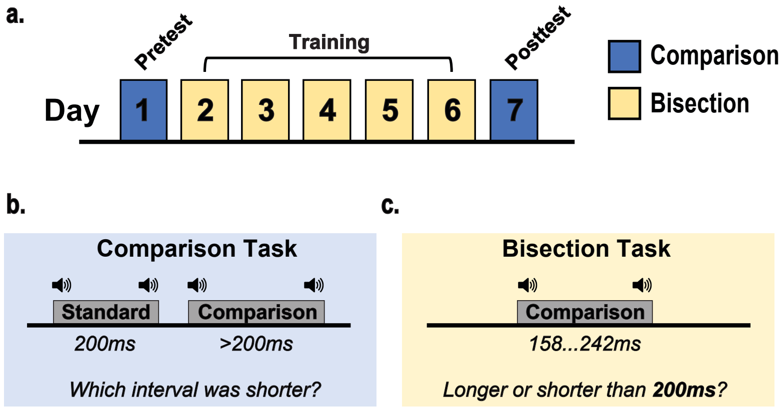

Figure 6. (a) Experimental procedure and task over seven days. (b) Task design for the untrained temporal comparison task. Participants indicated which of two auditory tones was longer in duration (i.e., the comparison interval). Presentation order was randomized on every trial. (c) Task design for the trained temporal bisection task. Participants indicated whether the comparison interval was longer or shorter than 200ms.

During the testing phase (Days 1 and 7), discrimination thresholds were measured using an adaptive staircase procedure (Levitt, 1971) with four conditions: 100ms, 200ms, 300ms at 1kHz, and 200ms at 4kHz. The presentation order for each condition was pseudo-randomized according to the Latin Square design for each participant and kept constant between pretest and posttest sessions. The task involves a two-interval comparison task (Figure 4b) using a 1-up-3-down staircase. Two auditory intervals were presented on every trial: a standard (t) and a comparison (t + Δt). Listeners must indicate which interval was the standard (i.e., shorter interval) by pressing either the “J” or “K” keys using their index and middle finger. The length of the standard and comparison was identical on the first trial of every block, forcing subjects to guess. Every correct response immediately following an incorrect response, and vice versa, is referred to as a reversal. The step size for the first five reversals is 5% of the standard and 1% thereafter. The inter-stimulus interval was jittered to minimize predictability between the offset of the first interval and the onset for the second interval. All methods and procedures were performed in accordance with the relevant guidelines and regulations set out by the IRB and human research protection program (HRPP) at Brown University. All demographic and threshold comparisons are presented in Table 2.

Table 1. Demographic information of participants in each experimental group, and the mean threshold improvements with training.

	FI Group	**RI Group**	**Control Group**
Age (Mean ± SD)	27.25 ± 9.04	25.23 ± 4.54	23.88 ± 5.30
Sex (Male:Female)	5:7	6:6	2:6
Threshold (pretest)	11.79	12.78	9.58
Threshold (posttest)	4.24	12.29	6.98
%Improvement ± SD	63.99 ± 29.65	3.82 ± 23.79	27.13 ± 38.45
Paired-sample t-test	t(11) = 2.92; p = .01	t(11) = 0.26; p = .48	t(7) = 0.74; p = .48

Results

Learning Specificity. To assess the amount of training-related change in performance between the FI and RI groups, we fit psychometric functions using the proportion of “long” responses at each comparison interval using the Quickpsy package (Linares & López-Moliner, 2019) in R (Figure 5). Based on the goodness-of-fit indicated by the coefficient of determination (r^2), we excluded data from 3 outlying subjects. Next, we calculated a maximum likelihood estimation of discrimination threshold (i.e., difference limen) using the average of the interquartile range of these fitted functions (Lapid, Ulrich, & Rammsayer, 2008, 2009a). The difference limen is often taken to be a reliable measure of perceptual sensitivity in standard 2-alternative forced choice tasks (Lapid, Ulrich, & Rammsayer, 2008, 2009a), and is hereon simply referred to as *threshold* throughout the rest of the paper.

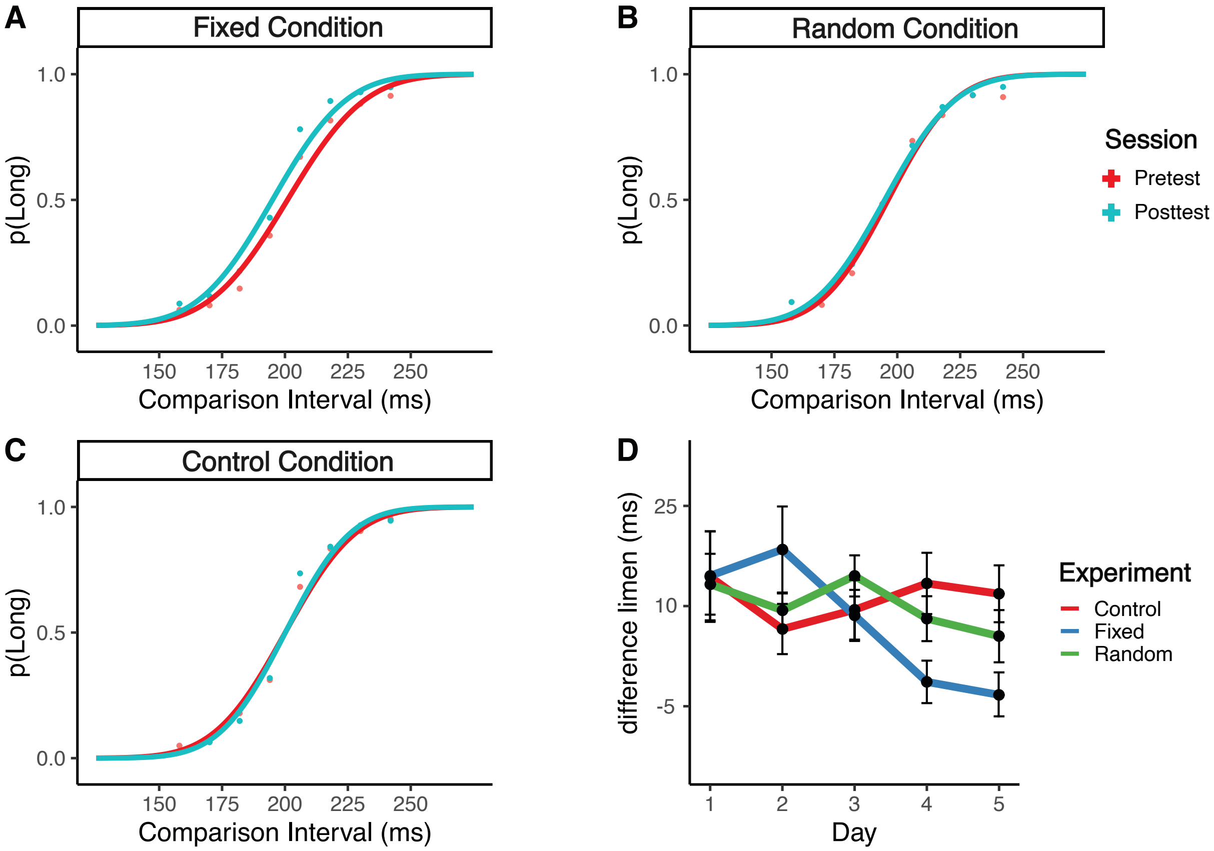

Figure 7. (a-c) Fitted psychometric functions for each group with training. (d) Individual and averaged changes in discrimination threshold (ms) across sessions. Each colored dot represents a single individual within their corresponding group, lines indicate group mean.

