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ELECTROPHYSIOLOGICAL MECHANISMS FOR PREPARING CONTROL IN TIME

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ELECTROPHYSIOLOGICAL MECHANISMS FOR PREPARING CONTROL IN TIME

by

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DISSERTATION

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Electrophysiological mechanisms for preparing cognitive control in time

by

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ABSTRACT

Cognitive control is critical in guiding goal-directed behavior, preparing neural resources and adapting processing to promote optimal action in a given environment. According to the Dual Mechanisms of Control theory (Braver, 2012), control can be dichotomized into proactive and reactive modes of control, utilized reciprocally in ahead-of-time preparation versus last-minute, stimulus-evoked reaction. Although a substantial body of work has tested differences between proactive control and reactive control, the underlying assumption of proactive control as a unitary process has not been systematically investigated. Very little is known as to how or when proactive control is initiated, sustained, or implemented.

As time is an integral building block of perception, cognition, and action (Buhusi & Meck, 2005), one should expect temporal information to be integrated into proactive control. Cognitive control is costly (Shenhav, Botvinick, & Cohen, 2013), and a temporally-guided modulation of control may offer substantial cost savings. By measuring proactive control on a sub-second time-scale, we can begin to gauge whether dissociable sub-types of proactive control are utilized demanding on temporal demands. Moreover, by comparing proactive control processes across different temporal demands, we can parse out *when* different aspects of control are computed and implemented.

Through a meta-analytic review and three empirical experiments, this dissertation provides insight into how timing dynamics may influence the computation, maintenance, and instantiation of proactive cognitive control. First, a meta-analysis on the cued control literature reveals that seemingly trivial experimental parameters shape the use of proactive versus reactive control. Two EEG studies then demonstrate how modulating timing dynamics influences prefrontal mechanisms for preparatory cognitive control. In a final EEG study, we compare the mechanisms utilized to retain control goals versus visuo-spatial working memory items.

Overall, this dissertation elucidates several novel electrophysiological mechanisms by which timing information is implemented in the computation and retention of cognitive control rules. Further, we provide evidence that individual differences in impulsivity and working memory shape distinct aspects of preparation. The findings reported here make clear that timing information is critical in guiding proactive control processes, and support a fundamental reconsideration of proactive control based on temporal dynamics.

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INTRODUCTION

Cognitive control is critical in guiding goal-directed behavior, preparing neural resources and adapting processing to promote optimal action in a given environment. According to the Dual Mechanisms of Control theory (Braver, 2012), control can be dichotomized into proactive and reactive modes of control, utilized reciprocally in ahead-of-time preparation versus last-minute, stimulus-evoked reaction (Braver, 2012; Braver, Gray, & Burgess, 2007; Braver, Paxton, Locke, & Barch, 2009). Proactive control utilizes context information to bias lower-level processes in order to prepare for an upcoming event, maximizing efficiency over flexibility. Reactive control favors a later stimulus-evoked re-activation of task goals, and results in slower and more variable responses (Braver, 2012; Braver et al., 2009). When a goal is known ahead of time, goal demands typically guide instantiation of certain preparatory, or proactive, control processes. As one must not only plan "what", but also *"when"*, we expect these processes underlying proactive control to be sensitive to temporal information

Although a substantial body of work has tested differences between proactive control and its reactive control "counterpart", the underlying assumption of proactive control as a unitary process has not been systematically investigated. In fact, very little is known as to how or precisely when proactive control is initiated, sustained, or implemented. As time is an integral building block of perception, cognition, and action (Buhusi & Meck, 2005), one should expect temporal information to be integrated into proactive control. Cognitive control is effortful and costly (Shenhav, Botvinick, & Cohen, 2013), and a temporally-guided, systematic modulation of control may offer

substantial cost savings. By measuring proactive control on a sub-second time-scale, we can begin to understand its component processes, and gauge whether dissociable sub-types of proactive control are utilized demanding on temporal demands. Moreover, by comparing proactive control processes across different temporal demands, we can parse out when different aspects of control are computed and implemented.

We have recently suggested that different timing-related parameters may induce different processes for control (Janowich 2015; Janowich & Cavanagh, under review A; Janowich & Cavanagh, under review B), and that seemingly trivial idiosyncrasies between studies may threaten external validity.

