READINESS TO LEARN: CHARACTERISTICS ASSOCIATED WITH IMPLICIT LEARNING APTITUDE

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ABSTRACT

Cognitive frailty is one of the biggest threats to healthy aging, and yet our basic understanding of cognitive aging is limited in at least two ways. First, while group differences in the cognitive performance of younger vs. older adults are well-documented, we understand little about the inter-individual variability occurring within age groups, which implies that some individuals are aging more successfully than others in the cognitive domain. Additionally, most cognitive aging research to date has focused on explicit cognitive functions and has neglected an entire subclass of implicit functions that have implications for maintaining health.

To begin addressing these limitations, this dissertation examined characteristics related to implicit learning aptitude. The first study showed that a neural characteristic—the strength of intrinsic connectivity between two learning-relevant brain regions (caudate and medial temporal lobe; MTL)—predicted how well young adults subsequently learned a complex regularity. This finding suggests that communication between learning-relevant regions prior to learning is important for understanding inter-individual variability in learning outcomes. The second study examined a behavioral characteristic—dispositional mindfulness—and revealed a novel negative relationship between mindfulness and implicit learning in two healthy adult samples, suggesting that mindfulness may not benefit implicit cognitive functioning. We posited that the negative association between these two variables might be due to the fact that the balance of
neural systems supporting mindfulness is not optimal for supporting implicit learning. The final study tested this hypothesis by examining how the connectivity of learning-relevant regions during learning related to individual differences in both learning and dispositional mindfulness in a sample of healthy older adults. Results showed that stronger connectivity between the caudate and MTL was positively related to implicit learning, and negatively related to mindfulness. Further, the strength of this connectivity mediated the relationship between mindfulness and learning, suggesting that this might be the neural mechanism by which mindfulness impairs this cognitive process. Taken together, the findings advance our understanding of which behavioral and neural characteristics are related to individuals’ propensity, or “readiness”, to acquire complex regularities implicitly, and suggest that such characteristics might modulate the complex interaction between learning systems.

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CHAPTER I: GENERAL INTRODUCTION

Both as a nation and as a world we are in the midst of an unprecedented demographic shift. By the year 2040 the world’s population aged 65 or older is projected to increase by 160 percent, and for the first time in history there will be more adults than young children in many developed countries (Kinsella & Wan, 2008). Consequences of this demographic shift include not only increases in the number of adults with Alzheimer’s disease and other age-related pathologies, but also increases in the number of people experiencing normal age-related cognitive declines. Cognitive frailty is therefore one of the biggest threats to successful aging that we face as a society. Understanding healthy cognitive aging will better enable us to design more effective strategies and policies to promote productivity and functional independence in old age, allowing us to maximize quality of life and to capitalize on the wisdom and resources this growing age demographic could offer to society.

Recent reviews in the cognitive neuroscience of aging paint a sobering picture of the trajectory of cognitive functioning across adulthood, even over the course of healthy aging (Hartshorne & Germine, 2015; Park & Reuter-Lorenz, 2009; Salthouse, 2010). Indeed, the overwhelming theme appears to be that of decline (e.g., in working memory, processing speed, long-term memory, inhibitory control), though a few cognitive functions (e.g., world knowledge) are consistently shown to plateau or slightly improve across adulthood. While the existing studies have provided valuable information about when/where cognitive functioning might be spared and impaired in adulthood, our understanding of healthy cognitive aging is still limited in at least two important ways.

First, the most popular approach to studying cognitive aging involves comparing
the average performance of groups of different ages. Group-level approaches, while informative, obscure the fact that some older adults perform just as well as, if not better, than their younger counterparts, indicating that age may simply be a proxy for other changes taking place over time, such as changes in the structure and functioning of brain regions, the rates of which vary across individuals (N. Raz & Rodrigue, 2006). Clarifying why some individuals are aging more successfully than others in the cognitive domain could therefore hold the key for promoting and maintaining cognitive functioning for those who are not. Thus, while the studies in this dissertation are motivated from a cognitive aging perspective and will include groups of younger and older adults, they all focus on examining the wide range of variability in cognitive performance occurring within these age groups.

Second, the majority of research in the field of cognitive aging has focused on explicit cognitive functions, or those that are goal directed and occur with conscious awareness. Explicit processes are clearly important, as it can be quite noticeable and problematic for everyday functioning when these functions (e.g., working memory, inhibitory control) decline in the course of healthy aging, or are impaired in certain clinical groups. However, our cognitive architecture, or the set of mental processes that enables us to behave adaptively and efficiently in our environment, also includes a body of implicit cognitive functions, or those that occur without goal-directed intent or conscious awareness. Although these implicit processes operate unbeknownst to us (i.e., beneath the surface of conscious awareness), they have important influences on our everyday functioning and overall health (e.g., environmental adaptation, developing habits and aversions; Wyer, 2014). Thus, they too are important to understand both in
terms of their typical developmental trajectories, as well as what can be done to maintain and promote them across adulthood. **This dissertation focuses on implicit cognitive processes, more specifically on implicit learning.**

**Implicit learning & implicit probabilistic sequence learning (IPSL)**

Throughout life, we acquire an impressive body of knowledge, procedural skills, and behavioral repertoires, enabling us to respond adaptively and efficiently to our complex environment. Luckily, this lifetime of knowledge and skill does not accumulate entirely through explicit learning, or that which occurs with conscious intent and awareness. Instead, we “soak up” some of it, without conscious awareness or intent, through a cognitive process called implicit learning (A. S. Reber, 1989).

*Implicit probabilistic sequence learning* (IPSL) is a special type of implicit learning, which involves becoming sensitive to complex environmental regularities that occur across time, or in sequences of events (C. A. Seger, 1994). Our ability to acquire and exploit environmental regularities in this way influences how effectively and efficiently we perform a variety of complex functions, including learning languages, developing new procedural skills and habits, and engaging in effective social interactions (Lewicki, Czyzewska, & Hoffman, 1987; Newport & Aslin, 2004; Wyer, 2014). Further highlighting the importance of IPSL for vital everyday functioning, symptoms of developmental disorders, such as dyslexia, have been linked to deficits in IPSL (e.g., Bennett, Romano, Howard, & Howard, 2008; James H. Howard, Howard, Japikse, & Eden, 2006; Jiménez-Fernández, Vaquero, Jiménez, & Defior, 2011). There is also evidence that IPSL declines in healthy aging (J. H. Howard Jr & Howard, 2013; Rieckmann & Bäckman, 2009; Stillman, Howard, & Howard, 2014), and that these
declines contribute to deficits in other, higher-order cognitive processes such as decision making (Mata, Josef, Samanez-Larkin, & Hertwig, 2011). Therefore, the things we learn when we aren’t consciously trying to learn (e.g., how to read, use a new cell-phone, make complex decisions) can influence the quality of our daily lives and enable independent living, making IPSL and the factors related to individual differences in the ability to learn in this fundamental way, an important topic for empirical investigation.

Traditionally, implicit types of learning and memory were thought to be spared in aging. This theory was built on the evolutionary reasoning that implicit functions are phylogenetically older than explicit functions and therefore should be more resilient to neurological insult due to aging, injury, and/or disease (A. S. Reber, 1992). Based on this same reasoning, implicit functions were also posited to show little inter-individual variability compared to explicit functions. However, there is now growing evidence that implicit learning, including IPSL, does indeed change with age and, as with explicit cognitive processes, there is a great deal of inter-individual variability in performance within age groups on IPSL tasks (J. H. Howard Jr & Howard, 2013; Janacsek, Fiser, & Nemeth, 2012). Perhaps due to the persistence of the traditional views about implicit processes, however, little is known about the underlying characteristics that might distinguish “good” from “bad” implicit learners—that is, what traits make some people better equipped to learn in this complex, non-conscious way than others? The studies reported in the following chapters investigate two such factors related to individual differences in IPSL aptitude, one neural (intrinsic functional connectivity) and the other behavioral (dispositional mindfulness).
Measuring IPSL

To measure IPSL in the laboratory, participants complete tasks where they are exposed to a series of stimuli in which a complex, probabilistic regularity is embedded, such that some sequences of stimuli occur more frequently than others. Although they are not told that there is a regularity, subjects become sensitive to it with practice, responding faster to more predictable than to less predictable events. Learning in these tasks is most often operationalized as a reduction in reaction time to high probability compared to the low probability events. In addition, the learning of this probabilistic information is often characterized as implicit in that, on subsequent recognition tasks, people are unable to distinguish between events that occurred more or less frequently during the task (J H Howard Jr., Howard, Dennis, & Kelly, 2008; Simon, Howard, & Howard, 2011) and cannot verbalize the predictive relationships amongst stimuli, even when asked increasingly leading interview questions about the task they just completed (e.g., Bennett, Howard, & Howard, 2007).

The original IPSL task, which is still widely used today, is the Serial Reaction Time Task (SRT; Nissen & Bullemer, 1987). In this task, participants make motor responses to denote the location of events (usually circles on a computer screen that fill in sequentially). The events follow a pre-determined repeated pattern in some blocks of trials and occur randomly in others. Participants eventually become sensitive to predictive relationship amongst the stimuli on the repeated blocks and respond faster than they do on random blocks. One limitation of the SRT is that the blocked arrangement of the repeated vs. random stimuli results in many participants becoming explicitly aware of the pattern, and some can subsequently use their explicit knowledge to improve their task
performance (Dennis, Howard, & Howard, 2006)—often called “explicit contamination”. Moreover, participants from some groups (e.g., younger adults) are more likely to become explicitly aware than those from others (e.g., older adults). **The studies presented in this dissertation avoid this particular limitation of the SRT by assessing IPSL using two SRT variants: the Alternating Serial Response Time Task (J. H. Howard Jr. & Howard, 1997) and the Triplets Learning Task (TLT; J. H. Howard Jr., Howard, Dennis, & Kelly, 2008).** The specifics of how these tasks differ from the original SRT are described in Chapters III and IV of this dissertation. In brief, one major benefit of using the ASRT and TLT as opposed to the SRT is that virtually no one becomes aware, reducing the possibility that individual differences observed in learning are due to differences in the ability to acquire explicit knowledge of the task regularity, rather than IPSL ability, the cognitive process of primary interest.

**The neural basis of IPSL**

Evidence from several distinct lines of research indicates that IPSL in the TLT and ASRT is supported by a core network of brain regions including the caudate, medial temporal lobes (MTL), and frontal cortices.

**The caudate & IPSL.** The striatum (especially the caudate) appears to play a central role in IPSL. First, IPSL is often reduced in Parkinson’s Disease and in other clinical disorders characterized by striatal dysfunction (Gamble et al., 2014; J. G. Smith & McDowall, 2004; Wilkinson, Khan, & Jahanshahi, 2009). Second, allelic differences in one gene regulating dopamine, a primary neurotransmitter in the dorsal striatum, are associated with individual differences in IPSL on the TLT in healthy adults (Simon, Stollstorff, et al., 2011). Third, fMRI studies of healthy younger and older adults during
IPSL tasks, including the TLT, have shown activation of the caudate (Gheysen, Van Opstal, Roggeman, Van Waelvelde, & Fias, 2011; Rieckmann, Fischer, & Bäckman, 2010; Rose, Haider, Weiller, & Büchel, 2002; Schendan, Searl, Melrose, & Stern, 2003; Simon, Vaidya, Howard, & Howard, 2012), as well as several other regions described in more detail below.

**The medial temporal and frontal lobes & IPSL.** In addition to the well-established role of the caudate in IPSL, a growing number of fMRI studies in both young and older adults have reported activation of the medial temporal lobes (MTL, especially hippocampal and parahippocampal gyri), and regions in the frontal lobes such as the dorsolateral prefrontal cortex (DLPFC), as well as primary, supplementary, and premotor areas during IPSL tasks (Rose et al., 2002; Schendan et al., 2003; Simon et al., 2012), suggesting that these regions may also contribute to IPSL.

**Interactions between brain regions.** While these regions may all be coactive during the task, the pattern of interaction between two specific regions in this network, the caudate and MTL, differs between young and older adults and has been linked to individual and group differences in learning. In young adults, the MTL is most active during the early stages of training, and the task-related activity of this region decreases over the course of the task. In contrast, the caudate is gradually engaged throughout training for younger adults, becoming more important in later stages of training (Rieckmann et al., 2010; Schendan et al., 2003; Simon et al., 2012). In older adults, however, MTL contributions are associated with better learning performance in all stages of training (Rieckmann et al., 2010; Simon et al., 2012), which has been proposed to reflect age-related declines in the structural and functional integrity of the striatum,
especially in the caudate (N. Raz et al., 2003; van Dyck et al., 2002). These age
differences in recruitment of the caudate and MTL, often considered to be compensatory
in older adults, may thus be indicative of decreased integrity/efficiency of communication
within the neural network supporting IPSL, explaining why older adults, on average,
attain a lower magnitude of learning, particularly late in training, compared to their
younger counterparts. Thus, it seems likely that an altered (and perhaps less efficient)
pattern of interaction/communication between the caudate and MTL may underlie age-
related deficits in IPSL.

Few fMRI studies of IPSL have focused on the functional communication between
task relevant brain regions and its potential relationship to learning outcomes. However,
there is some evidence supporting that communication between the caudate, MTL, and
frontal regions is important for IPSL. In a recent DTI study, for example, Bennett and
colleagues (2011) found that the integrity of white matter tracts connecting the caudate
and the hippocampus to the DLPFC predicted the magnitude of older and younger
individuals’ IPSL in the ASRT. Furthermore, post hoc tests showed that the integrity of
the caudate-DLPFC tract fully mediated age differences in IPSL performance (Bennett et
al., 2011). Together, these findings suggest that healthy adults differ in how well they
learn sequences of events implicitly, and this inter-individual variability is not necessarily
due to age, but rather is associated with individual differences in the functional and
structural integrity of brain regions in a core, task-relevant neural network comprised of
the caudate, MTL, and regions in the frontal lobe (e.g., DLPFC). One open question,
therefore, is whether states/traits known to influence the interaction between regions in
this task-relevant network relate to individual differences in IPSL.
Resting State Functional Connectivity

One characteristic that might relate to IPSL aptitude is the degree of functional communication between task-relevant brain regions, not only during IPSL tasks, but also in the time period prior to the task. This is because patterns of brain activity observed during a task-free state (termed intrinsic or resting state functional connectivity; rsFC) have been observed to mirror the patterns of brain activity observed during tasks (S. M. Smith et al., 2009). This intriguing property of the resting brain was first discovered in a landmark study by Biswal (1995) in which “spontaneous” fluctuations of the BOLD signal in the left somatosensory cortex were observed to correlate with the spontaneous BOLD fluctuations in both the right somatosensory cortex and medial motor areas in subjects who were simply resting between task blocks in the scanner. Interestingly, these same areas were coactivated while the same subjects were performing a simple motor tapping task, suggesting that neural regions that “work together” during cognitive tasks maintain their network configuration during rest (for review see Fox & Raichle, 2007).

Since Biswal’s groundbreaking study, other groups have replicated this finding (e.g., Lowe, Mock, & Sorenson, 1998; Xiong, Parsons, Gao, & Fox, 1999), and have extended it to show that rsFC relates to individual differences in performance on other, more complex cognitive tasks, such as those assessing working memory (Hampson, Driesen, Skudlarski, Gore, & Constable, 2006) and reading competence (Koyama et al., 2011). The fact that rsFC accounts for inter-individual variability in behavior, suggests that the efficiency of task-evoked interactions between brain regions during cognitive tasks may be related to the ability of these regions to maintain their functional
organization at rest (Biswal et al., 1995; Gordon, Stollstorff, & Vaidya, 2012; S. M. Smith et al., 2009).

**Measuring rsFC.** In what is now the typical procedure for measuring rsFC, study participants are instructed to remain awake in the scanner with their eyes either closed, or open and focusing on a fixation cross. They are also told to refrain from thinking of anything in particular. Their brain activity is then recorded in this unconstrained state, as opposed to the goal-directed state elicited when people are attempting to comply with the instructions of a particular cognitive task. The rsFC between two (or more) brain regions is calculated by assessing the degree of temporal correlations in the spontaneous activity of these regions in a non-goal-directed, resting state (Biswal et al., 1995). Regions with higher FC are thought to be more strongly functionally related during the time of measurement than regions with lower functional connectivity.

**rsFC and Learning.** Several recently discovered properties of resting networks suggest that rsFC may be particularly relevant for understanding individual differences in learning. One property, which has been the focus of most resting state studies on learning, is that resting networks are sensitive to past experience; that is, the strength of rsFC in specific networks, measured following learning, is associated with individual differences in learning performance. For example, relative to a pre-learning scan rsFC was altered (either increased or decreased) between task-relevant regions following training on visual discrimination (Lewis, Baldassarre, Committeri, Romani, & Corbetta, 2009), motor learning (Albert, Robertson, & Miall, 2009; Vahdat, Darainy, Milner, & Ostry, 2011), and virtual route learning tasks (Wegman & Janzen, 2011). Crucially, across all these studies, the amount of change in rsFC between regions within task-
relevant networks following training was correlated with learning outcomes, such that individuals who had exhibited superior performance on the preceding task tended to have the greatest changes in rsFC (either increases or decreases) from a pre- to post-learning resting scan. Such modulation of resting state networks by past learning experience might therefore reflect individual differences in neural plasticity associated with the consolidation of recently learned information (Albouy et al., 2008).

Another learning-relevant property of resting state networks is that the strength of neural connections at rest can predict subsequent learning and memory performance. For example, rsFC between task-relevant regions predicted subsequent performance on a free recall test (Wang et al., 2010), on recognition of face-name pairs, and on the Wechsler Memory Scale and the California Verbal Learning Test, two standardized measures of episodic memory ability (Wang et al., 2010; Ystad, Eichele, Lundervold, & Lundervold, 2010). Thus, there is mounting evidence that individual differences in memory performance are related to the baseline strength of resting state networks. Since the strength of network connectivity is thought to arise from repeated coactivation of brain regions over one’s lifetime (Dosenbach et al., 2007) and to be highly reliable (Zuo et al., 2010), these studies raise the intriguing possibility that rsFC can be used as a biomarker of one’s preparedness to learn and retain information.