To investigate the effects of varying stimulus structure on TPL, we compared the discrimination performance of the two groups before and after the 5-day training phase. We submitted the discrimination thresholds to a 2 x 2 mixed ANOVA with group (FI/RI) as a between-subjects factor and session (first/last) as the within-subject factor. In this analysis, we found an overall increase in performance with training, with a significant main effect of session ($F_{1,22} = 5.71$, $p = .026$, $\eta^2 = .06$), but not group ($F_{1,22} = 0.03$, $p = .86$, $\eta^2 = .001$). Over the 5 training sessions, the rate of learning for the FI group followed a significant negative linear trend ($y = -1.26x + 212$; $F = 19.54$; $p < .001$), a pattern that is consistent with what is commonly observed in other TPL studies (Bratzke, Schröter, & Ulrich, 2014; Wright et al., 1997; Wright, Wilson, & Sabin, 2010). It should be noted that in contrast to the rapid behavioral improvements within the first few sessions for VPL (1-3 days), improvements on auditory discrimination tasks generally reach a plateau only with an extended training period (3-5 days) (Bueti & Buonomano, 2014).

Importantly, the interaction between group and session was significant ($F_{1,22} = 4.34$, $p = .049$, $\eta^2 = .05$). A post-hoc t-test between the groups showed a significant decrease in discrimination thresholds from the first day of training (M ± SD = 213 ± 6.33ms) to the last day (M ± SD = 199 ± 8.67ms), only in the FI group ($t_{11} = 3.01$, $p = .036$; Figure 6). To further investigate this selective improvement, we calculated the percent change in individual thresholds based on pretest performance ([pretest-posttest]/pretest). In the FI group, which showed an average of 63.9% increase in discrimination performance, we found a significant training-related change in thresholds between sessions (mean change = 7.54ms, $t_{11} = 2.92$, $p = .014$) as compared with the RI group with only an average of 3.8% improvement (mean change = 0.49ms, $t_{11} = 0.26$, $p = .79$). In summary, we found that practice improved the auditory discrimination performance selectively for the group receiving a fixed number of training intervals, but not when the test intervals were presented in a randomized fashion. Our results do not support the low-level hypothesis because it suggests that similar to VPL, learning is dependent on the input structure of information during training, and that the degree of improvement might be influenced by our ability to discern statistical regularities in the training stimulus (Banai & Amitay, 2012).

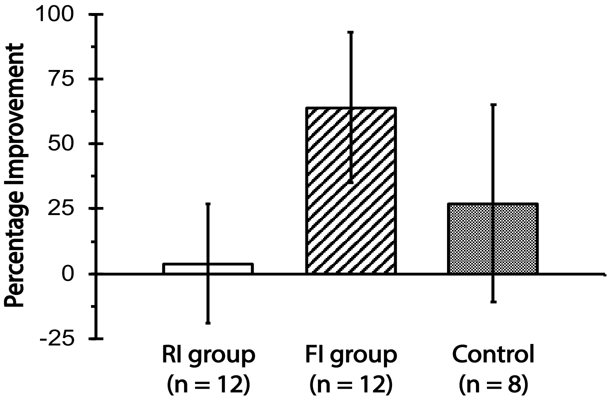

Figure 8. *Percentage improvement on the trained bisection task between the first and last training session normalized by initial performance. Error bars represent +/- SEM.*

To further understand how statistical regularity contributed to the selective performance improvement in the FI group, we recruited nine additional participants for a control condition. In the RI group, every test interval was selected at random from a normal/gaussian distribution with a mean of 200ms. This entails that a greater number of values are closer to 200ms than any other value within that range. In contrast, the FI group always compared the reference against 1 of 8 fixed intervals with equal (uniform) probability. The use of a fixed number of values therefore ensures a greater degree of statistical regularity both through (1) the stimulus distribution, as well as (2) an overall smaller number of possible interval values – either/both of which might have contributed to the observed differences in learning between groups. If the latter is true, changing the stimulus distribution of the RI group from gaussian to uniform would have minimal effect on learning since the overall degree of certainty/variability of the training stimulus remains much lower than the FI group.

Control group. To address this possibility, we recruited a control group whereby all stimuli and parameters are identical to the RI condition, with the exception that test intervals are now drawn from a uniform – not gaussian – distribution (Table 2). If TPL relies on regularities in the training stimuli, our manipulation would serve to equate the frequency of occurrence for all target intervals, leading to a similar behavioral improvement as observed in the FI group.

Table 2. *Summary of experimental conditions and main findings.*

	Comparison Values (milliseconds):	**Distribution of Comparison Values**	**Improvement?**	**Task-specific?**
Fixed Interval (FI)	*158, 170, 182, 194, 206, 218, 230, 242*	*Uniform*	*Yes*	*Yes*
Random Interval (RI)	*158, 159, 160…194; 206, 207, 208…242*	*Normal/Gaussian*	*No*	*Yes*
Control Experiment	*158, 159, 160…194; 206, 207, 208…242*	*Uniform*	*No*	*Yes*

Once again, we fit individual psychometric functions for each session, and calculated a percentage change in performance for each group. We did not find a significant change in performance before and after training in this new condition ($t_7 = 0.59$, $p = .57$), replicating our results from the RI group. To see if there were any differences in learning between the groups, we conducted a separate mixed model ANOVA with group (FI/RI/Control) and session (pretest/posttest) as factors. Our analysis of individual improvements again revealed a significant main effect of session ($F_{1,29} = 5.52$, $p = .026$, $\eta^2 = .03$), with lower thresholds after training in all three groups. However, this improvement was only significant in the FI group, as revealed through individual pair-wised t-tests with Bonferroni corrections (t_{11} = 2.77, p = .018). These results argue against the hypothesis that learning for the FI group is attributable to differences in the stimulus distribution (uniform vs. gaussian) during training.

Learning Generalization. In addition to learning in the trained task, we also tested generalization of learning using an untrained discrimination task with the same reference interval. Similar to estimation methods of previous studies (Wright et al., 2010; Wright et al., 1997), we calculated individual discrimination thresholds based on the average of last 6 reversals within each experimental block during pretest and posttest sessions. To compare discrimination performance across the 4 interval conditions (100ms, 200ms, 300ms at 1kHz and 200ms at 4kHz), Weber's Fractions (WF) were used (Figure 7).

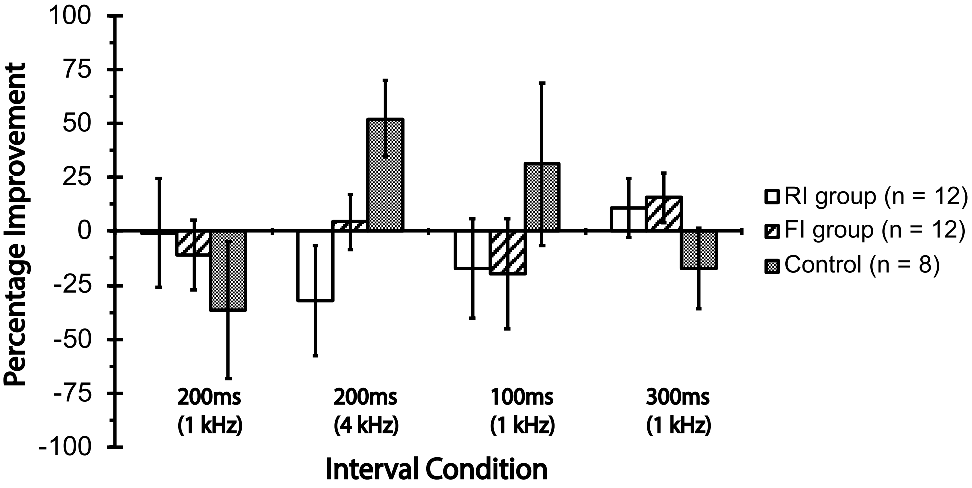

Figure 9. *Percentage improvement on the untrained comparison task for each interval condition. The trained 200ms at 1kHz condition did not show any significant changes between pretest and posttest sessions. Error bars represent +/- SEM.*