Research Approach

Neuro-cognitive testing

The AX-Continuous Performance Task (AX-CPT) (Carter et al., 1998; Cohen et al., 1997; Cohen, Barch, Carter, & Servan-Schreiber, 1999) and Dot Pattern Expectancy (DPX) (MacDonald et al., 2005) are popular cued cognitive control tasks, used to assess the role of expectancy in cognitive control. The two tasks are structurally identical, differing only in their use of letter versus dot pattern stimuli, and slight variations in cue-probe pair frequency (i.e.: 70% vs. 68.75% target pairs).

The expectancy version of the AX tasks was developed out of an earlier line of Continuous Performance Test (CPT) work in the 1950s (Rosvold, Mirsky, Sarason, Bransome Jr., & Beck, 1956) in order to study the effects of expectancy and context on cognitive control (J. Cohen & Servan-Schreiber, 1992; Servan-Schreiber et al., 1996). In the original continuous performance test, participants would detect target events in a

series of stimuli (e.g. “Respond to X” or “Respond to X only when it follows A”). Persons with Schizophrenia showed impaired performance on this task, and these deficits were exacerbated in versions of the task which depended on maintenance of task context (“…only when it follows”) (J. Cohen & Servan-Schreiber, 1992). Through computational models of performance in the continuous performance task and other attention-demanding tasks, it was shown that the internal representation of context information is critical for successful task performance, and researchers hypothesized that this may be the key functional deficit underlying behavioral impairments in people with Schizophrenia (J. Cohen & Servan-Schreiber, 1992). As such, the expectancy AX-CPT was designed to specifically elicit deficits in context processing (Servan-Schreiber et al., 1996).

Common A and rare B cues introduce different contexts, with distinct rules to follow for the forthcoming common X or rare Y probe stimuli. AY and BX sequences thus require the use of distinct types of cognitive control and are most commonly used as dependent variables of interest in AX-CPT and DPX tasks. AY pairs require reactive cognitive control to overcome the pre-potent AX response. Accordingly, errors on the Y trial are thought to result from greater use of proactive control (e.g. the typical AX response is over-prepared). Conversely, BX pairs require proactive cognitive control to maintain the rare B cue rule over the cue-probe delay period, so that the common X probe can elicit the correct, rare, BX response. Poor performance on BX trials is associated with failures in proactive control. The Behavioral Shift Index (Braver et al., 2009) serves as a composite measure of AY and BX error rates or reaction times ((AY – BX) / (AY +

BX)), to quantify the balance between proactive and reactive control styles within an individual.

Delay dynamics in AX/DPX

In AX-CPT and DPX, cue-probe delay parameters vary widely (Janowich & Cavanagh, 2018) and are often given scarce or no discussion. The majority of AX-CPT and DPX experiments use a known cue-probe delay length, consisting of either a single delay throughout the experiment, or delays varying by block. This makes it easy to develop a task rhythm and anticipate the timing of the upcoming probe stimulus. However, delay length is not always known. Some studies have jittered the cue-probe delay length within a small interval, adding some unpredictability to probe onset timing. In contrast, other studies have interspersed short and long delays within experimental blocks, such that the delay length for each trial could not be anticipated.

Throughout the AX-CPT and DPX literature, the delay length between an informative cue and a test probe (cue-probe delay, or CPD) has varied widely (between 0 and 10 seconds; Janowich & Cavanagh, 2018)), and is most often considered an incidental parameter. This is theoretically important, as information in the phonological loop of working memory is thought to decay in about two seconds, unless actively refreshed by some rehearsal process (A. D. Baddeley, Thomson, & Buchanan, 1975). If cue rule information is maintained differently over short versus long delays, variation in this parameter may assess distinct cognitive processes. Although there has not been a systematic test of delay parameters in AX-CPT or DPX, several AX-CPT and DPX fMRI studies have manipulated the cue-probe delay to assess *context maintenance* aspects of

cognitive control, as measured by BX performance (Barch et al., 2009; MacDonald et al., 2005). Context maintenance refers to an internal representation of information (e.g. task goals), held in mind in order to mediate an appropriate behavioral response (J. Cohen & Servan-Schreiber, 1992). Indeed, our recent work suggests there are reliable differences in brain activation to the rare B cue that solely depend on delay length (Janowich, 2015; Janowich & Cavanagh, under review A; Janowich & Cavanagh, under review B). Importantly, the majority of seminal studies on proactive control have been conducted with functional magnetic resonance imaging (fMRI) (Barch et al., 1997; Braver et al., 2009; Paxton, Barch, Racine, & Braver, 2008), which while excellent for precise spatial localization of brain function, does not have sufficient temporal resolution to resolve the precise temporal dynamics of these delay period processes.