What’s missing. Although there is accumulating evidence that rsFC is a promising tool for better understanding individual and age differences in IPSL performance, there are some gaps in our current understanding. In all of the existing studies relating baseline rsFC to subsequent learning performance: (1) task material was deterministic (as opposed to probabilistic) in nature, (2) learning of material was assessed after-the-fact via a
memory test, and (3) subjects were explicitly instructed to remember the task material for a later test. The study presented in Chapter II is the first to show that baseline communication (i.e., rsFC) between IPSL-relevant regions can predict performance on an implicit, probabilistic learning task in which subjects are not explicitly informed of the task goals and are ultimately unable to verbalize the subtle regularities they have acquired.

Mindfulness

In addition to neural characteristics of individuals (i.e., strength of their intrinsic connectivity networks), certain behavioral characteristics may also relate to IPSL aptitude. There is reason to suspect that mindfulness may be one such characteristic. Mindfulness refers to the ability to stay attentive and receptive to events and experiences taking place in the present, and to therefore disengage from habitual actions and thought tendencies (Brown & Ryan, 2003). An important distinction in the mindfulness literature is that there are different uses of the term “mindfulness”. For example, dispositional mindfulness refers to naturally occurring variation among individuals in their propensity for mindfulness, i.e., trait mindfulness. In contrast, mindfulness can also be cultivated through targeted training. For reasons discussed below, the studies reported in Chapters III and IV of this dissertation focused on the relationship between dispositional mindfulness and IPSL. However, evidence from mindfulness training studies is useful from a theoretical standpoint, as it provides the critical causal link between mindfulness and certain, key changes in emotional, cognitive and brain functioning that might be important for understanding individual differences in IPSL.
Measuring mindfulness. Mindfulness is most often measured in the laboratory using self-report scales. The most widely used to date is the Mindful Attention Awareness Scale (MAAS; Brown & Ryan, 2003). The MAAS is a single factor, self-report questionnaire designed to assess the ability to focus on experiences taking place in the present. The questionnaire contains 15 items, and participants rate on a 6-point Likert scale (1=almost always to 6=almost never) how often they experience each item on a day-to-day basis (e.g., “I break or spill things because of carelessness, not paying attention, or thinking of something else”, “I do jobs or tasks automatically, without being aware of what I’m doing”, “I break or spill things because of carelessness, not paying attention, or thinking of something else”). The questionnaire is scored by averaging participants’ responses across all items, so possible mindfulness scores range from 1 to 6. Higher scores indicate higher mindfulness. The MAAS has been validated using a variety of subject populations, including healthy younger and older adults (e.g., Brown & Ryan, 2003; Shaurya Prakash, De Leon, Klatt, Malarkey, & Patterson, 2012), and has been shown to have good psychometric properties—e.g., individuals generally receive the same score on the scale over repeated assessment, scores can reliably distinguish individuals engaged in targeted mindfulness practice from others, and scores correlate with, yet are distinct from, other relevant psychological constructs (Brown & Ryan, 2003; Carlson & Brown, 2005; S. Evans et al., 2008; Levinson, Stoll, Kindy, Merry, & Davidson, 2014; MacKillop & Anderson, 2007)

Cognitive/emotional functioning & mindfulness. Individual differences in dispositional mindfulness are associated with enhanced emotional and cognitive functioning. For example, people scoring higher in mindfulness report fewer symptoms
of anxiety and depression, lower levels of negative affect, and higher life satisfaction (Brown & Ryan, 2003; Keng, Smoski, & Robins, 2011). In the cognitive domain, dispositional mindfulness has been associated with better inhibitory control, decreased impulsivity, and better sustained attention, all abilities implicated in a group of functions known as “executive” cognitive functions (Oberle, Schonert-Reichl, Lawlor, & Thomson, 2011; Peters, Erisman, Upton, Baer, & Roemer, 2011; Schmertz, Anderson, & Robins, 2009).

One leading hypothesis is that the emotional and cognitive outcomes linked to mindfulness are not distinct from each other, but rather are tightly interwoven. For example, people with better explicit/executive cognitive abilities may be better equipped to regulate their emotions in challenging situations and to avoid certain maladaptive tendencies (e.g., rumination), thereby making them less vulnerable to psychological maladies and maladaptive behaviors (Coffey & Hartman, 2008; Mauricio R. Delgado, Nearing, LeDoux, & Phelps, 2008; Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008). Correlational studies of mindfulness therefore suggest that individuals’ propensity to be more/less mindful is related to their cognitive abilities (and related emotional health outcomes). Of course, one major limitation of correlational evidence is that it is not possible to infer that mindfulness caused these beneficial emotional and cognitive outcomes.

Training studies of mindfulness have provided the critical causal link between mindfulness and cognitive and emotional functioning. Studies comparing the outcomes of mindfulness-based training studies to various matched control groups have shown improvements in the same emotional and cognitive domains implicated in the
correlational studies. For example, mindfulness training has been shown to be an effective treatment for a wide range of clinical disorders, including depression and anxiety (Kim et al., 2009; Teasdale et al., 2000; Treanor, 2011). In healthy adults, mindfulness training also improves performance on a similar set of cognitive functions to those shown to be positively correlated with dispositional mindfulness, including inhibitory control and executive attention (Allen et al., 2012; N. D. Anderson, Lau, Segal, & Bishop, 2007; A. Jha, Krompinger, & Baime, 2007). Together, these training studies suggest that mindfulness can alter cognitive functioning and interwoven mental health outcomes in both healthy and clinical populations.

**Mindfulness and the brain.** A growing number of neuroimaging studies suggest that the cognitive and emotional health benefits linked to mindfulness are induced by changes in the structure and functioning of specific brain regions, many of which overlap with those in the core network supporting IPSL (i.e., caudate, MTL, and prefrontal regions). More detail on the neural mechanisms of mindfulness as it relates to IPSL will be provided in Chapters III and IV. Briefly, the majority of the evidence suggests that mindfulness exerts its beneficial effects on emotional and cognitive processes by upregulating both the structure and functioning of prefrontal brain regions involved in executive control (Tang, Hölzel, & Posner, 2015). Mindfulness training has also been shown to downregulate the functioning of some subcortical structures, including the striatum (Kirk, Brown, & Downar, 2014), but to upregulate others, particularly the hippocampus (K. C. R. Fox et al., 2014; Holzel et al., 2011; Tang et al., 2015).

Critically, the training-induced changes in the brain have been linked to *increases* in executive types of functions supported by prefrontal regions (Allen et al., 2012). They
have also been linked to reductions in habitual/automatic types of processes supported by striatal regions (e.g., caudate), such as consumption of addictive drugs and cue-related cravings (Garland, Froeliger, & Howard, 2014; Tang, Tang, & Posner, 2013). These findings suggest that mindfulness-related brain changes influence executive and habitual types of functions in opposing ways.

**What’s missing.** This dissertation addresses several important open questions in the mindfulness literature. One question is whether basic, implicit types of cognitive functions, or those that occur without goal-directed intent, relate to mindfulness. Few studies have included implicit lab-based tasks in their protocols (but see Whitmarsh, Uddén, Barendregt, & Petersson, 2013). Given the seemingly antagonistic relationship between cognitive functions supported by prefrontal regions (e.g., executive functions) and behaviors supported by the caudate (e.g., rumination, habits, addictions), it seems plausible that people’s propensity to engage in implicit functions might be negatively related to their propensity for mindfulness. **The study in Chapter III is the first to show that dispositional mindfulness negatively relates to IPSL performance.**

Another open question stems from the fact that most investigations of the neural basis of mindfulness have come from mindfulness training studies, or from cross-sectional studies comparing expert and novice meditators. However, it’s becoming increasingly clear that dispositional mindfulness and the process of cultivating it may in fact be very different (Davidson, 2010). For example, a recent study of dispositional mindfulness reported a negative correlation between mindfulness and caudate and hippocampus volumes (Taren, Creswell, & Gianaros, 2013), but both of these regions have been shown to increase in structure and function following mindfulness training.
(Holzel et al., 2011; Pickut et al., 2013), though there are mixed findings within the training literature as well (e.g., Kirk & Montague, 2015; Westbrook et al., 2013). Discrepancies such as these highlight the need to more fully characterize the neural correlates of dispositional mindfulness. **Chapter IV represents one step towards this goal; it is the first to show that connectivity of the caudate, a region central to IPSL aptitude (Chapter II), mediates the negative relationship between dispositional mindfulness and IPSL reported in Chapter III.**

**Overview of Chapters**

The chapters examine neural (Chapter II) and behavioral (Chapter III) traits related to IPSL aptitude, as well as the mechanisms by which they might relate to each other (Chapter IV).

*Chapter II: Can IPSL aptitude be predicted by intrinsic connectivity?*

*The goal of this chapter is to examine whether a neural characteristic of individuals, namely their resting state functional connectivity (rsFC), relates to IPSL aptitude.* Previous studies have demonstrated that the strength of rsFC between task-relevant regions can predict individual differences in cognitive performance suggesting that rsFC can be used as a biomarker of one’s *preparedness* to learn and retain information. However, so far no studies of rsFC have tested whether it can predict performance on implicit tasks in which subjects are not explicitly informed of the task goals and are ultimately unable to verbalize the subtle regularities they have acquired. In addition, the majority of fMRI studies of IPSL have focused on activation, and not on the communication between task-relevant regions. Thus, Chapter II addresses open questions
in both the rsFC and IPSL literatures by examining how the intrinsic functional connectivity of a region known to be central to IPSL (the caudate) relates to subsequent individual differences in IPSL performance.

Chapter III: Can IPSL aptitude be predicted by one’s propensity for mindfulness?

The goal of this chapter is to examine how mindfulness, a behavioral trait previously linked to cognitive functioning, relates to IPSL. As mentioned above, both dispositional mindfulness and mindfulness training have been linked to better performance on tasks measuring executive functioning. While there are hints from mindfulness training studies that mindfulness may actually impair habitual-types of behaviors, this hypothesis has so far not been tested directly because implicit cognitive tasks are rarely included in study protocols (but see Whitmarsh et al., 2013). Thus, the study reported in Chapter III addresses one major limitation of the existing mindfulness literature by testing how dispositional mindfulness relates to individual differences in the ability to implicitly acquire complex, sequential regularities.

Chapter IV: Does functional connectivity mediate the relationship between mindfulness and IPSL?

The final chapter of this dissertation has three goals. The first goal is to examine how functional connectivity of the caudate during IPSL relates to individual differences in learning outcomes (thus, extending the results of Chapter II). The second goal is to replicate the negative relationship between dispositional mindfulness and IPSL reported in Chapter III. Finally, the third goal is to examine whether functional connectivity of the caudate also relates to dispositional mindfulness and whether it
mediates the relationship between mindfulness and learning. In comparison to studies focused on elucidating the neural changes that occur following mindfulness training, few studies have examined the neural correlates of dispositional mindfulness. Thus, Chapter IV addresses another major limitation of the mindfulness literature, while also providing additional insight as to how the neural and behavioral traits examined in the previous Chapters relate to each other.
CHAPTER II: CAUDATE RESTING CONNECTIVITY PREDICTS IMPLICIT PROBABILISTIC SEQUENCE LEARNING


Introduction

Implicit learning refers to the effortless acquisition of information without explicit knowledge of what has been learned (A. S. Reber, 1989). Implicit probabilistic sequence learning (IPSL) is a specific type of implicit learning that involves extracting statistical regularities from sequences of events, a skill crucial for important life skills such as learning languages or developing new routines (Lewicki et al., 1987; Newport & Aslin, 2004). Here we focus on how the intrinsic functional communication among neural regions known to underlie IPSL relates to individual differences in learning performance.

To accomplish this we used the Triplets Learning Task (TLT; J. H. Howard Jr. et al., 2008). In the TLT, as in more traditional sequence learning tasks like the Serial Reaction Time (Nissen & Bullemer, 1987) and Alternating Serial Reaction Time (J. H. Howard Jr. & Howard, 1997) tasks, participants are exposed to a series of stimuli in which a probabilistic regularity is embedded, such that some sequences occur more frequently than others and therefore, some events are more predictable from prior events than others. During the task, subjects learn the regularity, responding increasingly faster to more predictable versus less predictable events, even though they are unable to distinguish between predictable and unpredictable events in subsequent recognition tests.
The TLT allows for precise control of event timing and reduces motor-response sequencing, enabling us to examine implicit learning uninfluenced by motor fluency.

Evidence from studies using a variety of methods (including patient groups, DTI, task-related fMRI, and genetics) indicates that IPSL in the TLT and related sequence learning tasks depends upon the functional and structural integrity of a subcortical-cortical network including the caudate, medial temporal lobes (MTL), and frontal cortices (Bennett et al., 2011; Gheysen et al., 2011; Rieckmann et al., 2010; Rose et al., 2002; Schendan et al., 2003; Simon, Stollstorff, et al., 2011; Simon et al., 2012; J. G. Smith & McDowall, 2004; Wilkinson et al., 2009). While frontal regions are thought to support the attentional and motor-planning demands of IPSL tasks, the caudate and, more controversially, the MTL are thought to underlie the formation of associations necessary for learning in the tasks (Curran, 1997; Schendan et al., 2003; Simon et al., 2012). These latter regions are the focus of the present study.

The fact that the caudate and MTL, regions once thought to subserve distinct and functionally incompatible learning systems (e.g., Robbins, 1996; Squire, 1987), are often coactivated in implicit sequence learning tasks suggests that optimal sequence learning performance may depend on the efficiency of their interaction (Henke, 2010). Efficient caudate/MTL interaction—whether competitive or cooperative during IPSL tasks—may be facilitated by their ongoing communication not only during IPSL tasks, but also during a task-free state. Patterns of temporally correlated brain activity during a task-free state (termed intrinsic, or resting state functional connectivity; rsFC) often mirror the brain
activation patterns observed during cognitive tasks (S. M. Smith et al., 2009), suggesting that functional networks during cognitive tasks maintain their network configuration during rest (for review see M. D. Fox & Raichle, 2007). Specifically, brain regions that share a similar functionality tend to be positively correlated in their spontaneous resting state activity, whereas regions having opposing functionality tend to be negatively or anticorrelated at rest.

Close correspondence between task-evoked and resting functional networks also suggests that individual differences in network function in the resting state should be associated with learning performance. Indeed, rsFC of task-relevant networks relates to individual differences in the consolidation of learned information, such that individuals who had exhibited superior performance on a preceding learning task displayed the greatest changes in rsFC from a pre- to post-learning resting scan (e.g., Albert, Robertson, & Miall, 2009; Vahdat, Darainy, Milner, & Ostry, 2011; Wegman & Janzen, 2011). In addition, the baseline (i.e., pre-task) strength of rsFC in task-relevant networks can predict individual differences in subsequent learning and memory performance, whereby individual differences in the strength of specific resting state networks relates to learning and memory ability (Baldassarre et al., 2012; Gordon, Devaney, Bean, & Vaidya, 2015; Wang, LaViolette, et al., 2010; Wang, Negreira, et al., 2010; Ystad, Eichele, Lundervold, & Lundervold, 2010). No studies so far, however, have examined whether rsFC can predict learning performance when subjects aren’t explicitly informed of task goals and are learning probabilistic relationships that they cannot verbalize.

Here, we investigate whether individual differences in IPSL can be predicted by the rsFC of a task-relevant region, the caudate. We measured rsFC of a bilateral caudate
seed either prior to learning or well outside the timeframe when consolidation processes might be expected to influence intrinsic connectivity patterns. We then correlated rsFC with sequence learning performance, as well as with average response speed on the TLT. Our primary interest was in the relationship between rsFC and sequence-specific learning, but we examined average response speed to test whether the striato-cortical networks supporting sequence-specific learning are distinct from those supporting other aspects of task performance. We examined whole-brain caudate connectivity but were particularly interested in correlations between the caudate and MTL, given evidence that these regions share a functional role in sequence learning in healthy populations (Rieckmann et al., 2010; Simon et al., 2012); we hypothesized that greater positive correlations in the spontaneous activity of these regions at rest would predict better sequence learning, but not response speed.

**Method**

**Subjects**

Twenty-two Georgetown University undergraduates (14 female) ages 18 to 22 years ($M \pm SD = 20.43 \pm .98$) participated for payment. They were recruited from a pool of 50 subjects in an unrelated experiment in which resting state scans were acquired. As a result of this recruitment procedure, behavioral testing occurred a varying number of days (17-367 days; $M \pm SD = 96 \pm 102$ days) after the resting state scan. In addition, two subjects who had completed behavioral testing 179 and 542 days before the resting state scan were retained because the long delay made it highly unlikely that learning-related consolidation influenced their resting state connectivity. Correlational analysis confirmed that the time between the scan and behavioral testing was unrelated to the behavioral
measures. Furthermore, our results did not change when these two subjects were removed.

Procedures were approved by Georgetown University’s Institutional Review Board. Exclusion criteria included 1) self-reported use of psychotropic medication (e.g., stimulants, anti-anxiety/depression); 2) self-reported history of neurological injury or disease, seizure disorder, psychiatric diagnosis; 3) contraindications for MRI – e.g., metal implants in the body, or pregnancy.

**Behavioral testing**

Subjects completed the TLT (J. H. Howard Jr. et al., 2008) on a separate test day either following \( N = 20; M \pm SD = 96 \pm 102; \) ranging from 17-367 days) or preceding \( N = 2; M \pm SD = 360 \pm 256 \) days) the scanning session. A schematic of the TLT is shown in Figure II-1. Subjects viewed a horizontal row of four open circles centered on a computer screen. On each trial, a three-event sequence of circles called a “triplet” filled in sequentially red, red, and then green. Subjects were instructed to observe the first two red “cues” and to indicate the location of the green “target” by pressing a spatially corresponding response button as quickly as possible with their right hand. Cues were displayed one after the other for 120ms each (150ms interstimulus interval) and were followed by the target, which remained in view until participants made a correct response. The next trial began after a 650ms delay. Repetitions (e.g., 111) and trills (e.g., 121) were not presented because subjects typically respond differently to these types of triplets (e.g., due to motor and perceptual priming or inhibition of return) than to triplets that do not have unique spatial characteristics (Boyer, Destrebecqz, & Cleeremans, 2005; Cleeremans & McClelland, 1991; J.H. Howard Jr. et al., 2008). Unbeknownst to subjects,
the TLT contained a probabilistic regularity such that for a randomly chosen set of 16 triplets the target was likely to follow the cues (High Probability triplets, p = .90) whereas for the remaining 32 triplets the target was unlikely (Low Probability triplets, p = .10) (Simon, Howard, et al., 2011).