We then submitted the WFs to a 3 x 2 x 4 mixed model ANOVA with group as a between-subjects factor, and session and condition as within-subject factors. Our analysis revealed a significant main effect for condition ($F_{3,87} = 4.01$, $p = .038$, $\eta^2 = .05$), with the 100ms condition having significantly higher discrimination thresholds during both pretest ($WF_{pretest} \pm SEM = 1.29 \pm .011$) and posttest ($WF_{posttest} \pm SEM = 1.42 \pm .026$) sessions than all other interval conditions – a finding commonly reported in other TPL studies (Bratzke, Seifried, & Ulrich, 2012; Lapid, Ulrich, & Rammsayer, 2009b; Warm, Stutz, & Vassolo, 1975). Importantly, we did not observe a significant effect of training ($F_{6,87} = .88$, $p = .45$), nor group by condition by session interaction ($F_{6,87} = 1.39$, $p = .22$). Together, these results suggest that given our current paradigm, training-related improvements on a temporal task does not generalize to an untrained task even if the interval used between the two tasks are identical. Of course, we must recognize that the two paradigms used in our study (i.e., temporal bisection and discrimination task) may not fully capture learning transfer across all types of temporal tasks, and that various task-related differences in structure, procedure, and design could potentially contribute to the null transfer observed in our experiment. However, our results provide an initial demonstration of task-specificity in TPL, possibly representing an additional constraint in the mechanisms of temporal learning.

Discussion

Performance on a variety of perceptual and motor timing tasks is improved with training (Karmarkar & Buonomano, 2003; Meegan, Aslin, & Jacobs, 2000; Westheimer, 1999a; Wright et al., 1997). This learning is largely interval-specific (Bueti et al., 2012; Hayashi et al., 2018; Karmarkar & Buonomano, 2003; Nagarajan et al., 1998; van Wassenhove & Nagarajan, 2007;

Wright, Wilson, & Sabin, 2010) which motivates the view that TPL improves the featural representation of a temporal interval. In contrast, relatively little is known about the degree to which non-temporal components of a task affect TPL. The present study focuses on the influence of stimulus- and task-specificity on temporal learning. In our experiment, we demonstrate that: (1) learning is sensitive to statistical regularities in the training stimulus – only the FI group, trained using a fixed number of interval values, showed a significant improvement in temporal discrimination; and (2) learning is specific to the response strategies of a trained task, with no generalization of learning to an untrained task.

Why did temporal discrimination performance selectively improve in the FI group, but not the RI group? Since the to-be-learned interval (i.e., 200ms) was identical in both groups, this difference in learning can first and foremost be explained through differences in response strategy. For example, in lieu of comparing each test interval against the reference interval, participants in the FI group might have opted to learn a specific set of decision weights based on the optimal stimulus-response relationship. In other words, TPL reflects the learning of the most appropriate response given each of the 8 fixed values. With a finite number of possible values, the FI group can effectively adopt this strategy. By comparison, the RI (and control) group was not able to extract any meaningful relationships based on an infinite number of possible intervals and their associated responses. This suggests that mechanisms of temporal learning might involve an optimization of connections between stable stimulus representations and relevant task decisions.

A related consequence of being exposed to greater variability in training input is the possibility of resulting differences in memory quality for the reference duration. Since the RI group was exposed to a greater number of test intervals during training, it is likely that their representation of the 200ms reference is inherently noisier and more easily contaminated by additional input. As a result, degradations in memory may have contributed to the observed differences in learning across groups. This interpretation is again consistent with the stipulation that top-down processes are necessary in perceptual learning because it suggests that top-down cognitive functions, such as attention and memory factors may influence perceptual processing at a very low-level stage of learning. With both considerations, our results suggest that TPL cannot rely *exclusively* on changes at the level of stimulus/interval representation, otherwise our manipulation of the comparison interval would not play a role in learning. Instead, we speculate that high-level processes must also be involved in the learning process, and it is this set of task-specific strategies that also become improved with training.

More broadly, our finding that TPL is sensitive to regularities in the training stimulus is consistent with what is often reported as “roving effects” in VPL (Yu, Klein, & Levi, 2004). With roving, the use of interleaved visual stimulus or task structures can impair learning across a number of visual discrimination tasks (Adini et al., 2004; Kuai et al., 2005; Otto et al., 2006; Yu, Klein, & Levi, 2004). This interference is suggested to result from activity in overlapping neural populations, and arising only when there is a high degree of similarity between a trained stimulus type and task (Tartaglia, Aberg, & Herzog, 2009; Zhang et al., 2008). In our study, the observation that learning was impaired for the RI group receiving interleaved training intervals therefore highlights a crucial similarity in the underlying learning mechanisms between temporal and visual learning. A finding by Parkosadze et al. (2008) showed that perceptual training under roving conditions may be mitigated by a more extensive training regimen (Parkosadze et al., 2008). Similarly, we might expect to see comparable learning outcomes for the RI group with a greater number of training trials.

Another novel finding in our study is the lack of learning transfer between a trained and untrained temporal task. For participants in the FI group, training-related improvements in discrimination performance was restricted to the practiced task condition with no comparable changes in the untrained task, even though the same reference interval was used. While this result might seem to contradict traditional views on TPL where learning is hypothesized to rely exclusively on duration-selective changes in interval representation (Karmarkar & Buonomano, 2003; Meegan, Aslin, & Jacobs, 2000; Nagarajan et al., 1998; Wright et al., 1997), we believe our finding of task-specificity can be better understood as representing an additional constraint on the learning process. Based on several current formulations of VPL, specificity in learning could reflect changes in a trained feature (i.e., reference interval) given a specific set of task- and context-specific demands (Sasaki, Nanez, & Watanabe, 2010; Sasaki, Náñez, & Watanabe, 2012; Seitz & Watanabe, 2005; Watanabe & Sasaki, 2015). Therefore, our results extend our current understanding for the mechanisms of TPL by constraining interval-specific learning within a broader framework of task-related processes.

CHAPTER THREE

In studying perceptual learning, many researchers have used the visual system as a guide for understanding brain plasticity. One feature of perceptual learning in the visual system is that our visual pathway must adapt to a wide range of inputs from the environment (plasticity), and at the same time maintain a certain level of resiliency to change so as to preserve what has already been learned (stability). This is known as the plasticity-stability dilemma (Abraham & Robins, 2005; Grossberg, 1980; Spanis & Squire, 1987) and constitutes a central constraint in optimizing learning in biological systems (Grossberg, 2013). Whereas plasticity is necessary during initial stages of exposure to a stimulus, stability is necessary in consolidating learned information. Too much plasticity would result in an inability to remember what has been learned, and too much stability would interfere with the encoding of new, incoming information (Mermillod, Bugaiska, & Bonin, 2013). Thus, the ability to transfer from a "plastic state" into a "stable state" during learning is critical for the acquisition and consolidation of a perceptual skill over time.

The results described in Chapter 2 hold important implications for the locus of plasticity in TPL. Whereas *specificity* implies plasticity in low-level brain areas which typically exhibits characteristics of duration selectivity, generalization entails plasticity beyond sensory representation – likely engaging higher-order brain areas. Therefore, the present chapter aims to further elucidate the involvement of high-level cognitive processes in TPL by exploring the involvement of non-sensory cortices during learning using MRS.