Neural mechanisms of cognitive control

When a situation arises that may require cognitive control, the dorsal anterior cingulate cortex (dACC) (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Shenhav et al., 2013) is thought to assess the identity and intensity of the control signals that are needed. The dACC communicates these control needs to lateral PFC (Botvinick et al., 2001; Kerns et al., 2004), and the lateral PFC and subcortical structures (Braver & Cohen, 2000; Shenhav et al., 2013) represent, maintain, and exert appropriate control procedures. Increased cognitive control demands have been shown in EEG to robustly upregulate theta (4-8 Hz) power (Cavanagh & Frank, 2014; van Driel, Swart, Egner, Ridderinkhof, & Cohen, 2015). In line with the pre-frontal medial to lateral communication described in the Expected Value of Control model (Botvinick et al.,

2001; Shenhav et al., 2013), mid-frontal theta activity has also been shown to synchronize with lateral frontal PFC during increased control needs (reviewed in Cavanagh & Frank, 2014). However, most studies have not addressed the *proactive* communication, representation, and retention of control goals.

Neural mechanisms of timing

While the role of timing demands in cognitive control remain largely unaccounted for, a robust timing literature has identified candidate mechanisms in prefrontal cortex for predicting temporal durations (Durstewitz, 2004; Mento, Tarantino, Vallesi, & Bisiacchi, 2015; Niki & Watanabe, 1979; Pfeuty, Ragot, & Pouthas, 2005; Quintana & Fuster, 1999; Rainer, Rao, & Miller, 1999). Intriguingly, several human EEG studies suggest that the slope of medial frontal ERP activity may differentiate timing-related dynamics (Gupta & Merchant, 2017; Macar & Vidal, 2003; Pfeuty, Ragot, & Pouthas, 2003; Pfeuty et al., 2005; Praamstra, 2006), but it is not known how these late sloping activities are modified by the intersection of timing demands and control demands, nor as a function of individual differences in preparation.

Timing in control

To cross a busy street, take a highway exit, or swing a baseball bat, we are tasked not only to plan an (goal-directed) action, but also to execute that action at the appropriate time in the future. This goal-directed preparation is ubiquitous in human life, enabling us to efficiently ready neural resources and optimize behavior for when it is

needed. Critically, however, it is unknown *how* we retain abstract cognitive control goal information ahead of near-future use.

It may be optimal to adjust the proactive processes for updating and/or retaining the upcoming goal based on the temporal context. For example, when driving down a highway, you may react differently to a sign indicating that your desired exit will appear in half a mile than to a sign acknowledging that your desired exit is 10 miles away. It also remains to be known how elevated control demands (like a rare left exit sign) might interact with the length of time (1/2 or 10 miles) over which a control goal (exiting the highway) must be maintained. Although in each scenario one must proactively update and retain this new goal, the timing demands on each are varied. We propose that these updating vs. retention processes may be conducted differently and thereby express dissociable signals based on *when* the goal is to be acted upon.

We hypothesized that proactive control is not a unitary construct, and that the influence of distinct sub-processes could be parsed based on temporal demands. This is an important idea, since the AX-CPT and DPX paradigms have been run in healthy and patient populations, with delay length often treated as a trivial parameter. Cue-probe delay length varies widely between studies in the AX-CPT/DPX literature, with mixed behavioral (for a meta-analytic review, see Janowich & Cavanagh, 2018) and neural findings (Janowich, 2016). As the literature fails to substantively address the role of delay in proactive control processes, here we set forth to empirically examine the behavioral consequences and neural manifestations of temporal delay. If delay dynamics do reliably alter behavior and/or neural mechanisms of proactive control, the field will need to re-

evaluate the findings and implications of cued control studies in light of their respective timing demands.