Subjects completed 750 trials in approximately 30 minutes. Short breaks occurred after every 50-trial block, during which the subject’s mean reaction time (RT) and accuracy were displayed along with instructions to “focus more on speed”, “focus more on accuracy”, or “speed and accuracy are about right”. The instructions were based on the subject’s mean accuracy for the preceding block of trials and were intended to drive all subjects to a similar level of accuracy (92%).

Calculating Sequence Learning Scores

As in previous studies using the TLT, we used Sequence Learning (SL) Scores, which measure learning unbiased by individual or group differences in overall response time (J. H. Howard Jr. et al., 2008; Simon, Howard, et al., 2011). To determine these scores, median RTs were calculated for all correct responses for each triplet for each subject (overall accuracy in the task was high, ~93%, so we omitted few trials). These median RTs were then correlated with the actual triplet frequencies for that subject. Subjects who show greater sequence-specific learning display greater negative correlations between RT and triplet frequency, since responses are faster to triplets that occur with greater frequency and thus have more predictable targets. For ease of interpretation, the correlations were multiplied by -1 so that higher SL scores reflect greater sequence learning.

fMRI data acquisition
Subjects were scanned for 5:04 minutes during the resting state, in which they were told to relax with eyes closed but to stay awake and to not think of anything in particular. All subjects verbally confirmed that they had remained awake for the duration of the scan. Imaging was performed on a Siemens Trio 3T scanner (Erlangen, Germany). For the resting scan, 152 whole-brain images were acquired using a gradient echo pulse sequence (37 slices, TR = 2000 ms, TE = 30 ms, 192x192mm FOV, 90 degree flip angle, voxel dimensions 3mm isotropic). The first 4 images of this run were discarded to allow for signal stabilization. This scan was followed by acquisition of a high-resolution T1-weighted structural scan (MPRAGE) lasting 4:18 minutes, with the parameters: TR/TE = 2300/2.94ms, TI = 900ms, 90 degree flip angle, 1 slab, 160 sagittal slices with a 1.0mm thickness, FOV = 256x256mm, matrix = 256x256, resulting in an effective resolution of 1.03mm isotropic voxels.

**Image Preprocessing**

Using SPM8 (Wellcome Department of Cognitive Neurology, London, UK) implemented in MATLAB (Version 7.10 Mathworks, Inc., Sherborn, MA), images were corrected for translational and rotational motion by realigning to the first image of the resting state scan. All subjects demonstrated less than 1.0mm of translational motion in any one direction (max translation = .94mm) and less than .5° of rotation around any one axis (max rotation = .35°). As micro-movements have been shown to lead to spurious correlations in previous functional connectivity studies (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012), framewise displacement ($M \pm SD = .18 \pm .08$mm) was included as a regressor of no interest in all group-level analyses reported below, a procedure recommended to reduce motion artifact while preserving the power of the
study’s design and reducing the likelihood of Type II error (Satterthwaite et al., 2012; Van Dijk, Sabuncu, & Buckner, 2012). Images were slice-time corrected, normalized to an EPI template, and smoothed using a Gaussian kernel with full-width at half-maximum of 8mm. For normalization, all functional images for each subject were realigned to the first image using 2\textsuperscript{nd} degree B-spline interpolation. This image was then used as the source image, which was transformed to a standard SPM-EPI template in MNI atlas space available in SPM8. The parameters used to transform the source image to the template were then applied to all functional images. The quality of the registration process was assessed by visual inspection.

Finally, a band-pass filter of .01-0.1 Hz was applied to the data to remove non-neuronal temporal trends and to restrict signal variation to the frequency range established in the literature for fluctuations in resting state data (Biswal, Yetkin, Haughton, & Hyde, 1995).

**Functional connectivity calculation**

**Seed ROI creation.** A bilateral dorsal caudate (DC) seed region of interest (ROI) based on coordinates from Di Martino, et al. (2008) was created using Marsbar (Brett, Anton, Valabregue, & Poline, 2002) as two spheres of radius 6 mm centered around the coordinates [13 15 9] and [-13 15 9]. The seed location is depicted in Figure II-2. Following Di Martino and colleagues, we chose our seed coordinates because they are consistent with findings from a meta-analysis of fMRI and positron-emission tomography human neuroimaging studies (Postuma & Dagher, 2006), which demonstrated that there are functionally distinct anatomical regions within the human striatum. Specifically, dorsal regions of the caudate (defined as those where \( z > 7 \) mm) were found to be more
coactivated with cortical regions involved in cognitive processes, while ventral regions are coactivated with cortical regions underlying limbic and motivational functions. In addition, this seed is consistent with a previous event-related fMRI study using the TLT, which reported greater task-dependent activation in dorsal regions of caudate body in response to sequences occurring with high versus low probability (Simon et al., 2012).

**Nuisance signal identification.** To identify the effects of motion and physiological noise (i.e., respiration, heart rate), time series approximating these signals were calculated for the resting state scan. Physiological noise was approximated by obtaining signal time series from white matter and CSF segmentations of the MPRAGE image (Van-Dijk et al., 2010). Motion was obtained from the six realignment parameter time courses from the motion correction preprocessing step. Global signal regression was not performed as a preprocessing step because studies have shown that this procedure can artificially induce negative correlations in functional connectivity data (Murphy, Birn, Handwerker, Jones, & Bandettini, 2009).

**Voxelwise resting state functional connectivity calculation.** For each subject’s resting state run, partial correlations were conducted between the bilateral DC seed time series and the time series of every voxel in the brain, while partialling out the motion and physiological noise time series. Each subject’s individual connectivity maps were visually inspected in order to confirm that they were not corrupted by motion artifact. The resulting $r$-values were converted to normally-distributed $Z$-scores using Fisher’s transformation to allow further statistical analysis of correlation strengths. This produced a brain map of intrinsic connectivity strength with the DC during rest for each subject.
**Overall connectivity.** We identified overall patterns of connectivity with the DC by entering subjects’ individual connectivity maps into a voxelwise one-sample t-test using SPM8. All group level results were restricted to gray matter using an explicit gray matter mask from the SPM toolbox. Monte-Carlo-based correction for multiple comparisons (Ward, 2000) was carried out using tools implemented in AFNI (Analysis of Functional Neuroimages) software (Cox, 1996). Briefly, we estimated the smoothness of the preprocessed data using the 3dFWHMx utility, and then used the 3DClustSim tool to conduct ten thousand Monte Carlo simulations of random noise activations with that same smoothness, within the same whole brain volume as the primary analyses. These simulations revealed that clusters exceeding both a voxelwise alpha level of \( p < .005 \) and a size of 100 voxels occurred less than 5% of the time, corresponding to a corrected \( p < .05 \) cluster-level significance threshold.

**Connectivity correlations with SL scores and response speed.** The single-subject whole-brain maps of DC connectivity strength were entered as the dependent variable into two regressions testing for correlations with subjects’ SL scores and average response speed, respectively, in a voxelwise fashion. Average response speed was calculated by determining each subject’s median RT for all correct responses in each 50-trial block, and then averaging across blocks to obtain a single mean RT value for each subject. Results were corrected for multiple comparisons at \( p < .05 \) using the Monte-Carlo correction threshold described above.
Results

Sequence Learning Performance

Subjects’ sequence learning (SL) scores indicated that they had become sensitive to the probabilistic regularity in the task: an independent sample t-test confirmed that overall SL scores ($M \pm SD = .19 \pm .08$) were significantly greater than zero, $t(21) = 10.81$, $p < .0001$. As predicted, subjects also responded significantly faster on average to high probability ($M \pm SD = 326 \pm 32$ ms) than to low probability ($M \pm SD = 343 \pm 35$ ms) triplets, $t(21) = 7.8$, $p < .0001$.

Importantly, individual SL scores did not correlate with subjects’ overall RT or accuracy, indicating that our learning measure was not biased by individual differences in speed or accuracy. Further, overall mean accuracy ($M \pm SD = .93 \pm .03$) indicated that the end-of-block feedback was successful at driving subjects to respond with approximately 92% accuracy.

DC connectivity networks

Mean resting state connectivity networks of the DC observed across all subjects are shown in Figure II-3 and Table II-1. Connectivity patterns were similar to those observed by Di Martino et al. (2008) using the same seed.

Correlations between DC connectivity and SL scores

Consistent with our hypothesis, voxelwise regression using individuals’ SL scores as the predictor resulted in a positive correlation with a cluster in the right parahippocampal gyrus extending into the right hippocampus ($k = 117$ voxels; peak MNI coordinates $[38 - 30 -14]$; $r = .74$, $p < .0001$), such that subjects who had greater connectivity between the DC and this region tended to show greater learning (Figure II-4). Notably, this was the
only positive correlation between whole-brain intrinsic connectivity of the DC and SL scores to survive correction. This correlation occurred despite the fact that the average value of intrinsic connectivity between the DC and this region was close to zero at the group level (\(M \pm SD = -.043 \pm .19\)).

Follow-up analysis revealed that the positive correlation between DC connectivity and SL scores was specifically driven by the right DC. We separately calculated the whole-brain connectivity maps of the left and right DC, and entered these as the dependent variables into two regressions testing for correlations with SL scores in a voxelwise fashion. As in the analysis using the bilateral DC connectivity maps, the regression using the right DC connectivity maps revealed a positive correlation with a similarly located cluster in the right parahippocampal gyrus (\(k = 139\) voxels; \([38 -32 -14]\); \(r = .76, p < .0001\)). This cluster was not present in the regression using the left DC connectivity maps.

In addition, there were three regions whose connectivity to the DC negatively correlated with SL scores, such that subjects with greater connectivity between the DC and these regions tended to show less learning: the left postcentral gyrus (BA1; \(k = 210\) voxels; \([-46 -16 28]\); \(r = -.78, p < .0001\)), right precentral gyrus (BA8; \(k = 108\) voxels; \([46 8 44]\); \(r = -.70, p < .0001\)), and the right medial superior frontal gyrus (BA8; \(k = 118\) voxels; \([12 28 46]\); \(r = -.71, p < .0001\); Figure II-5).

**Correlations between DC connectivity and response speed**

Average response speed correlated with connectivity of the DC to a cluster located in the right cuneus (BA 18; \(k = 125\) voxels, \([16 -88 12]\); \(r = -.66, p = .001\)) and left medial superior frontal gyrus (BA 10/32; \(k = 140\) voxels, \([-14 44 22]\); \(r = -.67, p = .001\)), such
that subjects with stronger connectivity between the DC and these regions tended to have faster average response times. No regions correlated negatively with response speed. Further, the correlation between DC-MTL connectivity and average response speed ($r = -0.15, p = 0.50$) was reliably smaller than that observed with SL scores ($z = 3.4, p = 0.0007$).

In sum, DC-MTL connectivity predicted sequence learning but not overall speed in the task.

**Discussion**

This study investigated whether DC connectivity at rest is related to individual differences in the implicit learning of sequential, probabilistic regularities in a sample of healthy young adults. Supporting our hypothesis, subjects with greater positive rsFC between the dorsal caudate and a cluster in the right MTL had superior implicit sequence learning. Importantly, individual differences in overall task performance cannot account for the relationship between rsFC connectivity and sequence learning that we observed. SL scores were not correlated with subjects’ overall speed or accuracy, and DC-MTL connectivity was not related to subjects’ overall response speed in the task. Faster overall response speed related, instead, to stronger connectivity of the DC with cuneus and medial frontal gyrus, regions associated with visual processing (Vanni, Tanskanen, Seppä, Uutela, & Hari, 2001) and response selection under uncertainty (Critchley, Mathias, & Dolan, 2001), respectively. Thus, the strength of a dorsal caudate-MTL network in the resting brain predicts how well one learns sequential probabilistic regularities, but does not predict overall task speed.

To our knowledge, this is the first study to show that IPSL performance is correlated with connectivity of a task-relevant region (the DC) at rest. As all scans were
collected either before learning or well outside the timeframe when consolidation processes might be expected to occur, our finding suggests that rsFC is an intrinsic factor predictive of implicit sequence learning aptitude. The relationships we observed between sequence learning performance and rsFC of the DC with the MTL and frontal motor regions may therefore reflect the integrity and functional segregation of a task-relevant neural network.

Our results are consistent with those of previous studies using task-dependent fMRI, which find that implicit probabilistic types of learning depend upon an interaction between the caudate and MTL. Specifically, MTL contributions to learning predominate early in training, while the caudate becomes particularly relevant to performance later (Albouy et al., 2008; Poldrack et al., 2001; Rieckmann et al., 2010; Schendan et al., 2003; Simon et al., 2012). Further, implicit motor sequencing tasks show that greater sequence learning is associated with a pattern of increasing striatal and decreasing MTL BOLD signal with practice, whereas individuals who do not show this pattern demonstrate less learning (Albouy et al., 2008; Rieckmann et al., 2010). These studies support the idea that both the caudate and MTL are important to IPSL and that a precisely coordinated sequence of interaction (i.e., a shift from hippocampus-dominant to caudate-dominant processing) between these regions is related to learning ability. As with these earlier task-dependent fMRI studies, our results also support the importance of both the DC and MTL to IPSL by showing that the magnitude of IPSL is related to the strength of their connectivity at rest. A stronger intrinsic functional association between these regions may enable more efficient interregional activation/inhibition during the course of learning (i.e., promote ‘readiness to learn’), thereby facilitating the observed interaction between
the DC and MTL during sequence learning. Future studies could examine this interpretation by assessing the functional connectivity between these regions during task-dependent fMRI.

An important caveat is that it is still unclear exactly how the caudate and MTL interact during IPSL; the task-dependent activation of these regions during implicit tasks has been interpreted as both competitive (e.g., Poldrack & Packard, 2003) and cooperative (e.g., Atallah, Frank, & O’Reilly, 2004). Interpretation is further complicated by the fact that there is some behavioral evidence of preserved sequence learning in patients with MTL damage (Nissen, Willingham, & Hartman, 1989; P. J. Reber & Squire, 1994), leading some to conclude that this region may not be necessary for IPSL. However, such clinical groups often show less learning than healthy controls, implying that other brain structures might not be able to completely compensate for MTL damage (Curran, 1997). Therefore, despite the mixed evidence from IPSL studies in clinical groups, the bulk of the (albeit correlational) evidence in healthy samples, such as the one tested here, suggests that both caudate and MTL are involved and might have distinct contributions to IPSL (Gheysen et al., 2011).

It is notable that resting state functional connectivity between DC and MTL predicts IPSL performance, even though there are few direct anatomical connections between these regions. This is not surprising in light of evidence indicating that a direct anatomical connection is not necessary for functional connectivity in the resting state (Honey et al., 2009). For sequence learning, our prior work using diffusion tensor imaging (DTI) tractography suggests that this DC-MTL functional relationship may be mediated via connections with the DLPFC (Bennett et al., 2011). Early in training,
sequence learning scores were positively correlated with the microstructural integrity of the white matter tract between the right MTL and DLPFC, while later in training, learning scores positively correlated with integrity of left caudate to DLPFC tract. Moreover, individual differences in the integrity of the left caudate-DLPFC tract mediated the age differences in late-training learning between younger and older adults, such that accounting for that variability eliminated age differences in learning. Thus, it is possible that the observed connectivity between caudate and MTL was mediated by the DLPFC, and further, that variability in caudate-DLPFC and MTL-DLPFC anatomical connections could underlie learning differences. Future studies could combine fMRI functional connectivity and diffusion tensor imaging to examine this possibility.

Although we did not predict any negative relationships, connectivity between DC and several motor planning regions was negatively correlated with sequence learning. Higher SL scores were predicted by less positive, more negative connectivity between the DC and clusters in the left postcentral gyrus (BA1), right precentral gyrus (BA8), and right medial superior frontal gyrus (BA8). These negative correlations are interesting in light of anatomical (e.g., Lehéricy et al., 2004) and functional neuroimaging evidence (e.g., Lewis, Dove, Robbins, Barker, & Owen, 2003) in humans suggesting that distinct striatal subregions underlie motor and cognitive processes. Specifically, the dorsal caudate may be primarily involved in networks supporting cognitive functions, receiving input from and projecting to the dorsal lateral parts of the frontal cortex, while the putamen may be primarily involved in motor functions, receiving input from and projecting to frontal motor areas (for reviews see Alexander & DeLong, 1986; Carol A. Seger, 2008). Thus, the superior learning we observed in subjects with less resting state
connectivity between the DC and these regions might indicate that sequence learning is maximized when the supporting motor and cognitive circuits remain weakly associated at rest. Importantly, the negative correlations we detected do not imply that frontal motor regions are unimportant for task performance, but rather that they might be involved in striato-cortical loops that are distinct from those supporting sequence-specific learning. Such functional segregation of motor and cognitive networks at rest might facilitate more efficient adaptation to the limited motor demands of the TLT and a greater commitment of DC and MTL activity to sequence-specific learning. Another possibility is that these negative correlations occur because the TLT does not involve motor sequencing, a key difference between this task and more traditional sequence learning tasks, such as the SRT. Replication using other tasks would therefore be informative.