The relationship between mechanisms of perceptual learning and neurochemical processing in the brain has received tremendous attention in recent years (Sasaki, Nanez, & Watanabe, 2010). Specifically in VPL, the relative balance between excitatory-to-inhibitory processing in the EVAs has been implicated as a proxy for neuroplastic changes which occur in close association with the behavioral improvements of perceptual learning (Bang et al., 2018; Sasaki, Nanez, & Watanabe, 2010; Shibata et al., 2017). Greater concentrations of the inhibitory neurotransmitter, γ-aminobutyric acid (GABA) – can suppress the firing of excitatory neurons (Kim et al., 2014; Stagg, Bachtiar, & Johansen-Berg, 2011), a process which is critical during the consolidation stages of perceptual learning to prevent interference with new learning (Bang et al., 2015, 2018; Shibata et al., 2017). Moreover, elevated resting-state GABA levels might play a role in mediating our subjective experience of time (Matthews et al., 2015). In this study, participants performed an interval discrimination task while MRS measurements were taken from V1. They found a positive correlation between GABA concentrations in the V1 and an underestimation of temporal intervals, highlighting a potential link between biochemical processes in the sensory cortices and temporal learning (Terhune et al., 2014).

Consistent with the high-level hypothesis, we speculate that improvements in temporal discrimination will be associated with neuroplastic changes in the IPC. To test this hypothesis, we trained participants using a two-interval discrimination task while simultaneously measuring learning-related changes in the excitatory-to-inhibitory ratio (E/I ratio) across a five-day period. The use of this intensive experimental design permits the comparison between *within-session* learning – revealed as changes in E/I ratio between baseline and post-task scans on each day, as well as *between-session* learning across days.

Methods

Participants. Ten healthy volunteers (6 females, mean age = 25.2 years) gave their written informed consent for participation in this experiment. All participants were determined to be right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971), had normal or corrected-to-normal hearing and vision, and no history of psychiatric disorders. All sessions were held at the same time during the day to minimize effects of circadian phase on temporal processing (Lustig & Meck, 2001). All procedures were approved and conducted in accordance with the guidelines outlined by the Institutional Review Board (IRB) and the Human Research Protection Program (HRPP) at Brown University.

Stimulus and Procedure. The experiment took place over five consecutive days with MRI sessions on the first (pretest) and last (posttest) session (Figure 8). During each MRI session, we obtained resting-state and post-task spectral measurements while participants performed the task in the scanner (*see* 'temporal discrimination task'). For the training sessions (Days 2 – 4), participants practiced the discrimination task for 800 trials per day with feedback. We justified the number of practice trials under the guidance of previous studies which have demonstrated substantial learning effects using ~2500 trials (Bratzke, Seifried, & Ulrich, 2012; Meegan, Aslin, & Jacobs, 2000; van Wassenhove & Nagarajan, 2007), and with as little as a single day of training with 900 trials (Westheimer, 1999). All stimuli were presented using MATLAB (MathWorks, Natick, MA), with Psychophysics Toolbox extensions, version 3.0.14 (Kleiner et al., 2007) and approved by the IRB at Brown University.

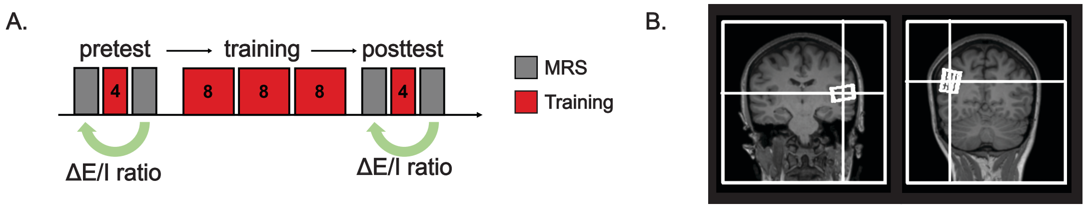

Figure 10. *(a) Experimental procedure. Numbers within each training session indicates the number of blocks. (b) An example of MRS voxel placement in the primary auditory cortex (left) and the inferior parietal cortex (right) corresponding to the supramarginal and angular gyrus.*

Temporal discrimination task. We used a two-interval temporal discrimination procedure with feedback (Figure 4). Two empty intervals were presented on every trial, each marked by a pair of tones presented aurally through fMRI-compatible insert earphones at a comfortable hearing level of ~80 dB adjusted prior to beginning the experiment. Interval length was demarcated by the offset of the first tone within the tone pair, and the onset of the second tone. Listeners were asked to indicate which of the two tone pairs – the standard (t) or the comparison (t + Δt) – was the *shortest* by pressing one of two keys on a fMRI-compatible response box (during MRI sessions) or a standard US keyboard (during training sessions) using their index and middle fingers of their right hand. Similar to previous studies (Bueti et al., 2012; Wright et al., 1997; Wright, Wilson, & Sabin, 2010), the two intervals were identical on the first trial of every block, forcing participants to guess. From thereon, the step size for the first five reversals of each block was 5% of the standard and 1% thereafter.

To ensure that participants were awake and alert during each MRS scan, they were asked to keep their gaze on a central white fixation cross presented against a black background (1.5 x 1.5 visual angle). After a random delay period (pseudorandomized between 1 – 8 seconds), the fixation changes color from white to a faded pink (RBG = [275 192 200]). Participants were asked to respond using their index finger as soon as they detect this change. Their response time, in milliseconds, was displayed immediately following each button press. Participants were asked to respond as quickly as possible without moving their head. A self-timed break was given between each of the 4 blocks. The averaged performance on the fixation task did not differ across the two MRI sessions for all participants, $F(1,18) = 2.08$; $p = .166$; $\eta^2 = .104$, suggesting that baseline arousal and activity was similar during each MRS acquisition.

MRI Acquisition. A 3T Siemens MRI scanner with a 32-channel head coil was used to acquire three high-resolution T1-weighted MPRAGE anatomical images from each participant (number of slices = 160 x 1mm per slice, voxel size = 1 x 1 x 1mm^3, TR = 1900ms, TE = 3.02ms, flip angle = 9°, FoV = 256mm, bandwidth = 230 Hz/pixel). Each single-voxel MRS sequence consisted of a concurrent quantification of Glutamate and Glutamine (i.e., *Glx*) using the PRESS sequence (TR = 3000ms, TE = 30ms, average = 64, acquisition duration = 819ms), and GABA using the MEGA-PRESS sequence with double-banded pulses (TR = 1500ms, TE = 68ms, average = 192, acquisition duration = 512ms) in a counter-balanced order. The final spectra were calculated by subtracting the signals from alternate scans with the selective pulse applied at 4.7 and 7.5 ppm (Edit OFF) and the pulse applied at 1.9 and 4.7 ppm (Edit ON) scans.

Shimming was performed using a vendor-provided automated shim tool. The average shim values did not differ significantly between pretest and posttest sessions, nor across the ROIs (Table 2). However, the PRESS sequence (M ± SD = 18.84 ± 3.26) consistently yielded slightly higher shim values than the MEGA-PRESS sequence (M ± SD = 15.97 ± 1.5; $t_{75} = 6.69$, $p < .001$, 95% CI = -3.73 to -2.02). Water suppression is achieved using a variable power RF pulses with optimized relaxation delays (VAPOR) method (Tká et al., 2001). All spectral data were analyzed using the LCModel software which fits each measured metabolite based on a predetermined set of basis functions (Provencher, 2001). Outliers in reliability for each neurochemical were identified using boxplots of signal-to-noise ratio, shim value, as well as a Cramer-Rao Lower Bound cut-off of 20% to minimize low-quality signal.

Table 3. Demographic information of participants and shim values across sessions for each GABA (MEGA-PRESS) and Glutamate (PRESS) acquisition before and after training.