Further, we sought to extend the proactive control literature to understand how control goals are retained over longer durations of time (instead of being immediately implemented). Do we engage active maintenance processes as if holding the rule/goal as a sensory item in working memory, or do we employ different processes and networks that may be less resource-demanding (Shenhav et al., 2013)?

Research Questions

To address how cognitive control is initiated, maintained, and implemented over different delay (temporal) demands, we orchestrated a meta-analytic review and three complementary research studies.

In the meta-analytic review (Chapter 2), we systematically reviewed the AX-CPT and DPX literatures to quantify the behavioral correlates of varying experimental dynamics. In particular, we tested how the proportional use of proactive versus reactive cognitive control varied with delay dynamics.

In Experiment 1 (Chapter 3), we tested the whether behavioral and neural delay-related changes in cognitive control observed in Janowich (2016) were reliable, replicable, and similar across cued control studies. In particular, this study elucidates whether delay-related changes are specific to verbalizable cue stimuli, or are generalizable to non-verbalizable (dot) stimuli.

In Experiment 2 (Chapter 4), our aim was to eliminated the potential confound of attentional differences that may occur when delay length is static by block, by varying delay length on a trial-wise basis. This study also tests how knowledge (vs no knowledge) of upcoming delay length differently guides control preparation.

In Experiment 3 (Chapter 5), we aimed to examine the role of working memory in the acquisition and retention of control-demanding task rules over a long delay.

CHAPTER 2

Delay Knowledge and Trial Set Count Modulate Use of Proactive vs. Reactive Control: A Meta-Analytic Review

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ABSTRACT:

The AX-Continuous Performance Task (AX-CPT) and Dot Pattern Expectancy (DPX) are the predominant cognitive paradigms used to assess the relative utilization of proactive vs. reactive cognitive control. Experimental parameters vary widely between studies and systematically between different modalities (i.e. fMRI vs. EEG) with unknown consequences for the implementation of control. This meta-analytic review systematically surveyed these literatures (k=43, 73 data points) to resolve how cue-probe delay knowledge, delay length, and trial set count modulate the preferential use of proactive versus reactive control. In healthy young adults, delay knowledge and increasing trial set count each bias participants toward greater proactive control. Further, the interaction of delay knowledge and trial set count accounts for ~40% of variability in proactive/reactive control performance. As trial count varies reliably between experimental modalities, it is critical to understand how these parameters activate distinct cognitive processes and tap into different neural mechanisms for control.

Subgroup analyses revealed important distinctions from our results in healthy young adults. Healthy slightly-older adults (age 30-45) performed more reactively than healthy young adults. In addition, participants with Schizophrenia showed evidence of more proactive control as trial set count increased.

In light of this meta-analytic review, we conclude that delay knowledge and trial set length are important parameters to account for in the assessment of proactive vs. reactive control. More broadly, this meta-regression provides strong evidence that cognitive control becomes more reactive when timing demands are not known, and that

both healthy persons and persons with Schizophrenia shift toward proactive control with increasing repetitions of a task set.

1
INTRODUCTION

1.1

Assessment of Subtypes of Cognitive Control

The Dual Mechanisms of Control framework (Braver, 2012) divides cognitive control into two distinct, reciprocally activated modes: proactive and reactive control, each important in enacting certain goal-directed behaviors. The AX-Continuous Performance Task (AX-CPT) (Carter et al., 1998; J. D. Cohen et al., 1997, 1999; Servan-Schreiber et al., 1996) and Dot Pattern Expectancy (DPX) (Henderson et al., 2012a; MacDonald et al., 2005) are commonly-used cue-probe cognitive tasks in which variation in cue and probe expectancy are used to assess the impact of (cue-derived) context on proactive (preparatory) and reactive cognitive control. The two tasks are structurally identical, differing only in their use of letter versus dot pattern stimuli, and slight variations in cue-probe pair frequency (i.e.: 70% vs. 68.75% target pairs). We have recently suggested that different timing-related parameters may induce different processes for control (Janowich, 2016; Janowich & Cavanagh, under review A), and that seemingly trivial idiosyncrasies between studies may threaten external validity. Considering how timing and temporal prediction are fundamental features of human neuro-cognition (Buhusi & Meck, 2005; Paton & Buonomano, 2018), we aim to assess if task timing-related parameters modulate the use of proactive versus reactive control across the representative literature.