**Alternative Interpretations**

One important alternative interpretation of the present results relates to the implicit nature of the TLT. Several published studies have used sensitive recognition tasks to show that learning in the TLT is implicit (J. H. Howard Jr. et al., 2008; Simon, Stollstorff, et al., 2011; Simon, Howard, et al., 2011; Simon et al., 2012), but our only measure of awareness in the present study came from an interview assessing their knowledge of the reoccurring pattern in the task (Simon, Howard, et al., 2011). Although no one accurately described the regularities from the TLT or reported using explicit strategies, this type of awareness test is arguably less sensitive than others used in prior studies. Therefore, one alternative interpretation for the present results is that subjects who displayed more effective cooperative interaction between explicit and implicit memory systems revealed enhanced learning. We cannot rule out this possibility here, nor
can we speak to the nature of caudate-MTL interaction during the task, as it is conceivable that more positive connectivity (implying increased communication) between these regions at rest enabled a more optimal/efficient competitive or cooperative interaction between them during learning.

**Limitations & Future Directions**

The present results should be interpreted in light of some limitations. First, the length of our resting scan was relatively short; longer scans may be more sensitive to individual differences (J. S. Anderson, Ferguson, Lopez-Larson, & Yurgelun-Todd, 2011; Birn et al., 2013). However, reliable estimates of functional connectivity can be obtained in as little as four minutes (Van-Dijk et al., 2010; pg. 15), suggesting our scan-length is sufficient. Second, our sample size is relatively small, although comparable (or larger) than that of other published studies using similar tasks (Bennett et al., 2011; Rieckmann et al., 2010; Schendan et al., 2003; Simon et al., 2012). Because the chances of Type I error increase in small samples, however, replication with a larger sample is desirable, and future studies focusing on individual differences should consider acquiring longer scans.

Third, our method of recruitment did not permit a tightly controlled interval between the scan and behavioral testing. Nevertheless, there was no evidence that the time interval separating the scan from behavioral testing influenced learning, and our pattern of results remained when the two subjects scanned after behavioral testing were removed from the analyses. Thus, our results do not reflect consolidation processes resulting from the learning task itself. More studies of rsFC are needed, however, in order
to better understand the stability (and experience-induced plasticity) of resting networks over time.

Conclusion

Our results are the first to show a relationship between IPSL and rsFC between the DC and task relevant regions and suggest that the predictive value of resting networks is not exclusive to explicit, goal-directed cognition. As predicted, subjects who had greater positive connectivity between the DC and MTL at rest revealed greater sequence learning, adding to existing fMRI and DTI evidence that the MTL supports IPSL in conjunction with the caudate. In addition, our unexpected finding that subjects with more negative connectivity between the DC and frontal motor regions at rest revealed less learning suggests that there may be functional segregation within neural networks not only during tasks, but also at rest. Future research will be necessary to extend these findings, perhaps by examining additional characteristics associated with resting state connectivity (e.g., age, genotype, lifestyle) and by combining resting state fMRI with task dependent fMRI and DTI techniques. Such research would help to bolster evidence that resting state connectivity is an intrinsic factor contributing to individual differences in a variety of cognitive processes, now including implicit probabilistic sequence learning.
CHAPTER II

Dispositional Mindfulness is Associated with Reduced Implicit Learning


Introduction

Mindfulness refers to the ability to stay attentive and receptive to events and experiences taking place in the present and thus disengage from habitual actions and thought tendencies. This construct has grown in popularity in recent years because it has been linked to a number of positive psychological and cognitive outcomes (Brown & Ryan, 2003). However, there may be tradeoffs to mindfulness, such that it benefits some domains of functioning but not others. The goal of the present study was to investigate the hypothesis that higher mindfulness is associated with reduced implicit learning, the type of learning that can take place without intent to learn or awareness of what has been learned (A. S. Reber, 1989).

Individual differences in the propensity, or disposition, for mindfulness, as assessed through self-report, are associated with enhanced psychological wellbeing. For example, people higher in mindfulness tend to have fewer symptoms of anxiety and depression (Brown & Ryan, 2003; Rasmussen & Pidgeon, 2011; Salmoirago-Blotcher, Crawford, Carmody, Rosenthal, & Ockene, 2011), lower levels of self-consciousness (Brown & Ryan, 2003; D. R. Evans, Baer, & Segerstrom, 2009), and lower levels of negative affect (Brown & Ryan, 2003). Dispositional mindfulness is also associated with
better performance on a wide range of cognitive tasks that have implications for maintaining psychological health. For example, higher mindfulness is associated with better performance on sustained attention (Mrazek, Smallwood, & Schooler, 2012; Schmertz et al., 2009) and inhibitory control (Oberle et al., 2011) tasks, and with increased persistence on challenging tasks, reflecting an enhanced ability of more mindful people to regulate their emotions and attentional resources in the face of frustration (D. R. Evans et al., 2009). Studies measuring dispositional mindfulness therefore suggest that being mindful can benefit cognitive and mental health.

Mindfulness can also be cultivated through practice. Studies comparing the outcomes of mindfulness-based training groups to various matched control groups provide evidence for a causal link between mindfulness and improved psychological wellbeing and cognitive functioning. In healthy adults, mindfulness training increases performance on cognitive tasks assessing executive functions, including working memory (Jha, Stanley, Kiyonaga, Wong, & Gelfand, 2010; Mrazek, Franklin, Phillips, Baird, & Schooler, 2013), attention (Jha et al., 2007) and inhibitory control (Allen et al., 2012). In the clinical realm, mindfulness-based therapies are effective at reducing symptoms and relapses of a wide range of psychiatric disorders, including depression and anxiety, chronic pain, addictions, and disordered eating (Barnhofer et al., 2009; Kabat-Zinn, 1982; Kristeller & Hallett, 1999; Rosenzweig et al., 2010; Shahar, Britton, Sbarra, Figueredo, & Bootzin, 2010; Tang & Posner, 2013; Teasdale et al., 2000).

These effects of mindfulness training provide clues about its underlying neural bases. Many of the disorders shown to be ameliorated by mindfulness training have been linked with abnormal functioning and/or structure in brain regions supporting emotional
control and processing, especially regions in the prefrontal cortex, including anterior cingulate and dorsolateral prefrontal cortices (Beauregard, Paquette, & Lévesque, 2006; Bishop, Duncan, Brett, & Lawrence, 2004; Luerding, Weigand, Bogdahn, & Schmidt-Wilcke, 2008; Uher et al., 2004).

The same prefrontal regions shown to have abnormalities in patient populations are consistent with those implicated in cognitive control and executive functioning in healthy populations (Cabeza & Nyberg, 2000; Miller & Cohen, 2001). Therefore, the mechanism by which mindfulness is hypothesized to exert its many salutary effects is by disengaging individuals from habitual response tendencies supported by subcortical neural systems (e.g., the striatum) and promoting engagement of executive control functions mediated by the frontal lobes (Hölzel et al., 2011, 2013; Teper, Segal, & Inzlicht, 2013). Supporting this mechanistic hypothesis, higher mindfulness is associated with smaller caudate (a region in the striatum) and amygdala volumes (Taren et al., 2013), and with increases in both volume and functioning of prefrontal regions implicated in cognitive control (Grant, Courtemanche, Duerden, Duncan, & Rainville, 2010; Hölzel et al., 2007; Modinos, Ormel, & Aleman, 2010; Tang et al., 2010, 2013). For example, Tang et al. (2013) demonstrated that the resting state activity of several regions in the prefrontal cortex (i.e., brain activity during non-goal directed tasks) increased following mindfulness training. The changes in resting brain activity coincided with decreases in subjective craving and objective smoking behavior in a subset of participants who were smokers with no prior intent to quit. The authors interpreted the results as suggesting that mindfulness-induced changes in the underlying structure and function of frontal regions may have lasting, tonic influences on self-control capacity.
and, consequently, smoking behavior. Together, these findings raise the possibility that mindfulness may exert its salutary effects on human behavior by strengthening one of two competing neural systems, increasing the relative involvement of frontal control in cognitive functioning. For example, greater mindfulness may strengthen reliance on cognitive functions driven by frontal control processes, resulting in improved performance on cognitive functions relying on frontal brain regions but not those relying on subcortical structures.

If, as the evidence presented above supports, mindfulness is associated with greater engagement and altered structure of frontal control regions, then people higher in mindfulness might be *worse* at implicit cognitive processes in which reduced frontal involvement has been shown to benefit performance. Findings from a recent study by Whitmarsh, Uddin, Barendregt, and Petersson (2013) support this hypothesis; they found that individuals higher in dispositional mindfulness displayed poorer learning of artificial grammar, a cognitive task thought to depend on subcortical structures and to be impaired by explicit task instructions (A. S. Reber, 1976). The authors propose that greater mindfulness reduces habitual responding to unconsciously acquired preferences in the task, perhaps by promoting a non-reactive and non-judgmental disposition. The findings from this study demonstrate the potential relevance and importance of dispositional tendencies like mindfulness on implicit types of learning and retrieval.

In the present study, we examined how mindfulness relates to implicit probabilistic sequence learning, hereafter referred to as *IPSL*. This is the process by which people acquire complex regularities occurring in sequences of events without intending to learn them and without subsequent awareness of what has been learned. The
ability to learn sequential relationships is important because it underlies essential functions of daily life; it contributes to our ability to perceive the world efficiently, to learn and use language, and even to engage in social interactions (Kuhl, 2004; Lieberman, 2000; Saffran, Newport, & Aslin, 1996).

Experimental studies of IPSL, including those using neuroimaging, highlight the role of subcortical structures, especially the striatum, for this type of learning (Bennett et al., 2011; J. H. Howard Jr & Howard, 2013; Rauch et al., 1997; Rieckmann et al., 2010; Simon et al., 2012). Crucially, there is also intriguing evidence that IPSL is impaired by engagement of frontal control processes (Filoteo, Lauritzen, & Maddox, 2010; Foerde, Knowlton, & Poldrack, 2006; D. V. Howard & Howard, 2001; Nemeth, Janacsek, Polner, & Kovacs, 2012). For example, IPSL improves following inhibitory theta burst stimulation (TBS) to the dorsolateral prefrontal cortex (Galea, Albert, Ditye, & Miall, 2009), and following hypnosis, a practice thought to temporarily disconnect frontal areas, such as the anterior cingulate, from other brain areas, such as the striatum (Nemeth et al., 2012). It has been argued that hypnosis therefore disrupts neural communication underlying executive and attentional control (Egner, Jamieson, & Gruzelier, 2005). Given the growing evidence that prefrontal engagement does not benefit (and in many cases hurts) IPSL, we chose to focus on this essential cognitive process to test our hypothesis regarding mindfulness.

Participants completed a widely used measure of dispositional mindfulness to assess their tendency to attend to experiences in the present without distraction. They then completed an IPSL task. Given that mindfulness and implicit learning may rely on opposing neural systems, we hypothesized that people with higher levels of mindfulness
would have a lower tendency to engage in habitual types of responding. We therefore predicted a negative relationship between mindfulness and IPSL. We tested this prediction in two different samples and using two different IPSL tasks.

**Study 1**

**Method**

**Subjects.** Sixteen college-aged adults (12 female) ages 18 to 26 years ($M\pm SD = 20.9\pm2.6$) were recruited from the Georgetown University Research Volunteer Pool. Characteristics of these participants are presented in Table III-1. All experimental procedures were approved by Georgetown University’s Institutional Review Board.

**Procedure.** Participants completed the Mindful Attention Awareness Scale (MAAS) (Brown & Ryan, 2003), on the first day of a larger, 3-day study. They then completed 3 sessions of an IPSL task, the Triplets Learning Task (TLT) (J. H. Howard Jr. et al., 2008). Both the MAAS and TLT are described in more detail below.

**The Triplets Learning Task (TLT).** Participants completed three abbreviated sessions (720 trials total) of the TLT (J. H. Howard Jr. et al., 2008) while in an fMRI scanner. A schematic of the TLT is shown in Figure III-1. In this task, participants view a row of four open circles centered on a computer screen. These circles fill in sequentially, red, then green in sequences of three events referred to as “triplets”. Each triplet constitutes a trial. Participants are instructed to observe the first two red cues (appearing for 120ms each, with a 150ms ISI) and to respond only to the location of the green “target” by pressing a spatially corresponding response button as quickly as possible. In the present version of the TLT, the target remains on the screen for a set amount of time after a response is made, and the next trial begins 1-3 seconds later. Short breaks were
provided after every block of 50 trials, during which the subject’s mean reaction time (RT) was displayed along with instructions to “focus more on speed”, “focus more on accuracy”, or “speed and accuracy are about right”. The instructions were based on the subject’s mean accuracy for the preceding block of trials and were intended to drive all subjects to a similar level of response accuracy (92%). The TLT took approximately 45 minutes to complete.

Unbeknownst to participants, the TLT contains a probabilistic pattern, such that an arbitrarily chosen set of 8 triplets occurs with high probability (HP), while another 40 triplets occur with low probability (LP) throughout the task. LP and HP triplets are presented in a 1:5 ratio in the present version of the TLT so that the frequencies of HP and LP trials are balanced, a characteristic that equates power in the two task conditions.

Measures of Implicit Probabilistic Sequence Learning (IPSL). IPSL in the TLT is assessed by comparing reaction time to HP vs. LP triplets (J. H. Howard Jr. et al., 2008) and can be quantified by one of two measures, both of which were examined in the present study:

Difference Scores. Difference scores, or the size of the triplet type effect, are calculated by subtracting a participant’s mean reaction time to HP from that to LP triplets. Larger difference scores reflect more learning.

Sequence Learning (SL) Scores. Because individual differences in the mean and/or standard deviation of overall response time could possibly influence the Difference Score measure of learning, we also examined Sequence Learning (SL) Scores. SL scores are computed by correlating for each subject, the number of times each unique triplet occurred with that participant’s mean reaction time to that triplet (J. H. Howard Jr.
et al., 2008). More negative correlations indicate more learning, in that the participant is responding faster to triplets occurring with higher frequency. These correlation values are then multiplied by -1 so that higher SL scores reflect more learning.

**Assessing Implicitness.** In order to assess whether learning in the TLT was implicit, participants completed a computer based recognition task immediately following the TLT. Participants were shown each possible triplet once. Thus, they saw the 8 high frequency and 40 low frequency triplets, as well as the 16 triplets that had never occurred during training. They then rated how often they thought each triplet occurred (1 = infrequently and 2 = frequently). The presentation timing of the two red cues and target are the same as in the TLT. This task is described in detail elsewhere (e.g., J. H. Howard Jr. et al., 2008; Simon et al., 2012).

**The Mindful Attention Awareness Scale (MAAS).** Participants completed the MAAS to assess their trait level of mindfulness disposition. The MAAS is a single factor, self-report questionnaire designed to assess the ability to focus on experiences taking place in the present and to disengage from habitual, automatic modes of functioning. The questionnaire contains 15 items, and participants rate on a 6-point Likert scale (1=almost always to 6=almost never) how often they experience each item on a day-to-day basis (e.g., “I break or spill things because of carelessness, not paying attention, or thinking of something else,” “I do jobs or tasks automatically, without being aware of what I’m doing,” “I find it difficult to stay focused on what’s happening in the present ”). The questionnaire is scored by averaging the participant’s responses across all items. Higher scores indicate higher mindfulness. The MAAS has been validated using a variety of subject populations, including healthy younger and older adults (e.g., Brown & Ryan,
2003; Shaurya Prakash, De Leon, Klatt, Malarkey, & Patterson, 2012), and has been shown to have good psychometric properties (Brown & Ryan, 2003; Carlson & Brown, 2005; S. Evans et al., 2008).

**Results**

Overall accuracy on the TLT was high ($M\pm SD = .94\pm.02$). A one sample t-test confirmed that participants learned in the TLT, in that both difference scores ($M\pm SD = 10.47\pm10.9$; $t(15) = 3.8, p = .002$) and SL Scores ($M\pm SD = .13\pm.12$; $t(15) = 4.3, p = .001$) were significantly above zero. Results from the computer-based recognition test revealed no evidence of explicit awareness. Participants’ ratings to HP ($M\pm SD = 1.61\pm.24$) and LP ($M\pm SD = 1.60\pm.18$) triplets did not differ from one another ($t(15) = .52, p = .61$), suggesting that they could not successfully identify which triplets had occurred more than others during the TLT. However, participants’ ratings to triplets that had never occurred during training were consistently lower than their ratings to both LP and HP triplets (all $ts>1.9, ps<.08$), indicating that participants understood and were complying with the instructions of the recognition task.

Consistent with our predictions and as shown in Figure III-2, there was a negative correlation between mindfulness and both SL Scores and Difference Scores in this sample. This correlation was significant for SL Scores ($r(16) = -.55, p = .02$) and marginal for Difference Scores ($r(16) = -.48, p = .06$).

Participants’ overall mean reaction time and accuracy in the task were not correlated with their mindfulness or learning scores (all $p’s > .31$), suggesting the mindfulness-learning relationships we detected are not attributable to individual differences in overall task performance.
Study 2

Next, we sought to replicate the correlation we detected in Study 1 between mindfulness and IPSL. A second sample of adults was tested to examine whether this relationship would occur in a different, older, sample of adults. In addition, we used a different IPSL task (the ASRT) and administered this task under different circumstances (i.e., in a behavioral testing room, rather than in the scanner).

Method

Subjects. Eighteen healthy older adults (15 female) ages 63 to 98 years (M±SD = 80.5± 9.0) participated in the study for payment. They were residents of a senior living community located in Northwest, DC and were recruited through advertisements placed in community common areas, or by word of mouth. Participants’ neuropsychological test scores confirmed that they were cognitively healthy (Table III-1). All experimental procedures were approved by Georgetown University’s Institutional Review Board.

Procedure. Participants completed 2 days of testing (in sessions separated by 1 day). All testing took place on-site in a quiet room centrally located to all participants. On the first day, participants completed a series of self-report questionnaires, including the MAAS and biographical and health questionnaires, and the Geriatric Depression Scale—Short Form (GDS) (Sheikh & Yesavage, 1986). They also completed an IPSL task, the Alternating Serial Response Time Task (ASRT) (J. H. Howard Jr. & Howard, 1997). The ASRT is described in more detail below. On the second day, participants completed the neuropsychological test battery and the Brief Test of Adult Cognition by Telephone (BTACT) (Tun & Lachman, 2006). The BTACT is a collection of cognitive measures assessing verbal episodic memory, working memory, executive functioning, processing
speed, and reasoning. These measures are modified versions of validated psychometric tests that have been adapted to be suitable for quick administration, even when testing in person is not possible. All adults in the present study, however, were tested in person.