			Shim Values (Hz)							
			Pretest				Posttest			
			MEGA-PRESS		PRESS		MEGA-PRESS		PRESS	
Subject	**Age**	**Sex**	Baseline	Task	Baseline	Task	Baseline	Task	Baseline	Task
001	24	F	15.2	19.7	15.4	16.8	16.75	20.12	17.69	19.13
002	24	F	17.1	16.9	15.2	14.8	16.9	24.2	25.5	25.4
003	24	F	14.3	14.3	16.1	15.4	16.2	24.9	16.1	15.9
004	24	M	16.3	16.2	12.8	13.3	17.1	24.2	15.2	20.5
005	21	F	16.6	15.1	16	17.2	17.5	21.9	21.1	17.8
006	32	F	16.5	18.1	15.7	15.1	17.9	17.9	16.3	16.3
007	26	M	13.2	15.3	16.9	17.6	15.1	17.6	17.3	17.6
008	28	F	16.5	18.6	19.6	19.7	17.8	18.7	18.8	23.1
009	25	M	15.7	15.6	16.9	14.9	16.2	16.8	17.4	16
010	23	M	16.1	16.8	14.9	15.4	23.5	18.8	15.9	24.8

Voxel Placement. Based on each anatomical scan, two voxels (voxel size = 2.5cm x 1.5cm x 2.0cm) were placed corresponding to the primary auditory cortex in the left hemisphere and the inferior parietal cortex of the right hemisphere. The A1 was identified using landmarks that demarcate the transverse temporal gyrus (Penhune et al., 1996). Since the number and morphology of the Heschl's Gyrus (HG) has been reported to be highly variable across individuals (Morosan et al., 2001), voxels were positioned manually from the T1 image immediately preceding each MRS acquisition and if there were more than one HG present, or if the HG is interrupted by the sulcus intermedius, the voxel was positioned along the first HG closest to the lateral sulcus.

Results

Performance Change. For the analysis of behavioral data, we used a 1-up-3-down staircase procedure to estimate the discrimination threshold for the temporal discrimination task at 79% accuracy (Levitt, 1971). Every correct response immediately following an incorrect response, and vice versa, is referred to as a reversal. The discrimination threshold is estimated based on the average of the last 6 reversals within each block, expressed as the Δt in milliseconds divided by the standard duration.

Overall, we found that performance on the temporal discrimination task was improved with training (Figure 9b). A repeated-measures analysis of variance (ANOVA) with Greenhouse-Geisser corrections revealed a significant reduction in discrimination thresholds following five days of practice ($M \pm SD_{pretest} = .187 \pm .05$; $M \pm SD_{posttest} = .131 \pm .03$; $F_{4,36} = 10.1$, $p = .001$, $\eta^2 = .22$). Consistent with previous studies, the averaged discrimination threshold function follows a typical learning curve, with performance reaching a plateau around the third day of training (Wright, Wilson, & Sabin, 2010).

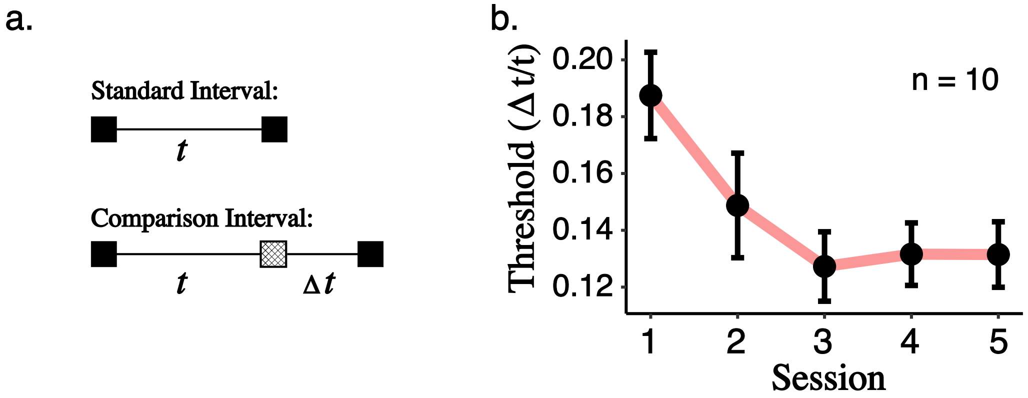

Figure 11. *Behavioral paradigm and results (a) Schematic representation of the auditory intervals presented in each trial. The length of* t *is always 200ms while Δ*t *is varied adaptively based on a 1-up-3-down staircase procedure (b) Average training-related interval discrimination thresholds (Δ*t/t *at 79% correctness) across the five experimental sessions. Error bars indicate ± standard error of the mean.*

Neurochemical Change. To quantify neurochemical change within each ROI, we first normalized the raw concentration of GABA and glutamate to creatine. Creatine has similar properties to our spectral peaks of interest, and is used as a standard reference resonance in many MRS studies (Bottomley & Griffiths, 2016). As a control analysis, we found no significant differences in creatine concentrations between sessions ($F_{1,9} = .82$, $p = .39$), scans ($F_{1,9} = .44$, $p = .52$), nor ROIs ($F_{1,9} < .001$, $p = .98$). Hereon we refer to these creatine-normalized values as concentrations of GABA and glutamate, respectively. Next, we calculated the ΔE/I ratio within each MRS session using the formula (Bang et al., 2018; Shibata et al., 2017):

$$\Delta E/I_{\text{session}} = \left(\frac{\frac{GLU_{baseline}}{GABA_{baseline}}}{\frac{GLU_{task}}{GABA_{task}}} - 1\right) \text{ x } 100$$

Here, the numerator represents the ratio of glutamate to GABA during baseline. The denominator represents the same measurements taken immediately after completing the discrimination task. Note that in the calculation of the ΔE/I ratio, the normalizing metabolite is cancelled out in the equation, therefore the use of creatine and N-acetylaspartate (NAA) is interchangeable in our analysis.

We then checked for any outliers in our dataset using the Grubbs test (Grubbs, 1950). In this analysis, one subject was excluded based on an abnormally high ΔE/I ratio during the posttest session ($G = 2.72$, $p = .02$), leaving a total of 9 subjects. All statistical tests conducted in this study were two-tailed using an alpha level of .05. Bonferroni corrections were used when multiple comparisons were necessary.

We first applied a two-way within-subject ANOVA to the ΔE/I ratios within each session (pretest vs. posttest) for both ROIs (A1 vs. IPC). If discrimination training differentially affects the excitation/inhibition balance in the sensory vs. associations areas of the brain, we would expect an interaction between the session and ROI factors as a result of learning. Consistent with this hypothesis, we observed a significant interaction effect ($F_{1,9} = 9.21$, $p = .014$, $\eta^2 = .16$), but no main effects of ROI or session alone ($p > .05$). Post-hoc tests of simple effects indicated a significant main effect of ROI only during the pretest ($F_{1,36} = 7.29$, $p = .02$), but not the posttest session ($F_{1,36} = 1.01$, $p = .32$). Whereas the ΔE/I ratio within the IPC was significant increased following training, the opposite pattern was observed in the A1 (Figure 10). These results suggest that the sensory and association areas might play complementary roles during initial stages of temporal learning, and did not lead to any long-term changes in E/I ratio across days (ROI: $F_{1,9} = 1.15$, $p = .31$; scan: $F_{1,9} = .05$, $p = .82$).