In AX-CPT and DPX, delay and trial count parameters vary widely and are often given scarce or no discussion. Does knowing the length of the cue-probe delay increase

use of proactive control, and is proactive control more strongly instantiated ahead of a known short delay? Further, does increased repetition of a task set over time strengthen one's preference for exerting proactive control? As cognitive control comes at the cost of valuable cognitive resources (Shenhav et al., 2013), we hypothesize that people might utilize distinct control processes to handle goals with different timelines or temporal expectations, and that the development of habitual response patterns over many trials is likely to moderate preparatory processes. This meta-analysis exploits the variation in the expectancy literature to advance our understanding of timing and repetition effects on cognitive control instantiation, as well as facilitating discussion on interpretation of the heterogeneous results in AX-CPT and DPX studies.

1.2

The Experimental Tasks

An example of AX-CPT / DPX task flow and parameters is depicted in Figure 1. In this task paradigm, a probe stimulus (X or Y) is presented following a paired cue stimulus (A or B) in 'target' and 'non-target' combinations. In a two-alternative-forced choice manner (2AFC), participants are instructed to respond to both cue and probe stimuli. The target AX sequence dictates a common target response set; whereas all other cue-probe pairs require an alternative response set. Because 70% of trials are composed of AX cue-probe target pairs, and AY, BX, and BY cue-probe non-target pairs are much more rare (10% trials of each), a strong expectancy (e.g.: habit) is generated to respond according to the AX rule (Servan-Schreiber et al., 1996).

This expectancy version of the AX tasks was developed out of an earlier line of Continuous Performance Test (CPT) work in the 1950s (Rosvold et al., 1956) in order to study the effects of expectancy and context on cognitive control (J. Cohen & Servan-Schreiber, 1992; Servan-Schreiber et al., 1996). In the original continuous performance test, participants would detect target events in a series of stimuli (e.g. "Respond to X" or "Respond to X only when it follows A"). Persons with Schizophrenia showed impaired performance on this task, and these deficits were exacerbated in versions of the task which depended on maintenance of task context ("…only when it follows") (J. Cohen & Servan-Schreiber, 1992). Through computational models of performance in the continuous performance task and other attention-demanding tasks, it was shown that the internal representation of context information is critical for successful task performance, and researchers hypothesized that this may be the key functional deficit underlying behavioral impairments in people with Schizophrenia (J. Cohen & Servan-Schreiber, 1992). As such, the expectancy AX-CPT was designed to specifically elicit deficits in context processing (Servan-Schreiber et al., 1996).

Common A and rare B cues introduce different contexts, with distinct rules to follow for the forthcoming common X or rare Y probe stimuli. AY and BX sequences thus require the use of distinct types of cognitive control and are most commonly used as dependent variables of interest in AX-CPT and DPX tasks. AY pairs require reactive cognitive control to overcome the pre-potent AX response. Accordingly, errors on the Y trial are thought to result from greater use of proactive control (e.g. the typical AX response is over-prepared). Conversely, BX pairs require proactive cognitive control to maintain the rare B cue rule over the cue-probe delay period, so that the common X probe

can elicit the correct, rare, BX response. Poor performance on BX trials is associated with failures in proactive control. The Behavioral Shift Index (Braver et al., 2009) serves as a composite measure of AY and BX error rates or reaction times ((AY – BX) / (AY + BX)), to quantify the balance between proactive and reactive control styles within an individual. Given that the inclusion of AY and BX means and standard deviations in most manuscripts facilitates the calculation of standardized mean differences, and that AY-BX error rate and reaction time indices capture complementary differences in exertion of proactive and reactive control, we use AY-BX differences as outcome measures of proactive vs. reactive control in this meta regression.

As described above, the DPX differs from AX-CPT in stimulus type, using dots instead of letters. Although prior work has found some differences in factors explaining performance of the two tasks (MacDonald et al., 2005), here we collapse across AX-CPT and DPX paradigms in order to gain statistical power and make broader conclusions about the impact of task *structural* parameters (vs. task stimuli).