**The Alternating Serial Response Time Task (ASRT).** A schematic of the ASRT is shown in Figure III-3. In this task, participants view a horizontal row of four open circles (outlined in black) centered on a computer screen. On each trial, one of the open circles fills in black. Participants are instructed to indicate the location of the black “target” by pressing a spatially corresponding response button as quickly as possible. If the first response is incorrect, the target remains on the screen until the correct response is made. After an accurate response is logged, the target is cleared and the next trial begins 120ms later.

Unbeknownst to participants, the version of the ASRT task used here contained a second-order probabilistic pattern, such that the location of the target on every other trial was determined by a repeating sequence, and the intervening trials were randomly determined. Therefore, there were 6 possible repeating sequences: 1r2r3r4r, 1r2r4r3r, 1r3r2r4r, 1r3r4r2r, 1r4r2r3r, and 1r4r3r2r. The numbers in these sequences refer to the location of the target from left to right, and the “r’s” refer to a random trial in which the target could occur at any of the four possible locations. The result of this sequence structure is that some triplets (e.g., 132 for sequence 1) occur with high probability (HP) and others (e.g., 231 for sequence 1) with low probability (LP) for a given participant. Each participant was randomly assigned one of these repeating sequences.

Participants completed 3,960 trials of the ASRT, which corresponded to 3600 repetitions of the 8-element sequence. The task was broken up into 45 88-trial blocks,
with each block containing 8 practice trials and 10 repetitions of the 8-element sequence. Short breaks were provided after every block, during which the subject’s mean reaction time (RT) was displayed along with instructions to “focus more on speed”, “focus more on accuracy”, or “speed and accuracy are about right”. The instructions were based on the subject’s mean accuracy for the preceding block of trials and were intended to drive all subjects to a similar level of response accuracy (92%). Participants were given the option to take a longer break after every 15 blocks. The task took approximately 60 minutes to complete. As in the TLT, IPSL in the ASRT is quantified by comparing responses to HP vs. LP triplets (J. H. Howard Jr & Howard, 1997), thus we again calculated Difference Scores and SL Scores.

**Assessing Implicitness.** To assess whether learning was implicit on the ASRT, participants were asked a series of increasingly leading interview questions. These questions were administered on Day 2 of the protocol (rather than at the end of Day 1), and we did not administer the recognition task from Study 1 at all. This is because some of the tasks administered after the ASRT on the second day were incidental or implicit and so we did not want to compromise their implicit nature by drawing attention to the structure of the ASRT.

**Results**

Overall accuracy in the ASRT was high ($M\pm SD = .95\pm.04$). A one sample t-test revealed that participants became sensitive to the regularity in the ASRT; learning scores were significantly above zero for both difference scores ($M\pm SD = 12.39\pm14.31; t(17) = 3.68, p =.002$) and SL Scores ($M\pm SD = .08\pm.15; t(17) = 2.17, p =.04$). Although awareness was not assessed immediately following training, none of our participants...
reported having gained knowledge of the regularity in the ASRT. Furthermore, previous studies using the ASRT show that virtually no one becomes aware in this task, even when training is extended (D. V. Howard et al., 2004), and when the sensitive recognition tests included in Study 1 are used (e.g., Bennett et al., 2011; D. V. Howard et al., 2004; J. H. Howard Jr & Howard, 1997). Moreover, when participants of a similar age to those tested here are explicitly told of the nature of the regularity in the ASRT and are instructed to look for it, they are still unable to do so (D. V. Howard & Howard, 2001). This previous evidence (coupled with the results of our interview) suggests that learning in the present study was implicit.

Most important, as in Study 1, there was a negative correlation between mindfulness and both ASRT Difference Scores and SL Scores (Figure III-4); This correlation was significant for Difference Scores \((r(18) = - .58, p = .01)\), and marginal for SL Scores, \((r(18) = - .44, p = .06)\).

As in Study 1, there was no correlation between mean accuracy and mindfulness or learning scores \((ps > .84\). However, unlike in Study 1 there was a significant negative correlation between mindfulness and mean reaction time \((r(18) = - .53, p = .02)\), as well as a non-significant positive correlation between mean reaction time and Difference Scores \((r(18) = .44, p = .08)\). We therefore tested whether the relationship between mindfulness and Difference Scores was accounted for by individual differences in mean reaction time. Controlling mean reaction time did not eliminate the relationship between mindfulness and learning \((r(18) = - .46, p = .06)\), but controlling for mindfulness did eliminate the relationship between mean reaction time and Difference Scores \((r(18) = .21, p = .41)\). This pattern of results suggests that the correlation between mindfulness and
learning we report in study 2 is not solely due to mean speed in the task.

In addition to our primary goal of replicating the relationship between mindfulness and IPSL, in Study 2 we also examined how mindfulness related to other measures with well-established associations with mindfulness. Higher dispositional mindfulness, for example, has been associated with fewer symptoms of depression and anxiety (e.g., Brown & Ryan, 2003; Cash & Whittingham, 2010; Rasmussen & Pidgeon, 2011), as well as increased subjective (and objective) physical well-being (Brown & Ryan, 2003). We therefore used participants’ scores on the GDS and their self-reported overall health (recorded as a score ranging from 1 = “poor” to 5 = “excellent”) in the health questionnaire to examine whether our results would be consistent with the previously established relationships between mindfulness and these measures. Because mindfulness has been associated with better executive functioning (Mrazek et al., 2013; Oberle et al., 2011), we also examined correlations between mindfulness and participants’ performance on various BTACT subcomponents tapping aspects of executive or explicit cognitive functioning. Consistent with the literature, mindfulness was negatively associated with scores on the GDS, $r(18) = -.51$, $p = .03$, and positively associated with self-reported health, $r(18) = .47$, $p = .05$. In addition, mindfulness was positively associated with higher accuracy on the experimental portion of the Stop and Go Test, $r(18) = .57$, $p = .01$, a measure of inhibitory control, as well as with better episodic recall on the delayed recall subcomponent of the BTACT, $r(18) = .46$, $p = .05$.

**General Discussion**

In two studies, we investigated the relationship between mindfulness and IPSL. Supporting our hypothesis, both studies revealed negative relationships between
participants’ scores on a self-report mindfulness scale and IPSL scores. In Study 1, this relationship emerged in a sample of healthy young adults who completed the learning task (the TLT) in a scanning environment. In Study 2, a similar negative mindfulness-learning relationship occurred in a sample of healthy older adults who completed a different learning task (the ASRT) in a more traditional testing environment (behavioral testing room). These key differences between the studies provide support that the novel relationship between mindfulness and IPSL is not limited to a specific age group, learning task, or testing context.

The correlations between mindfulness and other cognitive and wellbeing measures found in Study 2 were all in directions consistent with those previously reported in the literature. That is, we found that mindfulness was significantly correlated with two measures of wellbeing (negatively with depression scores and positively with self-rated health), as well as positively with performance on executive functioning and verbal episodic memory subcomponents of the BTACT. The fact that these correlations are consistent with earlier research helps to rule out other possible explanations for the negative correlation we observed between mindfulness and implicit learning, such as the possibility that unique characteristics of the participants (and not IPSL per se) were responsible for the effect.

The present results expand upon findings from studies examining relationships between individual differences in personality and IPSL performance. For example, Kauffman et al. (2010) found that people higher in Openness (assessed via the NEO five-factor questionnaire), higher in intuition (assessed via the Myers-Briggs Type Indicator), and lower in premeditation (assessed via the UPPS impulsivity scale) scored higher on
the Serial Reaction Time task, a task very similar to the ASRT used in Study 2. The authors posit that people higher in Openness and who deliberate less are better at IPSL because they have a wider focus of attention and focus on a wider variety of stimuli, which makes them more likely to capture relevant associations in complex tasks. Our results are consistent with this explanation: Having less of a tendency to focus on events and experiences taking place in the present (i.e., being less mindful), might ultimately make people more sensitive to the complex probabilistic patterns embedded in the TLT and ASRT. Thus, mindfulness may be another trait/disposition associated with one’s aptitude for IPSL. It is not possible to say from the present results whether participants lower in mindfulness also tended to be higher in openness, intuition, and impulsivity because we did not include additional personality measures in our studies. However, elucidating specific combinations of traits associated with IPSL ability would be a direction for future research.

Our results are also broadly consistent with findings from neuroscience, which suggest that mindfulness exerts its salutary effects by increasing structure (e.g., regional brain volume) and functioning (e.g., mean regional BOLD signal and resting activity) of frontal brain regions implicated in cognitive control (Grant et al., 2010; Modinos et al., 2010; Tang et al., 2010, 2013). The additional positive correlations of mindfulness with executive functioning we observed in Study 2 support this mechanistic hypothesis and replicate the results of previous studies. However, our results join other findings in suggesting that increased involvement of frontal brain regions may not be beneficial for all domains of cognitive functioning. Indeed, there is evidence of a competitive relationship between frontal and subcortical brain regions. In the case of IPSL, for
example, experimental manipulations that decrease functional activation and/or connectivity of frontal brain regions to the rest of the brain (e.g., TBS and hypnosis) increase learning performance (Galea et al., 2009; Nemeth et al., 2012). In fact, the Nemeth et al. study described in the introduction, which showed that hypnosis improved IPSL, did so using the same task (the ASRT) as used in our Study 2. Thus, one interpretation of the present results is that people lower in mindfulness engage frontal regions to a lesser degree during IPSL tasks compared to people higher in mindfulness, thereby enabling the task-optimal striatal system to dominate during training. Chapter IV combines behavioral with functional neuroimaging techniques to further examine this interpretation.

A recent behavioral study by Janacsek, Fiser, and Nemeth (2012) offers a similar competition-related explanation, but in their case to explain why IPSL is better in early childhood than in older age groups in the ASRT task. Janacsek and colleagues differentiate between learning based on internal models vs. that based on detection of raw probabilities. They posit that prior to adolescence learning of statistical regularities is not heavily influenced by previous experience and interpretations, i.e., by “internal models”. This is because the cortical regions that support the development and use of internal models, including the frontal and medial temporal lobes, are underdeveloped. Children instead rely on a basal ganglia-dependent system that enables them to readily detect raw statistical probabilities in environmental input, a strategy optimal for IPSL. In contrast, adolescents and adults have well-developed internal models that influence their interpretations of the raw probabilities in environmental input. While beneficial for efficiently adapting to more complex aspects of the world, this strategy impairs
sensitivity to raw statistical input and IPSL therefore declines. The idea that competition between the neural systems supporting internal models vs. the detection of raw probabilities provides an additional description, at a different level of analysis, for why mindfulness is negatively related to IPSL in the present studies. It is possible, for example, that sensitivity to raw probabilities is modulated not only by group differences in frontal/medial temporal cortical development, but also by individual differences in the propensity for mindfulness.

The present findings should be interpreted in light of some limitations. First, the present findings are correlational in nature. We therefore cannot determine whether mindfulness causes people to learn less on implicit IPSL tasks or whether there is a confounding factor driving this negative relationship. Training studies in which participants are tested both before and after mindfulness training would address this issue.

Second, our sample sizes are small. Since the chance of Type 1 error increases in small samples, replicating the present results with a larger sample is desirable. However, the fact that we detected the same negative mindfulness-learning relationship in two studies using participants of different ages, two different IPSL tasks, and across two different measures of learning, makes it less likely that these results are due to chance.

Third, the majority of participants in both study samples were female. This fact may limit the generalizability of these findings. However, it seems unlikely that the present results would be limited to females given that (to our knowledge) there are no studies reporting that mindfulness is associated with improved executive functioning in one gender, but not the other.
Finally, a fourth limitation of the present studies is that they investigated the relationship between mindfulness and one type of implicit learning (sequence learning). It is therefore not possible to determine whether mindfulness would also be negatively associated with other forms of implicit learning (e.g., implicit context learning). We also cannot tell whether mindfulness impairs IPSL performance across both beneficial and harmful domains (e.g., implicitly acquiring a good vs. bad habit). The laboratory-based tasks used in the present study were not designed to assess any specific real-life domain in which implicit sequence learning applies so we cannot draw any conclusions on this issue here. The fact that we used different IPSL tasks across our studies is a step in the right direction, but determining whether these results occur for different forms of implicit learning in the lab— and perhaps in both adaptive and maladaptive real-life contexts—would be informative.

**Conclusions**

Our results show a negative relationship between mindfulness and IPSL, suggesting that the beneficial effects of mindfulness do not extend to all domains of cognitive functioning. Cognitive functions, such as IPSL, which underlie habit formation may therefore be impeded by mindfulness. The fact that there may be tradeoffs to predominately adaptive traits such as mindfulness is not surprising. At the same time, however, being a poor sequence learner could sometimes be advantageous for cognitive and emotional wellbeing. For example, to the extent that this type of learning is involved in forming addictions and maladaptive habits, being higher in mindfulness may ultimately be protective against certain adverse health outcomes based on IPSL.
CHAPTER IV: CAUDATE FUNCTIONAL CONNECTIVITY MEDIATES THE ASSOCIATION BETWEEN MINDFULNESS AND IMPLICIT LEARNING

Introduction

Mindfulness refers to the ability to stay attentive and receptive to events and experiences taking place in the present (Brown & Ryan, 2003). This construct has become popular in both media and research realms alike because mindfulness is associated with a number of positive emotional and cognitive health outcomes. For example, it improves explicit cognitive functioning, or that which occurs with conscious intent and awareness (e.g., A. P. Jha, Stanley, Kiyonaga, Wong, & Gelfand, 2010; Mrazek et al., 2013, 2012; Schmertz et al., 2009). However, two recent studies have reported a negative relationship between mindfulness and implicit types of learning and memory, or those that occur without conscious awareness or intent (Stillman, Feldman, Wambach, Howard, & Howard, 2014; Whitmarsh et al., 2013). This apparent dissociation between implicit and explicit processes raises the possibility that mindfulness may not be beneficial to all cognitive domains.

The negative relationship between dispositional mindfulness and implicit probabilistic sequence learning (IPSL) reported in Chapter III (Stillman, Feldman, et al., 2014), and the potential neural mechanisms behind it, are the focus of the present fMRI study. In particular, we examine whether the relationship is mediated by the communication, or functional connectivity, between three brain regions: the caudate, prefrontal cortex (PFC), and medial temporal lobe (MTL). At the core of our hypothesis regarding these regions is the fact that the PFC and MTL are traditionally considered central regions of a distinct learning system which competes with the learning system supported by the caudate for control of behavior (Squire, 2004). Thus, the relative
balance of these systems (perhaps fostered by their functional connectivity) may be the neural mechanism by which mindfulness is negatively associated with IPSL.

**Functional connectivity & implicit learning**

**Caudate-MTL connectivity.** As a first step in examining the neural underpinning of the negative mindfulness-IPSL relationship, it is important to understand the balance of learning systems that is optimal for IPSL. The importance of the caudate for this type of learning is well-established (Gamble et al., 2014; Rieckmann et al., 2010; Simon, Stollstorff, et al., 2011; Simon et al., 2012). However, there is also evidence that the MTL, a region once thought to exclusively support functions of the explicit learning system, supports components of IPSL as well. For example, a number of studies have shown that the MTL is coactivated with the caudate during IPSL tasks, and that a specific temporal pattern of activation in these regions is associated with learning outcomes (Albouy et al., 2008; Gheysen et al., 2011; Rieckmann et al., 2010; Rose et al., 2002; Schendan, Tinaz, Maher, & Stern, 2013; Simon et al., 2012). In addition, the integrity of white matter tracts connecting both the MTL and caudate to the dorsolateral PFC has been shown to positively relate to IPSL (Bennett et al., 2011). These seemingly paradoxical findings suggest that more communication/coordination between regions belonging to two traditionally distinct and complementary learning systems is beneficial for IPSL.

Chapter II of the present dissertation (Stillman et al., 2013) further supports this idea, providing the first direct evidence that the *functional* communication between the caudate and MTL is related to IPSL aptitude. In this earlier study, we found that individuals with stronger, more positive intrinsic functional connectivity between the
caudate and right MTL learned more on a subsequent IPSL task. We interpreted these results as suggesting that perhaps positive connectivity between these regions prior to learning enables them to communicate and interact more efficiently during learning (i.e., promotes “readiness to learn”). We could not test this hypothesis directly because we did not collect fMRI data while participants were performing the IPSL task. However, these findings add to the body of fMRI and DTI evidence highlighting the importance of communication between the caudate and MTL for IPSL.

**Caudate-PFC connectivity.** There is also evidence, albeit more tentative, suggesting that communication between the caudate and PFC is related to IPSL. This evidence comes from behavioral studies showing that IPSL improves following a reduction in the involvement of frontal brain regions. For example, IPSL improves following inhibitory theta burst stimulation to the dorsolateral PFC, as well as following hypnosis, a procedure thought to disrupt the functional connections of prefrontal brain regions underlying cognitive control (Galea et al., 2009; Nemeth et al., 2012). While none of these studies measured functional connectivity between the caudate and PFC directly, one potential interpretation of these results is that less regulation of the caudate by prefrontal regions (and perhaps less connectivity between them) benefits IPSL.

**Functional connectivity & mindfulness**

In addition to its importance for IPSL, communication between the two learning systems may also be related to mindfulness.

**Caudate-PFC connectivity.** Several lines of evidence, for example, suggest connectivity between the caudate and PFC is relevant for mindfulness. However, there are two opposing views regarding how connectivity between these regions should relate
to mindfulness. The “regulatory” account suggests that mindfulness might increase the PFC’s ability to exert top-down regulation of subcortical systems (e.g., Chiesa, Serretti, & Jakobsen, 2013), while the “reduced reactivity” account posits that mindfulness might reduce the need for such top-down regulation (e.g., Shapiro, Carlson, Astin, & Freedman, 2006).