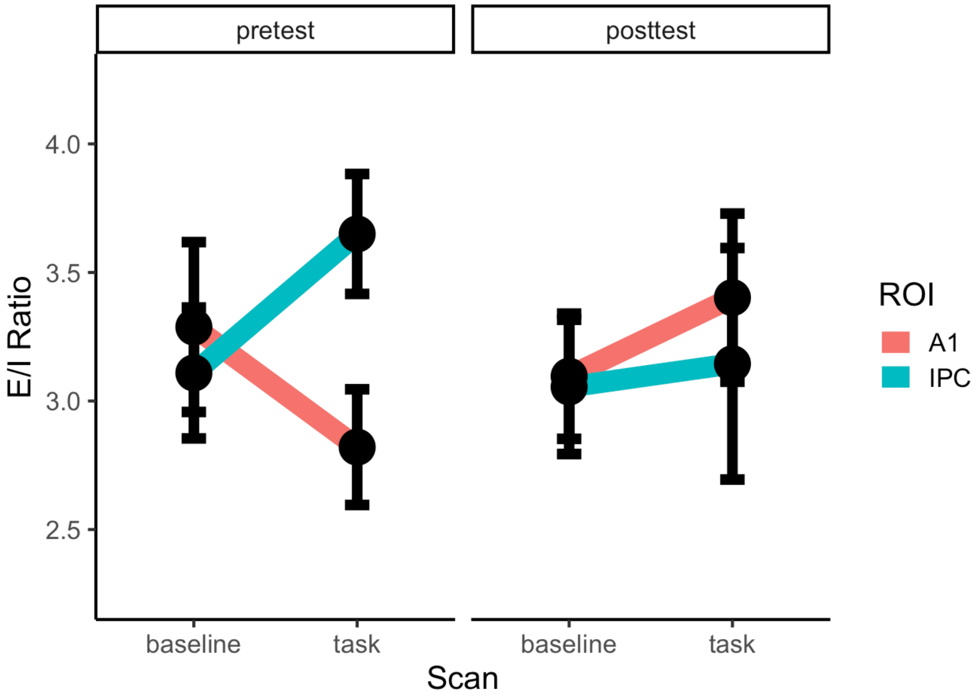

Figure 12. *(a) Changes in the E/I ratio within each session before (baseline) and after (task) training on the temporal discrimination task. A significant interaction was found between ROI and scan during the pretest session. No significant effects were found during posttest.*

To further understand how the ΔE/I ratio was related to performance improvement on the temporal discrimination task, we performed a set of Spearman's rank-order correlations between the percent change in ΔE/I ratio with the percent change in discrimination performance. We opted for the use of Spearman's ρ over Pearson's *r* analysis given the violation of sphericity in ΔE/I ratios using Mauchly's sphericity test. In all correlation analyses, the ΔE/I ratio is calculated based on the normalized difference between ΔE/I ratios during pretest and posttest sessions, analogous to the performance changes across days.

If our hypothesis of high-level involvement in TPL is correct, we would predict a correlation between overall improvement in temporal discrimination and metabolic changes in the IPC rather than the A1. Consistent with this prediction, we found that there was a tendency for performance gains on the temporal discrimination task to be linearly correlated with the ΔE/I ratio in the IPC (ρ = -.65, p = .05; A1: ρ = -.32, p = .41), however this relationship did not reach statistical significance. This tendency indicates that individuals who showed the greatest improvement on the discrimination task over training also had the greatest reduction in ΔE/I ratio of the right IPC (Figure 11a). These results demonstrate for the first time, an important link between TPL and inhibitory-dominant neurochemical processing in higher-order cognitive areas of the brain.

In addition to overall improvements in temporal discrimination, we also explored the possible relationship between ΔE/I ratios and the rapid performance gains on the discrimination task. We speculate that, consistent with multistage models of VPL, the A1 might be engaged at a different stage of the learning process as compared to the IPC. Whereas overall improvements in performance might be related to stabilization processes in the higher-order cognitive areas, it is possible that the A1 is engaged during the encoding stage of learning, likely involving the sensory representation of a temporal interval. Therefore, we hypothesized that similar to VPL, TPL might also involve multiple stages of information processing, which engages different brain areas, which not be revealed by only considering overall learning across days.

As illustrated in Figure 9b, the greatest improvement on the temporal discrimination task occurred within the first few days of training. Therefore, we calculated a separate learning index for the first day of learning. Since the greatest neurochemical change was found during the pretest session, we suspected that these changes might partially underlie the rapid improvement on the discrimination task. Indeed, we found a significant correlation between initial learning and a decrease in the E/I ratio in the A1 (ρ = -.73, p = .025), suggesting that greater performance gains within the first few days of training was related to more inhibitory-dominant processing in the early sensory areas (Figure 11a).

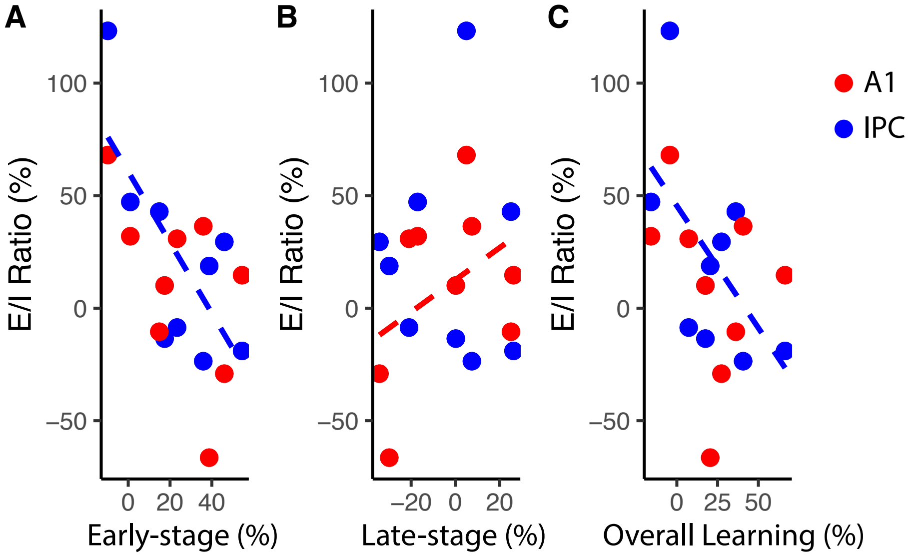

Figure 13. *Spearman's rank-order correlation between the percentage change in E/I ratio and learning for each individual. Dashed lines represent the best fit linear regression for the significant ROI. A significant negative correlation was found between (a) initial performance gains and E/I ratio changes in the IPC and (c) overall learning and E/I ratio changes in the IPC.*

Finally, we considered whether the post-task shift into inhibitory processing, manifesting through a decrease in ΔE/I ratio, reflect changes in the concentration of GABA in these areas. We conducted a separate 2 x 2 ANOVA on GABA using session (pretest vs. posttest) and scan (baseline vs. task) as within-subject factors. In this analysis, both the A1 and IPC showed a significant main effect for session (A1: $F_{1,9} = 8.13$, p = .019, $\eta^2 = .22$; IPC: $F_{1,9} = 7.94$, p = .02, $\eta^2 = .19$). However, whereas GABA measures in the A1 decreased significantly with training between pretest (M ± SD = .53 ± .14) and posttest sessions (M ± SD = .41 ± .096; t_9 = 2.85, p = .02), the opposite pattern was found in the IPC where GABA during pretest (M ± SD = .39 ± .13) was increased significantly after training (M ± SD = .59 ± .275; t_9 = 2.81, p = .02). Since the MRS measurements were obtained at the same time in both sessions, fluctuations in GABA levels are unlikely to be attributable to circadian changes throughout the day (Evans, McGonigle, & Edden, 2010). Compared to baseline measures, GABA levels in both ROIs did not change significantly immediately after the task (p > .05). It is possible that the time-course for these changes can only be detected after a longer delay period following the task (Shibata et al., 2017).