1.3

Delay Knowledge in AX-CPT and DPX Literature

The majority of AX-CPT and DPX experiments use a known cue-probe delay length, consisting of either a single delay throughout the experiment, or delays varying by block. This makes it easy to develop a task rhythm and anticipate the timing of the upcoming probe stimulus. However, delay length is not always known. Some studies have jittered the cue-probe delay length within a small interval, adding some unpredictability to probe onset timing. In contrast, other studies have interspersed short

and long delays within experimental blocks, such that the delay length for each trial could not be anticipated. Here we formally investigate differences between small, largely imperceptible interval variation due to jitter (<500 ms) and large "unknown" delay variations that may more meaningfully interact with time estimation.

Because the use of known versus unknown delays changes the structure and prediction demands of the task, we hypothesized that studies with different delay lengths would alter peoples' use of proactive vs. reactive control. First, we hypothesized that full knowledge of the upcoming delay would significantly bias participants toward the use of proactive control, as they would be able to prepare to respond at the appropriate time. In contrast, we expected that studies with a jittered delay would bias participants toward exerting reactive control, and that this effect would be exacerbated by a completely unpredictable upcoming delay.

1.4

Delay Length in AX-CPT and DPX Literature

Throughout the AX-CPT and DPX literature, the delay length between an informative cue and a test probe (cue-probe delay, or CPD) has varied widely, and is most often considered an incidental parameter and given no or scarce discussion. This is theoretically important, as information in the phonological loop of working memory is thought to decay in about two seconds, unless actively refreshed by some rehearsal process (A. D. Baddeley et al., 1975). If cue rule information is maintained differently over short versus long delays, variation in this parameter may assess distinct cognitive processes. Indeed, our recent work suggests there are reliable differences in brain

activation to the rare B cue that solely depend on delay length (Janowich & Cavanagh, under review).

In several AX-CPT and DPX studies, manipulation of the cue-probe delay has been used to assess *context maintenance* aspects of cognitive control, as measured by BX performance (Barch et al., 2009; MacDonald et al., 2005). Context maintenance refers to an internal representation of information (e.g. task goals), held in mind in order to mediate an appropriate behavioral response (J. Cohen & Servan-Schreiber, 1992). By quantifying whether proactive/reactive control behavior differs based on delay parameters, we can begin to understand whether context maintenance is utilized similarly/universally in all delay contexts, or is subject to timing demands.

In addition to the effects of cue-probe delay on context maintenance, this meta-analysis addresses how cue-probe delay may also alter goal-switching control upon encountering a rare AY cue-probe sequence. The current meta-regression offers a distinct and important contribution to the literature, in that the focus specifically on the AX-CPT and DPX tasks enables us to bring to light how delay conditions may alter both goal-switching control (AY) and context maintenance (BX).

In our healthy young adult meta-analysis sample, we hypothesized that short cue-probe delay lengths would bias participants toward (over-) exerting proactive control, such that the immediacy of the upcoming probe would require use of a strong pre-potent stimulus-response preference. Conversely, long cue-probe delay lengths may shift participants toward reactive control, as it might be too cognitively taxing to undergo many seconds worth of active rehearsal.

Some may question whether the inter-trial interval (ITI) is (also) important in shaping the interaction between proactive and reactive control; therefore we have included ITI as a moderator in our analyses although we have no specific hypotheses about this parameter.

1.5

Trial Set Count in AX-CPT and DPX Literature

AX-CPT and DPX tasks are premised upon the exertion of control over *rare* cue and probe stimuli, yet the number of trials of repeated behavior (over which habits to respond are developed and strengthened) varies widely. Trial set counts are defined in this manuscript as the number of trials performed on a distinct task set. We hypothesized that studies with a greater number of trials of repeated behavior will cultivate stronger predispositions to respond to the common (vs. rare) stimulus-response rule, and thus bias toward the use of proactive control.

1.6

Standard versus Distractor AX-CPT and DPX Comparison

Recently, many investigators have modified the AX-CPT and DPX paradigms to include mid-delay distractors (Braver et al., 2001; Fröber & Dreisbach, 2016; Gómez-Ariza, Martín, & Morales, 2017; Maraver, Bajo, & Gomez-Ariza, 2016; Morales, Gómez-Ariza, & Bajo, 2013). This modification may be useful in increasing the difficulty of maintaining cue stimuli over the delay and preventing 'ceiling' performance in healthy young adults. However, the ramifications of mid-delay distractors on proactive

versus reactive control usage has yet to be reviewed. We hypothesized that mid-delay distractors would generally increase the use of reactive control, as the distractors would make it more difficult to maintain the cue and prepare a response. As contending with distractors would occupy considerable cognitive resources, we did not anticipate that control metrics would be moderated by trial set count or delay length.