The majority of evidence favors the regulatory account. For example, many studies suggest that training in mindfulness increases the structure (e.g., regional brain volume and white matter integrity) and functioning (e.g., mean BOLD signal and resting state activity) of frontal brain regions involved in cognitive control and explicit cognitive functions (Grant et al., 2010; Luders, Toga, Lepore, & Gaser, 2009; Tang et al., 2009, 2010). In addition, training-induced changes in PFC activity and structure have been shown to lead to reductions in habitual/automatic types of processes supported by striatal regions (e.g., caudate), such as consumption of addictive drugs and cue-related cravings (Garland et al., 2014; Tang et al., 2013). These studies suggest that mindfulness may increase PFC connectivity to subcortical regions, thereby promoting top-down regulation of functions that are otherwise habitual.

Importantly, however, there is recent evidence from the mindfulness literature that instead supports the alternative reduced reactivity account. In a study of cue-induced craving, for example, habitual smokers reported a reduction in cravings when trained to view smoking-related cues in a mindful state (Westbrook et al., 2013). However, unlike in the studies cited in support of the regulatory account above, the reduction in craving in the mindfulness condition was associated with decreased activity in frontal regions (anterior cingulate cortex, ventromedial prefrontal cortex), as well as a decrease in
functional connectivity between these regions and a network of habit-related brain regions, including the caudate. The authors reasoned that instructing participants to “notice and accept” in the mindful condition rather than to try to regulate or suppress their cravings resulted in this pattern of behavioral and neural effects. In addition, mindfulness training has also been shown to decrease activity in striatal regions in reward-related tasks (Kirk & Montague, 2015), and dispositional mindfulness is associated with smaller volumes in subcortical regions (Taren et al., 2013). Although the reduced reactivity account is less pervasive in the mindfulness literature, these studies raise the possibility that mindfulness may be associated with less connectivity between the caudate and PFC. Thus, while caudate-PFC connectivity might be related to mindfulness, it is ultimately hard to predict the direction of this relationship based on the mixed (and predominately indirect) nature of the existing evidence.

**Caudate-MTL connectivity.** It is similarly difficult to predict how caudate-MTL connectivity—another link between the two learning systems—might relate to mindfulness, as few studies of mindfulness have focused on these regions. There is evidence, however, that the structure and functioning of the caudate and MTL change following mindfulness training (Holzel et al., 2011; Kirk & Montague, 2015; Lutz et al., 2014; Pickut et al., 2013; Tang et al., 2009; Zeidan et al., 2011). The structure of both of these regions has also been shown to negatively relate to dispositional mindfulness (Taren et al., 2013). This evidence, coupled with the fact that caudate-MTL connectivity is important to IPSL, led us to reason that caudate-MTL connectivity might be a mechanism by which the balance of the implicit and explicit learning systems is modulated.
Present Study

The present study has three main aims. The first aim is to replicate the negative relationship between mindfulness and IPSL reported in Chapter III (Stillman, Feldman, et al., 2014). The second aim is to identify functional connections during the task related to individual differences in learning, thus extending the results reported in Chapter II (Stillman et al., 2013). Finally, a third aim is to assess whether either of the functional connections between learning systems discussed above (caudate-PFC or caudate-MTL) mediates the relationship between mindfulness and IPSL.

Participants completed a self-report questionnaire assessing their level of dispositional mindfulness. They then completed three sessions of an IPSL task (the TLT) while undergoing MRI. Based on the results of Chapter III, we predicted that there would be a negative relationship between mindfulness and IPSL. Based on the results of Chapter II and the broader IPSL literature, we predicted that caudate-MTL connectivity would be positively correlated with learning, but that caudate-PFC connectivity might be negatively correlated with learning. Based on indirect evidence from the mindfulness literature, we predicted that caudate-PFC and caudate-MTL connectivity would be correlated with mindfulness. However, we were not able to make a clear prediction regarding the direction of these relationships, as the existing evidence implicating these connections is mixed and comes predominately from studies of mindfulness training.

Materials & Methods

Subjects
Fifty-one community-dwelling older adults ages 60 to 90 years were recruited from Georgetown University or the surrounding Washington DC area to participate in a
multi-day study. The majority of these participants (N=47) completed an fMRI-scanning
day, the data from which are the focus of the present study. Exclusion criteria included
self-reported use of 1) psychotropic medications (e.g., stimulants), 2) neurological injury,
disease or psychiatric diagnosis, 3) contraindications for MRI (e.g., presence of
irremovable metal in the body or pregnancy), and 4) left-handedness. Five participants
were excluded from the final imaging sample due to technical difficulties during scanning
(N=1), inability to complete the scan (N=2), or because it was subsequently determined
that they met one or more study exclusion criteria (N=2). The final sample for the present
study therefore consisted of 42 adults (mean ± SD age = 70.4±6.1; range: 60-90 years; 19
females). Neuropsychological functioning was assessed on a behavioral testing day prior
to the scan; all participants were deemed cognitively healthy based on their scores (Table
IV-1).

All participants gave informed consent in accordance with the guidelines of the
Declaration of Helsinki and the Georgetown University Institutional Review Board. They
were compensated with a $50 gift card for their participation in the fMRI component of
the study and $25 for the behavioral components.

fMRI Paradigm: The Triplets Learning Task (TLT)

The TLT was a shorter and slightly modified version from that reported in
Howard et al. (2008) and identical to that used in Chapter III (Figure III-1). Participants
viewed three open circles on a computer screen displayed against a light gray
background. Each trial, or “triplet”, consisted of three events: the sequential presentation

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1 Forty-five young adults ages 18 to 37 years were also tested as part of the larger,
multi-day study. However, the present study focuses only on the older adult sample,
as the mindfulness-learning correlation of interest was significant in the older, but
not in the younger group.
of two cue events, each consisting of one of the open circles filling in red, followed by a target event in which one of the circles filled in green. Each cue was displayed for 120ms and the green target remained on the screen for 750ms, with 150ms separating each event within a trial. Participants were instructed to observe the first two red events and to respond to the location of the green target as quickly as possible using spatially corresponding buttons held in the left and right hands (2 buttons in each hand).

Unbeknownst to participants, some triplets occurred more often than others; thus there was a probabilistic regularity embedded in the task.

Forty-eight triplets (out of a possible 64) were presented. On half the trials, one of eight high probability (HP) triplets occurred; on the other half of trials one of 32 low probability (LP) triplets occurred. This created an 80:20 ratio of HP vs. LP triplets as in the original version of the task, but, unlike the original task, resulted in an equal number of trials in the HP vs. LP conditions. Participants completed 3 runs consisting of 240 trials each with brief breaks provided every 48 trials. Each run was composed of 120 HP and 120 LP trials presented in a rapid, event-related design with a temporally jittered inter-trial interval ranging from 1-3 seconds. Trial and jitter order was presented in the same fixed, pseudorandomized sequence for all participants, optimized using the afni make_random_timing tool (http://afni.nimh.nih.gov/afni/).

Calculating Implicit Learning Scores. Learning in the TLT was assessed by comparing reaction time to HP vs. LP triplets. Median reaction times (RTs) were calculated for correct responses to each triplet type in each block of 48 trials. We then averaged these block medians, obtaining a single mean RT for each participant, for each of the two triplet types for each run. A RT difference score was then computed for each
run. Difference scores from the final run (run 3) were used as the learning outcome measure for all analyses reported below, as scores in the final run are thought to represent the cumulative amount learned at the end of exposure to the probabilistic regularity in the task. Higher scores indicate higher learning.

**Additional Behavioral Testing**

**The Mindful Attention Awareness Scale (MAAS).** On the behavioral test day prior to the scan, participants completed the Mindful Attention Awareness Scale (MAAS) to assess their dispositional mindfulness.

**Practice TLT.** Just prior to the scan, participants completed an abbreviated practice run of the TLT in a mock scanner within the imaging facility to ensure that participants were comfortable in a scanning environment and understood the task instructions. The practice task was identical to the version of the TLT described above, except that there was no probabilistic regularity that could be learned (i.e., triplets were presented at random) and participants completed only 96 trials.

**Computer-based Recognition Task and Interview.** Following the scan participants completed two sensitive measures to assess their explicit awareness of the probabilistic regularities in the TLT. They first completed a computer-based recognition task in which they were shown all 48 triplets that occurred during the scan, as well as the remaining possible 16 triplets that had never occurred; after each, participants indicated via keyboard button press whether they thought that triplet had occurred frequently (“2”) or infrequently (“1”).

After completing the computer-based recognition task, participants were asked a series of increasingly leading questions to probe for strategy use and explicit knowledge.
Questions ranged from general (e.g., “Do you have anything to report regarding the task?”) to highly specific (e.g., “In fact, there were some regularities or “triplets” that occurred more often than others. Can you name them?).

**fMRI data acquisition**

The scan was performed on a Siemen’s Trio 3-T scanner (Erlangen, Germany). A technician positioned participants in the supine position with a circularly polarized head coil, and fitted padding was inserted to minimize head movements. A mirror mounted on the head coil allowed participants to view task stimuli during scanning.

Functional data were acquired along the AC-PC line using T2*-sensitive gradient Echo Planar Imaging pulse sequence with the following parameters: TR/TE = 2500ms/30ms, 192mm x 192mm FOV, 64mm x 64mm acquisition matrix, and a 90° flip angle for an effective resolution of 3x3x3mm. Forty-seven contiguous 3mm thick axial slices were acquired interleaved in the transverse plane. We acquired three event-related runs of the TLT, with 368 volumes per run.

The scan concluded with the acquisition of a high-resolution T1-weighted structural scan (MPRAGE) lasting 4:18 minutes, with the parameters: TR/TE = 1900/2.52ms, TI = 900ms, 9 degree flip angle, 1 slab, 176 sagittal slices with a 1.0mm thickness, FOV = 250x250mm, matrix = 250x250, resulting in an effective resolution of 1 mm isotropic voxels.

**Preprocessing of functional images.** The first two images of each functional task run were discarded prior to preprocessing, as they had been included for signal stabilization. Preprocessing was conducted using SPM8 (Wellcome Department of Neurology, London, UK) implemented in Matlab (Version 2013a Mathworks, Inc.,
Sherborn, MA). Images in each run were corrected for translational and rotational motion by realigning to the first image of the run. They were then slice time corrected, normalized to an EPI template, smoothed using a Gaussian kernel with full width at half maximum of 8mm, and temporally filtered using a 128s highpass filter.

**Functional connectivity calculations**

**Seed region-of-interest-creation.** A bilateral caudate seed region of interest (ROI) was created using the anatomical aal atlas included in the WFU pickatlas toolbox implemented in Matlab2013a (Maldjian, Laurienti, & Burdette, 2004; Maldjian, Laurienti, Kraft, & Burdette, 2003; Tzourio-Mazoyer et al., 2002). The caudate was chosen as the seed given its well-established role in implicit sequence learning in older and younger adults (Aizenstein et al., 2006; Rieckmann et al., 2010; Schendan et al., 2013; Simon, Stollstorff, et al., 2011; Simon et al., 2012), as well as our *a priori* hypotheses regarding the relevance of functional connectivity between the caudate and medial temporal/prefrontal cortex to individual differences in learning.

**Nuisance Signal Identification.** To identify the effects of motion and physiological noise, time series approximating these signals were calculated for each participant and run. Physiological noise was approximated by obtaining signal time series from white matter and CSF segmentations of the MPRAGE image (Van-Dijk et al., 2010). Motion was obtained from the six realignment parameter time courses from the motion correction preprocessing step and their temporal derivatives. The six motion parameters were also used as first level regressors of no interest. To further control for the effects of motion, a threshold of >.5mm framewise displacement was also used to deweight potentially motion-corrupted timepoints from the task data prior to the
calculation of connectivity values, as recommended by Power and colleagues (2012). The global signal was not included as a nuisance signal since recent work has suggested that this procedure may reduce the accuracy of connectivity estimates within and between groups (Saad et al., 2012).

**Voxelwise functional connectivity calculation.** For each participant and for each run, partial correlations were conducted between the bilateral caudate seed timeseries and that of every other voxel in the brain, while partialling out motion and physiological noise timecourses. The resulting r values were converted to Z-scores using Fisher’s r to z transformation to increase normality of the distribution and allow for further statistical analyses of correlation strengths. This produced a whole brain map of the seed’s connectivity during each run of the TLT for each participant.

**Connectivity correlations with learning scores.** In order to examine task connectivity of the caudate seed that was correlated with individual differences in learning (aim 2), participants’ whole brain connectivity maps were entered as the dependent variable into an ANCOVA model using the GLMFlex extension for SPM8 (http://mrtools.mgh.harvard.edu/index.php/Main_Page). Second-level models created using this extension include additional corrections for between-subjects and within-factor error, thus reducing the chances of false positives compared to second-level repeated measures analyses conducted in SPM. Run 3 learning scores were included as a covariate of interest, while participants’ age and mean task RT were included as covariates of no-interest for all analyses.

Monte Carlo-based correction for multiple comparisons (Ward, 2000) was carried out using tools implemented in Analysis of Functional Imaging (AFNI) software (Cox,
Briefly, we estimated the smoothness of the preprocessed data (3dfwhmX utility), and then conducted 10,000 simulations of random noise activations with that same smoothness and within the same whole-brain volume as the primary analyses (3DClustSim tool). These simulations revealed that clusters exceeding both a voxelwise alpha of p<.0005 and a size of 64 voxels occurred less than 5% of the time, corresponding to a p<.05 whole brain cluster-level significance threshold. Unless otherwise noted, the results reported below are corrected using this threshold.

Results

Did participants learn?

Participants were highly accurate in the task (M = .90, SD = .08) so few trials were eliminated. A one-sample t-test revealed that, on average, RT–based learning scores in the final run (run 3) did not differ significantly from zero, t(41) =1.4 , p =.16 . However, there was substantial inter-individual variability in learning performance (range of LP-HP difference scores = -32.5ms to 42.2ms). Further, learning scores were not correlated with any of the neuropsychological measures reported in Table IV-1, nor were they correlated with age, mean task reaction time, or mean task accuracy (all ps >.12), suggesting that individual differences in these measures cannot account for the wide range of learning scores. This pattern of results therefore lends itself nicely to examining other characteristics, such as mindfulness and/or the hypothesized functional connections, that might better account for the variability in learning success.

Was learning implicit?

Participants’ mean frequency ratings on the recognition task were entered into a one-way ANOVA with triplet type (HP, LP, and unseen) as a repeated measures factor.
There was a main effect of triplet type, $F(1, 82) = 8.87, p < .0001$, demonstrating that frequency ratings differed across the three types of triplets presented during the recognition task. Follow-up t-tests revealed that participants rated triplets they never saw during training significantly lower ($M = 1.46, \ SD = .25$) than they rated the LP ($M = 1.54, \ SD = .22; \ t(41) = 3.12, p = .003$) and HP triplets ($M = 1.58, \ SD = .26; \ t(41) = 3.5, p = .001$) that they had seen during training. This pattern of responding suggests that participants understood the instructions for the recognition task and were complying with them. Critically, however, there was no difference in ratings of the HP vs. LP triplets ($t(41) = 1.44, p = .16$), suggesting that participants could not report which had occurred more often in the task, even though they could reliably distinguish between triplets they saw during training and those they did not.

We next examined participants’ responses to the verbal interview for signs of awareness. Out of the forty-two participants, only two were able to name a HP triplet (reported 1 HP triplet: $N = 1$; reported 2 HP triplets: $N = 1$), and only one participant reported noticing a pattern in the task. Beyond this, however, participants were unable to accurately describe the regularity in the TLT. Overall, therefore, the recognition data from these two measures suggest that learning in the TLT was largely implicit.

**Is learning correlated with mindfulness?**

Consistent with our prediction (aim 1), as well as the results of Stillman et al. (2014) reported in Chapter III above, participants’ learning scores were negatively correlated with their MAAS scores, $r(42) = -.35, p = .02$ (Figure IV-1). The relationship remained significant after controlling for age and mean task RT, $r(42) = -.36, p = .02$.

**Does caudate functional connectivity relate to learning success?**
Whole brain results. Consistent with our hypothesis, the ANCOVA results revealed an effect of learning in the left (peak MNI x, y, z = -24, -13, -17; k = 177) and right (peak MNI x, y, z = 45, -13, -26; k = 69) medial temporal lobes (MTL). These were the only two clusters to survive whole brain correction, and there were no other significant effects or interactions. The lack of a learning x run interaction implies that stronger, more positive connectivity between the caudate and MTL during all runs of the TLT is associated with better learning in the final run. This implication was subsequently confirmed with follow-up analyses assessing the correlation between caudate-MTL functional connectivity and learning in each run individually ($r > .41$, $p < .006$). Since the relationship was consistent across all runs, the cross-run average connectivity between the caudate and MTL clusters is presented in Figure IV-2a and is used for the mediation analyses reported below.

Prefrontal-specific results. Contrary to our hypothesis, the whole brain analysis did not reveal any prefrontal clusters whose connectivity to the caudate seed covaried with individual differences in learning. However, because we also had a specific a priori hypothesis about caudate-PFC connectivity we conducted a follow-up analysis in which we repeated the ANCOVA described above, this time restricting the results to prefrontal regions using an anatomically-defined mask. The frontal mask was created using the aal atlas within the WFU pickatlas toolbox for SPM and included bilateral orbitofrontal, anterior cingulate, middle frontal, and superior frontal cortices. These regions were chosen because their activity, connectivity, and/or volume have been shown to be modulated by mindfulness training or to covary with dispositional mindfulness (for reviews see Tang & Posner, 2012; Vago & David, 2012). This analysis revealed a cluster
in the anterior right middle/superior frontal gyrus (BA10; peak MNI x,y,z = 30,59,19; k = 201) whose connectivity with the seed was positively correlated with learning (Figure IV-2b). The cluster survived a Monte Carlo-based correction threshold calculated for the masked volume at p < .05 (corresponding to an uncorrected threshold k = 103, p =.005).