In addition, we asked whether differences in individual metabolic measures at pretraining could predict how much learning would occur with discrimination training. To this end, we correlated the overall Δthresholds on the temporal task with baseline pretraining levels of glutamate and GABA (Figure 12). We found that pretraining GABA in the IPC was moderately related to overall learning, but this relationship did not quite reach significance (ρ = -.63, p = .07). This analysis did not reveal any other remarkable relationships.

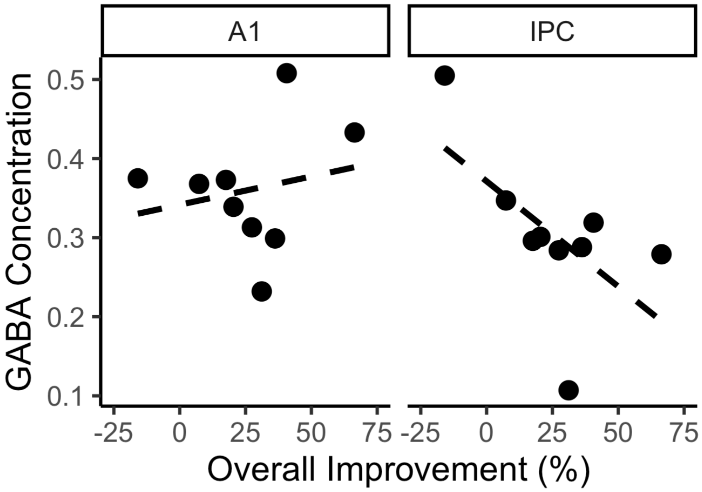

Figure 14. *Changes in concentrations of GABA (left) and glutamate (right) within and across sessions. Significant main effects of session was found in the GABA concentrations for both ROIs, with a reduction in A1 and an increase in IPC following training.*

Discussion

Informed by multiple lines of behavioral (Bratzke, Schröter, & Ulrich, 2014; Karmarkar & Buonomano, 2003; Meegan, Aslin, & Jacobs, 2000; Nagarajan et al., 1998; Wright et al., 1997; Wright, Wilson, & Sabin, 2010) and neurophysiological (Bueti et al., 2012; Bueti & Macaluso, 2010; Hayashi et al., 2015, 2018; van Wassenhove & Nagarajan, 2007) evidence, discrimination training in the subsecond range can lead to interval-specific improvements in timing. This learning is further hypothesized to arise from duration-selective tuning mechanisms in both sensory and association areas of the brain (Bueti, Bahrami, & Walsh, 2008; Hayashi et al., 2015, 2018; Protopapa et al., 2018; van Wassenhove & Nagarajan, 2007). In particular, the right IPC have been shown to activate in response to temporal intervals across a wide range of durations (Harrington et al., 2004; Hayashi et al., 2013; Lewis & Miall, 2003a). What is far less clear however, is the nature of the relationship between the IPC and primary areas of representation.

In the study outlined in this chapter, we sought to characterize the neurochemical signatures of temporal learning. Using ^{1}H-MRS in conjunction with behavioral measures, we demonstrate for the first time, a learning-induced reduction in plasticity following temporal discrimination training. Moreover, this observed shift to inhibitory-dominant processing was only evident during initial stages of learning in the IPC. This pattern of results is similar to what is reported by Penhune & Doyon (2002, 2005), where initial activation of the cerebellar mechanisms were involved in adjusting motor timing during low-level stages of learning, they were no longer necessary during later learning. It was hypothesized that the representation of time has become stabilized with training, and is distributed across higher-order cortical areas including the premotor and parietal lobes. Therefore, neuroplastic changes in these areas of representation, as indicated by the E/I ratio, contributes an important piece of confirmatory evidence in support of the mechanisms underlying behavioral improvements observed with perceptual training.

In VPL, learning is particularly fragile immediately after training (Seitz et al., 2005; Shibata et al., 2017; Yotsumoto, Watanabe, & Sasaki, 2008) – a state that is highly correlated with increases in BOLD activation (Furmanski, Schluppeck, & Engel, 2004; Schwartz, Maquet, & Frith, 2002; Yotsumoto, Watanabe, & Sasaki, 2008) and higher plasticity (Shibata et al., 2015, 2017) of the primary visual cortex. Consistent with these findings, we also noted a significant increase in pretraining E/I ratio of the IPC immediately following the temporal task. Since the E/I ratio can be taken as an index of cortical plasticity (Bavelier et al., 2010; Hensch, 2005), our results highlight the potential role of the right IPC as a locus of temporal learning, analogous to the V1 in VPL. Our results add to the long-established role of the IPC in temporal processing (Bueti et al., 2010, 2012; Harrington et al., 1998, 2004; Harvey et al., 2013; Hayashi et al., 2013, 2015; Rao, Mayer, & Harrington, 2001; Roitman, Brannon, & Platt, 2012), and further demonstrate its neurochemical involvement in adapting to learned information.

In this experiment, we also note the novel relationship between pretraining stabilization in the IPC and overall performance improvements in temporal discrimination. This post-task reduction in excitability has been hypothesized to reflect the stabilization of a learning state, making it resilient to subsequent learning (Shibata et al., 2017). Following this line of reasoning, our result would therefore suggest that immediately following learning, metabolic activity within the A1 and IPC shifted to become inhibitory-dominant in order to preserve the newly acquired temporal skill, and further prevent interference with this fragile learning state. Moreover, the same stabilization process was not observed following five days of training, suggesting that once a temporal skill has been learned, the neurochemical mechanisms return to baseline and is no longer disrupted by further activation. A similar time-course has been reported by Shibata et al. (2017), where hyper-stabilization led to an immediate shift in the neurochemical environment of the V1 following training, but gradually returned to baseline a few hours after the task.

We further propose that these changes in plasticity, as indexed by the E/I ratio, can offer important insights into the mechanisms of temporal learning. One of the key characteristics of TPL is interval-specificity, whereby perceptual training selectively improves the discrimination of a trained interval (Bueti & Buonomano, 2014). This temporal selectivity has been thought to rely on duration-tuning mechanisms throughout the brain (Buonomano & Mauk, 2004; Lewis & Miall, 2003b; Rao, Mayer, & Harrington, 2001). One hypothesis which follows from this is that metabolic changes at the cellular level, particularly in relation to the excitation/inhibition balance, can contribute to sensory adaptation in these temporally selective areas. Specifically in the auditory cortex, short-term plasticity is widely regarded as a viable mechanism for stimulus-specific adaptations (Reyes, 2011; Zucker & Regehr, 2002) and recently, have been linked to sensory timing in a number of species and stimulus modalities (Motanis, Seay, & Buonomano, 2018). Therefore, our findings raise the possibility that auditory discrimination training strengthens the synaptic relationship of temporally selective neurons through neurochemical processes, which facilitate the learning of interval-specific information.

CHAPTER FOUR

The ability to improve the discrimination of short temporal intervals remains one of the most unique and profound demonstrations of neural plasticity in the perceptual system. Since temporal information is accessed through multiple perceptual channels, a careful examination of the mechanisms of TPL can effectively isolate the locus of perceptual learning in the absence of any dedicated sensory processing pathway. The goal of this dissertation is to explore the contribution of high-level processes to temporal learning using a combination of behavioral and neurochemical measures. Consistent with predictions of hybrid models outlined in chapter 1, we hypothesized that TPL involves changes beyond sensory refinement, and can be appropriately reflected through plastic changes in high-level cortical areas. In this section, we first summarize the results from our experiments, followed by a discussion their relevance to current models of perceptual learning, as well as limitations and future directions of the work.