1.7

Young versus Slightly-Older versus Older Adult Comparison

Age has been known to be associated with performance in AX-CPT and DPX tasks, with older (elderly) adults demonstrating decrements in proactive control and increases in reactive control (slowed BX performance (Braver et al., 2001; Paxton et al., 2008) and more accurate (Braver, Satpute, Rush, Racine, & Barch, 2005) and faster AY performance (Paxton et al., 2008) relative to healthy young adults. We only identified three AX-CPT studies (cited immediately above) conducted with older adults, and as such report only basic summary comparisons between age groups. Because of the very small number of studies, we are underpowered to analyze the effects of moderator variables on older adult performance. As this review focuses on the influence of task parameters on normative task performance, we do not focus further on studies run in older adult samples.

Many studies include slightly-older healthy adults (age 30-45), typically matched to participants with schizophrenia. The potential difference in performance between these slightly-older healthy adults versus college-aged students has not been addressed. This is important because it is unclear whether this age-related change in proactive vs. reactive

control occurs in middle adult-hood, and whether it interacts with delay-related factors mediating control. We hypothesized that younger adults would show stronger proactive control than slightly-older healthy adults.

1.8

Schizophrenia Sub-group Comparison

AX-CPT and DPX tasks have been used to quantify abnormalities of proactive and reactive control in special populations, particularly aging and participants with Schizophrenia. These special populations are characterized by disproportionate difficulty on BX (context maintenance) trials (Barch et al., 2009; J. D. Cohen et al., 1999), suggesting poorer proactive control. However, with common variation in task parameters it is difficult to ascertain the underlying cognitive processes responsible for these deficits. We hypothesized that the population of people with Schizophrenia would show a bias toward reactive control (as has been reported widely in the literature), and that this bias toward reactive control would be strengthened with increasing delay length due to increased difficulty on BX context maintenance trials.

1.9

The Current Investigation

In this meta-regression, we aimed to test the following three *a priori* hypotheses: 1) delay knowledge, 2) delay length, and 3) trial set count moderate the use of proactive vs. reactive control. We also tested the effects of mid-delay distractors and ITI parameters on control, although we had no specific hypotheses about these parameters.

To understand how control varies in different experimental populations, we investigated if prior findings of reduced proactive control in elderly adults extend to slightly-older adults (age 30-45), and if findings of reduced proactive control in persons with Schizophrenia are dependent on these parameter differences between studies. Finally, we detail descriptive patterns across literatures and methodologies, as we have noticed that EEG studies tend to use different parameters than behavioral or fMRI studies. Implications for this parameter difference between modalities are discussed further.

2

METHODS

A series of meta-regressions (Berkey, 1995, Van Houwelingen, Arends, & Stijnen, 2002) were conducted to describe the effects of delay knowledge, cue-probe delay length, and trial set length on AX-CPT and DPX (here forward, expectancy task) measures of proactive vs. reactive control. All analyses were conducted using the *metafor* package (Viechtbauer, 2010) written for *R* (version 3.2.2; http://www.R-project.org).

2.1

Study Identification, Screening, and Inclusion

Study selection was structured according to the Meta-Analysis Reporting Standards (JARS, 2008). A full outline of study selection procedures is depicted in Figure 2. ScienceDirect and PubMed databases were queried using the keywords ("AX-CPT", "DPX" and "cognitive"), to gather an initial sample of English-language literature

in which the AX-CPT paradigm was used (through September 2017). This yielded 309 abstracts. Peer-reviewed research studies with novel data using AX-CPT and DPX were assessed further; all review papers or re-analyses of prior published data were excluded.

Further discussion on study selection will differentiate between manuscript selection ("k") and data-point selection ("dp"), which distinguishes each data set obtained with a distinct delay length, both between experiments within a manuscript, as well as between delay lengths within an experiment. For studies utilizing multiple cue-probe delay lengths and reporting distinct probe behavioral measures, each cue-probe delay length was used as a separate data point. Studies selected for inclusion are accessible in Appendix 1 (full raw data is available on Mendeley Data).