**Do the functional connections related to learning success also relate to mindfulness?**

Having identified three functional connections associated with learning, we next tested whether the strength of any of these connections was also associated with mindfulness. We found that caudate-lMTL (r(42) = -.35, p =.02) and caudate-rMTL connectivity (r(42) = -.35, p = .02) were negatively correlated with mindfulness (Figure IV-3). However, caudate-BA10 connectivity was not correlated with mindfulness (p = .23).

**Does functional connectivity mediate the learning-mindfulness relationship?**

Finally, we tested the two functional connections correlated with both mindfulness and learning (caudate-lMTL, caudate-rMTL ) as mediators of the relationship between these two behavioral variables (Figure IV-4a). We did not examine the caudate-BA10 connection identified as correlating with IPSL above, because it did not correlate with mindfulness scores, indicating it did not qualify as a potential mediator of the mindfulness-IPSL relationship (Baron & Kenny, 1986).

Each potential mediator was tested in a simple mediation model by calculating bias-corrected 95% confidence intervals using a bootstrapping procedure with 1,000 resamples using the PROCESS macro for SPSS (Hayes, 2013; Preacher & Hayes, 2008). There was a significant indirect effect of mindfulness on learning through caudate-lMTL connectivity, b = -6.0, p = .02, BCa CI [-12.68, -.62]. This represents a medium- to large-
sized effect, $\kappa^2 = .21$, BCa [.03, .40]. There was also a significant indirect effect of mindfulness on learning through caudate-rMTL connectivity, $b = -5.48$, BCa [-11.74, - .20], which represents a medium-sized effect, $\kappa^2 = .19$, BCa [.02, .36].

Figure IV-4b depicts the amount of variance in learning explained by mindfulness alone compared to when caudate-lMTL or caudate-rMTL connectivity was included in the model. When mindfulness was the sole predictor of learning, a significant portion of the variance was accounted for (12%). However, when either caudate-lMTL or caudate-rMTL was also entered into the model, each was an independently significant predictor, accounting for a significant 38% and 32.8% of the variance in learning, respectively. Further, mindfulness no longer accounted for a significant portion of the variance in learning (1.9% and 2.4%, respectively) following the inclusion of these connections, suggesting that caudate-MTL functional connectivity fully mediated the relationship between mindfulness and learning.

To further calculate the degree to which connectivity attenuated the amount of variance in IPSL that can be explained by mindfulness, the amount of variance uniquely associated with mindfulness after removing variance attributable to caudate connectivity to the l- or r-MTL was subtracted from the amount of variance associated with mindfulness as the sole predictor, and then divided by the amount of variance with mindfulness as the sole predictor (Bennett et al., 2011; Salthouse, 1991). This calculation revealed that connectivity between the caudate and l- and rMTL attenuated mindfulness-related variance in IPSL by 84% and 80%, respectively.
Discussion

The present study examined the neural mechanisms underlying the negative relationship between dispositional mindfulness and implicit probabilistic sequence learning (IPSL) reported in Stillman et al (2014). We first replicated the negative relationship between these two behavioral variables in a sample of healthy older adults. Then, using a seed-based connectivity approach, we identified functional connections associated with individual differences in both learning and mindfulness. The main finding was that caudate-MTL connectivity was positively correlated with IPSL and negatively correlated with mindfulness. Further, the strength of connectivity between these regions mediated the negative relationship between mindfulness and IPSL. Thus, the functional communication between two learning-relevant regions can account for the relationship between mindfulness and IPSL. Discussion of these findings is organized in terms of the three study aims below.

Aim 1: Behavioral Replication of Mindfulness-Learning Association

One important behavioral finding from this study is that older adults did not show evidence of learning at the group level. This was not expected given that we usually find a group-level learning effect for older adults in the TLT, although the magnitude of this effect is often reduced compared to younger adults (J. H. Howard Jr & Howard, 2013; Rieckmann & Bäckman, 2009). The lack of a group effect in the present study could reflect changes made to the traditional TLT to make it more suitable for the scanner (e.g., fewer trials, jitter, balanced number of HP vs. LP events), or might have been imposed by characteristics of the imaging environment.

Nonetheless, the broad range of inter-individual variability in learning within the
group, is a pattern that is common in aging populations (Lindenberger & Baltes, 1997). We therefore capitalized on this variability by examining correlations between learning outcomes and the trait of interest (i.e., mindfulness). As in Stillman et al (2014) we observed a negative relationship between mindfulness and IPSL in healthy older adults, which could not be attributed to individual differences in age or overall task performance. This represents the second replication of the effect in healthy adults and provides further support for the hypothesis put forth in Stillman et al (2014) that dispositional mindfulness does not benefit implicit learning.

In addition, the present behavioral findings extend our earlier study in several ways. First, we observed the mindfulness-IPSL correlation in a sample more than double the size used in either of the studies reported in Stillman et al (2014), thus addressing a major limitation of those studies. In addition, present sample was more balanced in terms of the gender composition, whereas the samples in our earlier study were mostly female. Finally, the older adults in the present study completed the TLT in the scanner, whereas those in Stillman (2014) (study 2) completed a different IPSL task (the ASRT) in a behavioral testing room. Thus, these results further support that the relationship between mindfulness and IPSL is not limited to a particular gender, learning task, or testing context. However, future work testing whether the relationship between dispositional mindfulness and learning holds using different implicit tasks and/or age groups would be informative, particularly because we failed to replicate this relationship in the younger adult sample in the present study. One possibility, for example, is that the relationship between mindfulness and cognitive functioning (e.g., IPSL) is stronger in certain age groups than in others.
Aim 2: Task connectivity related to learning

**Caudate-MTL connectivity.** Consistent with our prediction, caudate-MTL connectivity was related to IPSL in the TLT. Specifically, more positive connectivity between the caudate and clusters in the left and right MTL (at every session) was correlated with higher learning scores in our sample of healthy older adults. This pattern of results extends those reported in Stillman et al, (2013) in which we demonstrated that more connectivity between these regions at rest predicted better subsequent learning in healthy young adults. Because we did not collect fMRI data in that earlier study, however, it was not possible to tell how the caudate and MTL interacted during learning.

The present results are therefore the first to show that more functional connectivity between the caudate and MTL during an IPSL task is beneficial for learning. Since more connectivity between brain regions at the time of measurement is thought to reflect their shared functionality (M. D. Fox & Raichle, 2007), this finding lends further support to a hypothesis put forth in previous fMRI activation studies of IPSL, as well as recent reviews of learning and memory systems, both of which have posited that both the caudate and MTL support learning-related functions during IPSL, despite the fact that this particular type of learning occurs implicitly (Henke, 2010; J. H. Howard Jr & Howard, 2013; Schendan et al., 2013; Simon et al., 2012).

An important caveat to these findings is that the present sample consists of healthy older adults, and so it is possible that the relationship between caudate-MTL connectivity during task and learning would be different in a younger sample. Indeed, there is evidence of functional reorganization of learning systems in older adults, perhaps stemming from the fact that the striatum declines at a faster rate than the MTL during...
healthy aging (Naftali Raz et al., 2005). Furthermore, fMRI studies of IPSL have reported that MTL activation is correlated with better learning at all stages of training for older adults, while it is only correlated with better learning in the early stages of training in younger adults (Rieckmann et al., 2010; Simon et al., 2012). For younger adults, learning in later stages of training is typically correlated with caudate activity, suggesting that MTL activation in late training in older adults may be somehow compensating (albeit not completely successfully) for striatal dysfunction in this age group. The finding that caudate-MTL connectivity at all three runs correlated positively with participants’ run 3 learning score in this study could therefore reflect a compensatory mechanism by which some older individuals are able to optimize IPSL despite age-related neural changes through the persistent communication between these regions. However, the fact that a similar relationship was found in younger adults in a pre-task resting state (Chapter II) suggests that the positive relationship between caudate-MTL connectivity and learning is not limited to older adults.

**Caudate-PFC connectivity.** Contrary to our predictions, caudate connectivity to a cluster in the right anterior middle/superior frontal gyrus (BA10) was positively related to learning. We had initially predicted that we would observe a negative relationship between learning and caudate-PFC connectivity based on the popular hypothesis that a prefrontal-based explicit hypothesis testing system competes with a striatal-based implicit procedural system for control of behavior (Filoteo et al., 2010; Poldrack & Packard, 2003). Previous behavioral studies of IPSL have reported results consistent with this latter hypothesis. For example, studies have demonstrated that IPSL improves following inhibitory theta burst stimulation to the DLPFC, as well as following hypnosis (Galea et
al., 2009; Nemeth et al., 2012). Both of these procedures are thought to disrupt the connectivity of a prefrontal region underlying executive control (especially the DLFPC) from other brain regions, such as the caudate, suggesting that decreasing prefrontal regulation maximizes striatal types of learning (Halligan & Oakley, 2012).

The findings from the present study, however, suggest that the interplay between these learning systems may be more nuanced than originally thought. For example, there are several distinct frontostriatal loops known to support complex cognitive functions, including implicit ones such as IPSL (Chudasama & Robbins, 2006). Thus, one possible explanation for the positive relationship between learning and caudate-PFC connectivity that we detected is that the nature of the caudate-PFC interactions during ISPL differs by anatomical region. Consistent with this interpretation, the prefrontal cluster we identified (i.e., in the middle/superior frontal gyrus) is located anterior to the dorsolateral prefrontal regions that are the most often implicated in theories of competition (Galea et al., 2009; Halligan & Oakley, 2012; Nemeth et al., 2012). Rather than supporting regulatory functions per se, this particular region of the PFC is thought to be involved in integrating complex information over time (Prabhakaran, Narayanan, Zhao, & Gabrieli, 2000). Thus, stronger connectivity between the caudate and this region might enable individuals to more efficiently integrate the complex probabilistic relationship occurring amongst the sequentially presented cues in the TLT, providing a potential explanation for why the connectivity between the caudate and this particular PFC region is positively related to learning success.

Aim 3: Mediation results

The third goal of this study was to identify neural mediators of the mindfulness-
IPSL relationship. Contrary to our predictions, the caudate-PFC connection identified as being related to learning was not related to mindfulness, and so it did not meet the criteria for mediation (Baron & Kenny, 1986). However, the two caudate-MTL connections identified as being related to learning did qualify as potential mediators, as they were negatively correlated with mindfulness scores. The results of the (separate) mediation analyses on these connections revealed that both were full mediators of the relationship between mindfulness and IPSL, attenuating the amount of variance in IPSL that could be attributed to mindfulness by 84% and 80%, respectively.

While communication between the caudate-MTL has been posited to be important to IPSL in previous studies (as discussed above), this is the first time that the communication between these regions has been linked to dispositional mindfulness. Because of the novelty of this finding, it raises many questions for future research. For example, it is not clear whether mindfulness alters connectivity between the caudate and MTL systems directly, or by influencing one (or both) systems individually thus indirectly altering their connectivity.

According to the direct account, higher levels of dispositional mindfulness leads to reduced communication between the striatal and MTL learning systems, enabling one (e.g., the MTL system) to more effectively dominate behavior and leading to some of the health benefits linked to mindfulness (Chiesa, Calati, & Serretti, 2011; Chiesa & Serretti, 2011; McDonald & Hong, 2013). Since optimal IPSL may depend on efficient interaction/coordination between both the striatal and MTL systems (J. H. Howard Jr & Howard, 2013; Paul J. Reber, 2013; Rieckmann & Bäckman, 2009), this interpretation would explain why reduced communication between the caudate and MTL leads to lower
learning scores; less communication between the two regions might enable the MTL system to dominate throughout the course of IPSL, which would lead to less learning since the striatal system is thought to be optimal in later stages of training (J. H. Howard Jr & Howard, 2013; Simon et al., 2012).

In contrast, the indirect account suggests that mindfulness-induced functional and structural changes to these regions (mostly reported in mindfulness training studies) have downstream consequences on their functional communication. In other words, the negative relation between mindfulness and caudate-MTL connectivity in the present study could be a byproduct of other changes to these brain regions that are linked to mindfulness, that in turn lead to reduced communication between them. For example, recent fMRI studies have reported that (compared to novices) experienced meditators show less activity in striatal regions during both the anticipation and response phases of reward conditioning tasks (Kirk et al., 2014; Kirk & Montague, 2015). The meditators’ diminished striatal responses in these studies is thought to reflect their ability to dampen and/or override anticipatory dopamine responses to reward-related cues following mindfulness training, thereby allowing them to act in more controlled, non-reactive (i.e., non-habitual) ways (Kirk & Montague, 2015). Since dopaminergic projections are the main mechanism by which the caudate communicates with other brain regions, the reduced reactivity of striatal regions observed in meditators may result in this region becoming more functionally segregated from other brain regions (including the MTL), thereby leading to less learning on tasks, such as IPSL where communication/coordination between these regions may be critical. Both of the above accounts are consistent with the mediation model we propose. However, future research
is needed in order to distinguish between them.

**Methodological Considerations & Future Directions**

**Inferring Cause.** Both of the interpretations we offer above for the mediation results assume that mindfulness is leading to the observed reduction in caudate/MTL connectivity, rather than the reverse. Our ability to make causal inferences regarding the direction of the relationships amongst mindfulness, connectivity, and learning is limited by the correlational nature of our design. For example, it is possible to imagine various arrangements of the mediation model presented in Figure IV-4a, since it is difficult to establish a temporal ordering of these variables. However, there is theoretical evidence (e.g., from mindfulness training studies) supporting the *a priori* directionality assumptions we made when conceptualizing the casual pathways in this model.

Another, related point is that we only examined dispositional mindfulness and not the effects of mindfulness training. While we relied on evidence from training studies to form our hypotheses and interpret our results, it is possible that the neural mechanisms of mindfulness training differ from those underlying dispositional mindfulness. This is still an area of ambiguity in the mindfulness field in general, however, and is therefore not a limitation unique to our study (Davidson, 2010). Future work should include implicit learning tasks in neuroimaging studies both before and after mindfulness training in order to test whether the mediation model we propose is supported in the training domain as well.

**Chosen Seed.** We chose to use a caudate seed to identify candidate connections for our mediation analyses given the centrality of this region in implicit types of learning. In addition, we had *a priori* hypotheses regarding how the functional connections of this
region might also be modulated by mindfulness. However, we acknowledge that the pattern of results we report would likely differ if other seed regions or approaches to calculating functional connectivity were used. Future studies could examine these possibilities, as the relationships between functional connectivity, mindfulness, and specific cognitive functions/behaviors have rarely been investigated to date and thus remain poorly understood (Tang et al., 2015).

**Psychophysiological Interactions vs. General Task Connectivity.** It should be noted that the present study did not use the popular psychophysiological interaction (PPI) analyses for examining condition-specific changes in connectivity between brain regions during fMRI tasks; we instead collapsed across the HP and LP task conditions for our analyses. Because of this, it is possible that the connections we identified as being related to individual differences in learning (caudate-MTL and caudate-PFC) were not supporting learning per se, but rather some other aspect of the task related to learning outcomes. However, PPI analyses are known to have a higher rate of Type II error in event-related compared to block-designs (O’Reilly, Woolrich, Behrens, Smith, & Johansen-Berg, 2012), and so we chose to use this alternative approach to decrease the chances of spurious null results, given our even-related design. Future fMRI studies could administer IPSL tasks in a blocked design (e.g., pattern vs. random blocks) in order to more effectively implement PPI analyses.

**Conclusions**

The present results implicate functional connectivity between the caudate and MTL as the neural mechanism underlying the previously reported behavioral relationship between dispositional mindfulness and IPSL (Stillman, Feldman, et al., 2014). These
findings contribute to our understanding of how specific traits (i.e., mindfulness) might influence our aptitude for basic cognitive functions, such as acquiring complex regularities without awareness or intent. They also highlight the need for more studies examining the complex interplay between mindfulness (even one’s natural propensity for it), the brain, and behavior.
CHAPTER V: GENERAL DISCUSSION

This dissertation presents three studies examining neural and behavioral characteristics associated with individual differences in IPSL aptitude. The characteristics investigated (mindfulness and functional brain connectivity) were selected because they had previously been associated with individual differences in functioning in other cognitive domains. Further, both can be changed with experience/training, making them good candidates for future work aimed at changing cognitive functioning. The findings advance our understanding of how certain traits may modulate the complex interaction between learning systems, thereby influencing individuals’ propensity, or readiness, to learn in this essential way.

Chapter II examines a neural characteristic—resting state functional connectivity between task-relevant brain regions—that might promote readiness to learn. Though intrinsic connectivity had previously been shown to predict individual differences in cognitive performance (see Vaidya & Gordon, 2013 for review), it had never been used to predict performance on an implicit task in which participants were not informed of the task goals. The findings reported in Chapter II were therefore the first to demonstrate that better subsequent IPSL can be predicted by stronger intrinsic connectivity between the caudate and MTL, two regions traditionally considered to serve functions of distinct, functionally incompatible learning systems (Squire, 2004). Combined with evidence from task activation studies demonstrating that both of these regions are coactive during IPSL (albeit on different time scales), this finding suggests that communication between them prior to learning may promote their optimal interaction during learning. Supporting this idea, Chapter IV extends the resting state
findings from Chapter II to the task state, as well as to healthy older adults, demonstrating for the first time that more functional connectivity between the caudate and MTL during all three event-related fMRI runs of an IPSL task is associated with better IPSL. Thus, more communication between the caudate and MTL systems prior to and throughout learning may promote healthy adults’ readiness to implicitly acquire complex regularities occurring over time.

Chapter III focused on a behavioral characteristic—dispositional mindfulness—that might also relate to readiness to learn. Mindfulness had previously been shown to be positively associated with explicit cognitive functioning (Mrazek et al., 2012; Oberle et al., 2011; Schmertz et al., 2009), but only one previous study had examined its relationship to performance on an implicit (artificial grammar learning) task (Whitmarsh et al., 2013). However, in this earlier research implicit learning was inferred through grammaticality judgments made after the task, which could also imply that mindfulness is correlated with a deficit in consolidation or retrieval rather than implicit learning, per se. No previous studies, therefore, had examined how mindfulness might relate to implicit learning of probabilistic regularities occurring over time in a task in which learning can be measured online (i.e., as it is occurring, through response speed measurements collected during the task). The studies in Chapter III are therefore the first to show dispositional mindfulness is negatively associated with IPSL. Importantly, the two studies reported in Chapter III differed in the age group tested (young vs. older adults), task used, and testing environment, and so the association between these two variables could not be explained by specific sample or study characteristics. Instead, we proposed a candidate neural mechanism for the negative mindfulness-IPSL association involving the
competitive interaction between the striatal and prefrontal systems in IPSL (Galea et al., 2009; D. V. Howard & Howard, 2001; Nemeth et al., 2012). Specifically, we reasoned that the balance of these neural systems that is promoted by mindfulness, namely an upregulation of the PFC control system, may be suboptimal for implicit learning.