Summary of Results

In the set of experiments described in chapter 2, we sought to address the question of what is improved after learning in a temporal task. Specifically, we considered whether TPL is affected by context-specific factors such as stimulus and task structure during the training phase. We first trained two groups of participants using a single-interval auditory discrimination procedure over five days. Training stimulus consisted of either eight fixed values, or random on every trial. Before and after training, we also measured discrimination thresholds on a separate, untrained comparison task. We first found a selective improvement in performance for the FI group, but not the RI group. In addition, this learning did not generalize between the trained and untrained tasks even though the same interval (i.e., feature) was used.

While the findings in our first experiment differ from typical learning generalization patterns reported in previous studies (e.g., Meegan, Aslin, & Jacobs, 2000; Nagarajan et al., 1998; Rammsayer, 1994), one way to reconcile these perspectives emphasize the ease of generalization between trained and untrained conditions. Specifically, we speculate that learning generalization may be inversely proportional to task complexity during training. In Buonomano et al. (2009) for example, training of temporal discrimination using a short interstimulus interval (ISI) resulted in learning specificity for the trained condition, whereas the use of a longer ISI was able to benefit performance in untrained conditions (Buonomano, Bramen, & Khodadadifar, 2009). Similarly in Chen & Zhou (2013), transfer effects were robust for a visual Ternus display when trained using auditory/tactile intervals, but similar benefits were not observed in the visual modality. These results are consistent with the idea that learning generalization increases with training (Wright, Wilson, & Sabin, 2010), and practice using a more complex or cognitively demanding stimuli would impair transfer to untrained conditions (Bakhtiari, Awada & Pack, 2020). Conversely when training is conducted using easier (e.g., longer ISI) or modality-dominant (e.g., auditory) stimuli relative to testing conditions, learning transfer is typically observed (Bratzke, Seifried, & Ulrich, 2012). This suggests that differences in the relative ease in accessing unisensory temporal information can predict intermodal generalization patterns in untrained conditions. More broadly, our results highlight learning specificity to a trained stimulus and task structure, suggesting that TPL must engage high-level cognitive mechanisms beyond changes in sensory processing.

Consistent with these behavioral results, we further explored the neurochemical involvement of high-level cognitive brain areas in association with TPL. Using MRS, we identified learning-induced shifts in the excitatory and inhibitory balance of primary sensory and association cortices in ten young adults. In the experiment described in chapter 3, we note a significant correlation between overall improvements in temporal discrimination and decreases in the E/I ratio of the right IPC. We also found a dissociable effect of task-related processing between the sensory and association areas during initial stages of learning, which disappeared following five days of training. Taken together, these results suggest that TPL acts to immediately consolidate a learning state through shifts in the excitatory and inhibitory balance of high-level brain areas, and serve as the first evidence of neurochemical processes underlying the perceptual learning of time. More importantly, these neurochemical signatures of learning corroborate with our behavioral findings, which together support the involvement of late-stage mechanisms in the temporal processing hierarchy.

A Two-Stage Model of TPL

Based on these results, we hypothesize that TPL can be characterized as involving two distinct stages of processing whereby a low-level enhancement in interval representation is accompanied by high-level optimizations in temporal behavior. In support of low-level enhancements in temporal discrimination, previous studies often report interval-specific generalizations across nontemporal dimensions of a stimulus. For instance, benefits obtained from auditory discrimination training are unspecific to untrained frequencies of the same interval length (Wright et al., 1997). These improvements are typically interpreted as the effect of perceptual training on modifying the local neural circuitry tuned to the temporal aspects of a temporal stimulus. While higher cognitive skills such as attention and memory are thought to inevitably be involved in the learning process, these processes are not generally assumed to undergo training-related changes themselves.

The findings described in this dissertation build on these perspectives by demonstrating the involvement of top-down influences in temporal learning. In our first study, the low-level statistical properties of the training stimulus was identical in both the FI and RI groups, but only the FI group was able to improve on the task, which indicates that differences in learning must involve changes in high-level rule-based behavior. If TPL relies exclusively in modifications to the local representation of a temporal stimulus, learning should be relatively insensitive to changes in high-level parameters or the optimal task-processing strategy. Our result that TPL was influenced by regularities in high-level, task-specific processing highlight the inability of low-level theories in explaining learning behavior. Moreover, if learning was indeed restricted to changes in sensory-level processing, TPL related neurochemical activity should be accordingly reflected in the primary sensory cortices associated with a trained temporal stimulus. However, as we demonstrated in chapter 3, plastic changes linked to discrimination performance was only found in the IPC – a high-level processing area for time – rather than the immediate sensory representation area, A1. Therefore, we propose that learning engages both sensory and decision stages of temporal processing. Whereas specificity might be best predicted by changes in sensory-level changes in interval discrimination, we predict that generalization patterns might better reflect similarities in decision-level processes between the trained and untrained experimental conditions.

Future Directions

Despite the findings reported in this dissertation, a number of important questions remain about the mechanisms of top-down influences on temporal learning. In chapter 2, we hypothesized that stimulus and task parameters play a role in the degree of learning generalization to untrained conditions, but did not speculate about the precise mechanism underlying this specificity. One possibility is that TPL enhances the post-synaptic readout of bottom-up units which could be accomplished for example, through selective reweighting of a centralized circuitry. This view would predict generalization if the optimal stimulus-response weighting relationship is consistent across tasks, and specificity otherwise. Another possibility discussed by Amitay and colleagues (2014) suggest that perceptual learning reflects a noise-reduction process ranging from the lowest level of processing, to the highest. Therefore, learning can be both a sensory and non-sensory phenomenon, depending on the locus of greatest noise.

In addition, the precise involvement of the right IPC in temporal discrimination learning was not tested directly in the present research. Converging evidence from neuroimaging and TMS studies indicate a lateralization of the parietal lobe for the processing of time (Bueti, Bahrami, & Walsh, 2008; Hayashi et al., 2013). For example, TMS over the right posterior parietal cortex have been shown to significantly impair temporal judgments, whereas no similar impairments were found when the TMS site was localized to the left parietal cortex (Alexander, Cowey, & Walsh, 2005). Moreover, TMS over the right parietal cortex has also been shown to improve temporal discrimination accuracy (Oyama, Ishibashi, & Iwanaga, 2017) and facilitate repetitive duration judgments in the visual modality (Hayashi et al., 2015). These studies are consistent with the idea that the right parietal lobe acts as an amodal representation hub for time, and part of a more generalized magnitude system, responsible for the processing and integration of temporal, spatial, and numeric information (Bueti & Walsh, 2009; Walsh, 2003). The study outlined in chapter 3 is consistent with this view, and in addition, highlight a neurochemical involvement of the IPC in temporal discrimination. However, further research is necessary in exploring the exact role of the parietal lobe in TPL, and its interaction with other, related cortical areas.

Concluding Remarks

In conclusion, the present dissertation provides evidence in support of a two-stage model of TPL whereby a combination of low-level refinements in stimulus representation and high-level optimizations of task-relevant behaviors collectively contribute to successful learning of temporal discrimination. It is important to note that the purpose of this research is not to claim that TPL relies *exclusively* on high-level processes, or that low-level changes are neither necessary nor involved in the learning process. Instead, the goal is to highlight the importance of nontemporal processes in TPL. The precise nature of the interaction between, and relative contributions of low- and high-level mechanisms is beyond the scope of this dissertation and remains to be elucidated by further research. We simply note here a functional improvement extending beyond the sensory stage of temporal processing. The results of this work therefore sets the ground for constructing a unifying theory of perceptual learning within and across modalities, and provides key insights into the mechanism underlying temporal perception.

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