Chapter IV replicates the negative correlation between mindfulness and IPSL reported in Chapter III in a new sample of healthy (older) adults. In this fMRI study, we were also able to examine the neural mechanism underlying this effect, using a seed-based connectivity approach. The findings demonstrated a pattern of correlations consistent with the idea that caudate-MTL connectivity mediates the relationship between mindfulness and implicit learning: Caudate-MTL connectivity was positively associated with learning, but negatively associated with mindfulness, and the strength of connectivity between these regions accounted for nearly all of the variance in IPSL that had previously been attributed to mindfulness--i.e. mindfulness was no longer a significant predictor of IPSL when connectivity was entered first into the model, consistent with full mediation. Chapter IV thus extends the results of both previous chapters by using functional brain connectivity during task (i.e., instead of the resting state connectivity examined in Chapter II) to examine the neural bases for the novel mindfulness-implicit learning relationship reported in Chapter III. **The findings from this study are the first to propose a mediating neural mechanism for the novel mindfulness-IPSL relationship reported in Chapter III.**

Taken together, the studies from all three studies suggest that healthy adults’ aptitude for IPSL is linked to the nature in which specific learning-relevant systems interact/communicate. These findings also suggest certain behavioral traits, such as
mindfulness, may play a role in influencing interactions between learning-relevant neural systems, thereby influencing individuals’ behavioral propensities.

**Limitations**

**Direction of Cause**

The studies in this dissertation should be interpreted in light of some common limitations. One limitation stems from the fact that all of the studies were correlational. This makes it impossible to infer causality and leaves open the possibility that some additional, unmeasured factor could be influencing the associations in each of the studies reported. Even though the study reported in Chapter IV statistically tested for causal relationships between mindfulness, brain connectivity, and IPSL (i.e., via use of a mediation model), the mechanistic model in that study was limited by the fact that we could not definitively establish the temporal ordering of these variables. While we can establish proximate temporality because of the order in which we administered the tasks (i.e, MAAS first, followed by the event-related IPSL task) we cannot say which was established first—an individual’s dispositional mindfulness or the strength of specific neural connections in that person’s brain. That is, it is possible that having a higher propensity for mindfulness over one’s lifetime changes the brain’s intrinsic caudate-MTL connectivity, influencing the task connectivity relationships we observed, or visa versa. Therefore, future work could extend the findings reported in these chapters by conducting controlled, longitudinal training studies measuring connectivity and mindfulness before and after training. These studies would address intriguing open questions related to the direction of cause, such as whether becoming more mindful changes the brain’s intrinsic
and task-related connectivity, or whether interventions that change caudate-MTL connectivity also lead to changes in mindfulness.

**Age groups investigated**

Another limitation of these studies was that all relied on healthy young or older adult samples in order to examine factors related to individual differences in IPSL. Because we focused on adult age groups only it is not possible to infer whether the detected associations would differ (or even exist) in other developmental periods, such as early childhood and adolescence. This limitation is particularly relevant for the functional connectivity relationships reported in Chapters II and IV, as functional and structural brain networks are still maturing well into adolescence and are also known to change in late life in both healthy and pathological aging populations (Damoiseaux et al., 2007; Uddin, Supekar, Ryali, & Menon, 2011). Given that brain networks change across the lifespan, it is also important to note that the fMRI study in Chapter IV focused only on older adults. We had focused on older adults in this study due to the fact that the negative mindfulness-IPSL relationship of interest was only replicated in this sample. However, it is possible that even if the same behavioral relationship between mindfulness and IPSL were detected in other age groups (e.g., as it was in Chapter III), the neural mechanisms underlying this relationship could differ. Future work should therefore extend these studies to additional age groups to assess the generalizability of the results across the lifespan.

**One type of learning**

Finally, a third limitation is that the studies in this dissertation examined neural and behavioral characteristics associated with a specific type of implicit learning, which
involves the acquisition of complex, probabilistic regularities occurring in sequences of events. However, there are many different types of implicit learning, each with slightly different neural substrates (P. Reber, 2013). In fact, some types (e.g., repetition priming) do not rely on the MTL and striatal systems much at all (e.g., Schacter & Buckner, 1998). Thus, it is likely that the relationships reported in these studies do not extend to other types of implicit processes, especially those in which interactions between the caudate and MTL systems are not as central. Another, related point here is that due to the differences in neural substrates across different types of implicit learning, traits/states that are negatively associated with some types of learning might be positively associated with others. Including a battery of different implicit learning tasks in future studies would therefore be informative.

**Methodological Approach**

An important methodological caveat to take into consideration when interpreting the functional connectivity results of Chapters II and IV is that both used a seed-based approach. Further, both of these studies used a caudate seed because of the *a priori* relevance of this region to implicit learning. While such seed-based approaches provide useful information about how the activity of a specific region correlates with that of the rest of the brain, their focus on a single region inherently limits the amount of information they can provide. Because these studies centered on the caudate, it is possible that the connectivity-behavior relationships detected are driven by some third region (or network of regions), which was not detected. Thus, in order to fully understand the relationships reported in these studies it will likely be necessary to go beyond a single
seed-based approach, as well as to elucidate the roles that brain structure and activation might play in these findings.

Implications & Remaining Questions

Correlational studies, such as the ones reported in this dissertation, are important for identifying factors that may contribute to individual differences in essential cognitive functions. However, an important direction for future research aimed at promoting successful aging is to develop strategies and interventions to change cognitive functioning. Though there are undoubtedly many characteristics of individuals that are relevant towards this goal, the two characteristics examined in this dissertation are promising in that both can be modified by prior experiences and/or training (Albert et al., 2009; Chambers, Lo, & Allen, 2008; Rajab et al., 2014; Shapiro, Brown, & Biegel, 2007; Wegman & Janzen, 2011). But the elephant in the room implied by the finding that mindfulness is negatively related to IPSL (and the neural connection supporting it) is that training mindfulness might actually decrease one’s aptitude for this type of learning. Given the essential role IPSL is thought to play in enabling functional independence across the lifespan, this paradoxical finding suggests that increasing mindfulness may have negative implications for health. As will be discussed below, however, this conclusion might be premature, so more research is necessary before the implications of this novel relationship can be fully appreciated.

One critical question that must be addressed stems from the ambiguity surrounding the extent to which dispositional mindfulness and the act of cultivating it are the same vs. distinct. A major theoretical assumption made in Chapters III and IV was that dispositional mindfulness and mindfulness that has been cultivated through targeted
meditation training are identical, and should thus work through the same neural mechanisms to influence behavior. As was discussed in more detail within those chapters, there is indirect evidence for this assumption given that dispositional mindfulness is positively associated with the same types of cognitive functions that are improved by mindfulness training. In addition, dispositional mindfulness scores on the MAAS have been shown to change following mindfulness training, implying that dispositional mindfulness and mindfulness training are overlapping constructs (Chambers et al., 2008; Shapiro et al., 2007).

Despite convergence at the behavioral level, the literature is not as clear on the extent to which the neural mechanisms of dispositional and trained mindfulness are the same. Studies focused on functional and structural changes following mindfulness training sometimes report contradictory findings, and many of these findings have not been replicated. In addition, most of the evidence for the brain basis of mindfulness comes from cross-sectional studies comparing experienced vs. novice meditators rather than from controlled longitudinal studies, making it possible, for example, that there were pre-existing brain differences between the two groups. Further clouding the comparison of the neural bases of dispositional and trained mindfulness, only a few studies to date have examined the neural basis of dispositional mindfulness. Therefore, it is possible that the neural substrates of dispositional and trained mindfulness are different, or that they may initially overlap (e.g., in early stages of mindfulness training), and then diverge once mindfulness has become habitual (e.g., in later stages of training) (Tang et al., 2015). An intriguing hypothesis arising from this latter possibility is that training may initially impair IPSL, but that this relationship would be reversed following more extensive
training. Including both implicit learning tasks and the MAAS in longitudinal imaging studies of mindfulness training would therefore be useful in providing insight on this issue, as would testing implicit learning in highly skilled long-term practitioners.

Another direction for future studies is to examine whether the negative mindfulness-IPSL association we detected could serve some adaptive purpose. That is, there could be situations in which too much IPSL is detrimental for health, suggesting that there may be a balance of cognitive functioning underlying optimal behavior. For example, one leading theory regarding certain clinical disorders, such as obsessive compulsive and substance abuse disorders, is that the habit-formation system is over-active while control-related systems are underactive, resulting in the ritualistic and compulsive thoughts and behaviors that characterize these disorders (Gillan & Robbins, 2014; Graybiel & Rauch, 2000; Koob & Volkow, 2009). Given that the neural regions implicated in disorders of compulsion (e.g., caudate, PFC, and hippocampus) overlap with those supporting IPSL, it is plausible that individuals with less of a propensity for IPSL may be less vulnerable to obsessive and addictive behaviors. An interesting direction for future research would therefore be to compare the cognitive and neural profiles of healthy and clinical populations to examine this possibility.

**Conclusions**

The findings from this dissertation highlight the importance of communication between learning-relevant brain regions (and traits that might influence such communication) for individuals’ ability to absorb regularities from their environment without intent or awareness. By identifying the ways in which neural and behavioral traits relate to individual differences in cognitive aptitudes, we might eventually come to a
better understanding of how abnormal functioning arises, as well as how to best capitalize on individuals’ natural propensities. Such understanding may leave us better equipped to develop personalized interventions that will one day enable all individuals to age more successfully.
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### Tables

#### Table II-1. Whole brain connectivity of the DC seed.

<table>
<thead>
<tr>
<th>Seed</th>
<th>Relationship</th>
<th>Region</th>
<th>BA</th>
<th>MNI coordinates (x, y, z)</th>
<th>Peak Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>DC</td>
<td>Positive</td>
<td>Caudate body</td>
<td></td>
<td>-14, 2, 12</td>
<td>7.49</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anterior cingulate</td>
<td>32</td>
<td>10, 30, 24</td>
<td>6.18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Middle cingulate</td>
<td>24</td>
<td>6, 28, 12</td>
<td>5.77</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Superior frontal gyrus</td>
<td>10</td>
<td>-22, 54, 8</td>
<td>6.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Middle frontal gyrus</td>
<td>8</td>
<td>-4, 32, 38</td>
<td>5.90</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inferior parietal lobule</td>
<td>39</td>
<td>-48, -66, 42</td>
<td>4.94</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>40</td>
<td>-60, -50, 22</td>
<td>2.66</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inferior parietal/Superior temporal gyrus</td>
<td>40/22</td>
<td>44, -48, 26</td>
<td>2.67</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Middle occipital gyrus</td>
<td>19</td>
<td>48, -74, 36</td>
<td>3.50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inferior/Middle temporal gyrus</td>
<td>21</td>
<td>-46, -26, -8</td>
<td>4.20</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20, -48, -30, -10</td>
<td>3.97</td>
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<td></td>
<td></td>
<td>37, -52, -48, -18</td>
<td>2.87</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>Middle cingulate</td>
<td>24</td>
<td>-18, -2, 38</td>
<td>4.88</td>
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<tr>
<td></td>
<td></td>
<td>Posterior cingulate</td>
<td>31</td>
<td>-20, -18, 32</td>
<td>4.78</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>23</td>
<td>-26, -32, 42</td>
<td>3.01</td>
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<tr>
<td></td>
<td></td>
<td>Postcentral gyrus</td>
<td>2</td>
<td>-28, -32, 42</td>
<td>4.00</td>
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<td></td>
<td></td>
<td>43</td>
<td>-38, -12, 24</td>
<td>3.55</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Precuneus</td>
<td>7</td>
<td>24, -50, 48</td>
<td>3.42</td>
</tr>
</tbody>
</table>
Table III-1. Characteristics and neuropsychological test scores of participants.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>20.9(2.6)</td>
<td>80.5(9.0)</td>
</tr>
<tr>
<td>Education</td>
<td>14.2(1.7)</td>
<td>15.4(2.4)</td>
</tr>
<tr>
<td>MAAS</td>
<td>4.1(.88)</td>
<td>4.4(.88)</td>
</tr>
<tr>
<td>MMSE</td>
<td>----</td>
<td>28.7(1.8)</td>
</tr>
<tr>
<td>NAART</td>
<td>14.5(6.0)</td>
<td>11.8(9.6)</td>
</tr>
<tr>
<td>GDS</td>
<td>----</td>
<td>3.9(.73)</td>
</tr>
<tr>
<td>BDS</td>
<td>8.7(2.7)</td>
<td>6.6(2.1)</td>
</tr>
</tbody>
</table>

Note: For the NAART and GDS, higher scores reflect worse performance and higher levels of depression, respectively. For the other measures, higher scores reflect better performance. MAAS = Mindful Attention Awareness Scale, MMSE = Mini Mental State Examination; NAART = North American Adult Reading Test; GDS = Geriatric Depression Scale; BDS = Backwards Digit Span.
<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean(SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>70.4(6.1)</td>
</tr>
<tr>
<td>Education</td>
<td>18.0(3.0)</td>
</tr>
<tr>
<td>NAART&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8.3(5.7)</td>
</tr>
<tr>
<td>BDS</td>
<td>6.7(1.9)</td>
</tr>
<tr>
<td>DSST</td>
<td>66.0(14.1)</td>
</tr>
<tr>
<td>MMSE</td>
<td>29.0(1.0)</td>
</tr>
<tr>
<td>MAAS&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4.5 (0.68)</td>
</tr>
<tr>
<td>Self-Reported Health&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4.5(0.73)</td>
</tr>
</tbody>
</table>

Table Notes: <sup>a</sup>For the NAART, higher scores reflect worse performance. For all other measures, higher scores reflect better performance. <sup>b</sup>Self reported health scores ranged from 1 (poor) to 5 (Excellent). BDS = Backwards Digit Span; DSST = Digit Symbol Substitution Test; MAAS = Mindful Attention Awareness Scale; MMSE = Mini Mental State Examination; NAART = North American Adult Reading Test.
Figures

**Figure II-1. Schematic of the Triplets Learning Task.** Each trial, or “triplet”, consists of the sequential presentation of two red cues and a green target. Subjects are instructed to view the first two red cues of each triplet and to respond only to the location of the green target using a corresponding response button.

**Figure II-2. Location of the bilateral dorsal caudate (DC) seed.** The seed was created as two spheres centered around coordinates [13 15 9] and [-13 15 9].
Figure II-3. Resting State functional connectivity (rsFC) network associated with a bilateral DC seed across all subjects. Red represents positive connectivity, and blue represents negative connectivity. Results are corrected for multiple comparisons at $p < .05$.

Figure II-4. Positive correlation between rsFC of the dorsal caudate seed (DC) and sequence learning (SL) scores. (A) Positive correlation between Sequence Learning (SL) scores and DC connectivity was observed in a cluster in the right parahippocampus, extending into the right hippocampus (peak $Z = 3.70$). (B) Scatter plot depicting the z-transformed correlation coefficients between the DC and this cluster (x-axis) and SL scores (y-axis). MTL, medial temporal lobe.
Figure II-5. Negative correlations between resting functional connectivity of the DC seed and SL scores. As depicted in the left column of the figure, negative correlations between SL scores and DC resting connectivity were observed in clusters in the left postcentral gyrus (peak $Z = 4.38$), right medial superior frontal gyrus (peak $Z = 4.81$), and right precentral gyrus (peak $Z = 4.10$). On the right are scatter plots depicting the $z$-transformed correlation coefficients between the DC and these clusters (x-axis) and SL scores (y-axis).
Figure III-1. The Triplets Learning Task (TLT). On each trial, participants observe the first two red cues and then respond to the location of the green target. These discrete, 3-event sequences are called “triplets”. Unbeknownst to participants, certain triplets occur with high frequency and others with low frequency in the task.

Figure III-2. Correlation between dispositional mindfulness and TLT Difference Scores (a) and TLT Sequence Learning (SL) Scores (b) in Study 1.
Figure III-3. The Alternating Serial Response Time Task (ASRT). Participants respond to the location of sequentially presented targets using response buttons that spatially correspond to the target’s location. Unbeknownst to participants, the location of the target on every other trial is determined by a repeating sequence.
Figure III-4. Correlations between dispositional mindfulness and ASRT Difference Scores (a) and ASRT Sequence Learning (SL) Scores (b) in Study 2.

Figure IV-1. Negative correlation between self-reported mindfulness and implicit learning.
Figure IV-2. Functional connectivity of the caudate is associated with individual differences in implicit learning. (A) Functional connectivity (FC) of the caudate to the left (peak MNI x,y,z = -24,-13,-17; k = 177) and right (peak MNI x,y,z = 45,-13,-17; k = 69) medial temporal lobe (MTL) was positively associated with learning in the TLT. The clusters were corrected for multiple comparisons at a whole brain threshold of P<.05. (B) Functional connectivity of the caudate to the right medial/superior frontal gyrus (BA10; peak MNI x,y,z = 30,59,19; k = 201) was positively associated with learning in the TLT. This cluster was identified using a frontal mask, and was corrected for multiple comparisons within the masked volume at P<.05. Pearson’s r values are shown for descriptive purposes only in both panels.
Figure IV-3. Functional connectivity of the caudate to the l- and rMTL is also associated with mindfulness.

Figure IV-4. (A) Conceptual model testing potential mediators of the association between mindfulness and learning. (B) Percentage of variance in learning accounted for by mindfulness before and after caudate-MTL functional connectivity is entered into the model.