2.1.1

Study Selection: Healthy Young Adults and Schizophrenia Patients

Inclusion of manuscripts required AX-CPT or DPX behavioral data from human samples consisting of healthy young adults (ages 18-45). For manuscripts also using patient groups, multiple retests, or an experimental intervention, data points were extracted exclusively for the healthy young adults in the control/baseline condition. Data from participants with Schizophrenia (k=7, dp=11) were included for a later sub-group analysis. Owing to the small selection of studies assessing persons with Schizophrenia, the sample of studies includes patients with and without medication (noted in Table 1), and with varying disease duration lengths. One manuscript separated data by patient medication status; each medication group is included as a separate data point.

2.1.2

Study Selection: Expectancy Paradigm

To ensure comparison across similar expectancy paradigms, studies were included only if they used standard cue/probe proportions (70% AX, 10% each of AY, BX, and BY), or AX proportions within a negligible margin of 70% (+/- 10%). We included 18 AX-CPT data-points (from k=9 studies) deviating slightly from the 70% AX standard (deviant mean= 70.40%, mean deviation from 70% = 5.38%, AX range= 60-79%). Inclusion required standard AX-CPT or DPX stimuli (intact letters or dots), and a two-alternative-forced-choice response format. Studies in which distractors were presented during the delay (k=6, dp=7) were also not included in the primary analyses, but are included in later sub-analyses.

2.1.3

Study Selection: Age

The expectancy literature consists primarily of studies conducted in college-aged students (k=31, dp=46, mean age = 22.2 +/- 2.14 SD, range 19.4-26.0), but also includes many studies using slightly-older healthy adults typically matched to persons with schizophrenia (k=5, dp=10, mean age = 37.8, range= 31.6-43.6). As the college-aged and slightly older adults included in expectancy studies appear to be two distinct populations (with statistically different ages ($t = -13.007$, $df = 10.843$, $p < .001$)), we conducted our main analyses on the majority group of studies with mean participant age less than 30 years. Later sub-group analyses examined studies with a mean participant age greater than 30.

Expectancy studies meeting our standard criteria only include three studies of older (elderly) adults (k=3, dp=6, mean age = 72.27). As the goal of our review was to understand the role of task parameters in commonly studied populations, we did not find it appropriate to include this small population in our analyses, nor were we sufficiently powered to conduct moderator analyses on older (elderly) adult data. However, to better situate our contrast between young and slightly-older adults, we conduct post-hoc comparisons of accuracy and reaction time between older (elderly) adults, young adults, and slightly-older adults.

2.1.4

Study Selection: Available Data

For inclusion in the meta-analysis, studies were required to include information sufficiently describing experimental parameters, including cue-probe delay length, inter-trial interval, and trial set count. When multiple delays were included within a study, we needed to know whether delay lengths were separated by block or mixed unpredictably by trial, and see behavioral results parsed by delay length and delay knowledge. For inclusion in accuracy and/or reaction time analyses, studies were required to include the relevant means and standard deviation for probe types 'AY' and 'BX'. When only standard errors of the mean were available, we computed standard deviation from the SEM and study sample size.

2.1.5

Study Selection: Missing Data

In the case of any study with missing data, the corresponding author was contacted by email and asked to furnish the supplemental data. 19 authors were contacted on behalf of 24 manuscripts. From this, authors of 8 of the manuscripts provided us with the necessary supplemental data. In cases in which data were not furnished, but graphs of behavioral data were available, we computed precise estimations of behavioral means and standard deviations using ruler functions in Adobe Illustrator.

2.1.6

Study Selection: Summary

Based on these criteria, 25 studies, consisting of 45 data points and 1367 unique healthy young adult participants, were included in the primary meta-analyses. Mid-delay distractor analyses included 6 manuscripts and 7 data points. Sub-group analyses for Schizophrenia patients included 7 manuscripts and 11 data points. Slightly-older adult analyses included 5 manuscripts and 10 data points.

Figure 2.1: Example of AX-CPT/DPX Task Design. In A-C, typical AX-CPT task designs with known (A), jittered (B), or unknown (C) cue-probe delays are depicted. A probe stimulus (X or Y) is presented following a paired cue stimulus (A or B) in 'target' and 'non-target' combinations. In a two-alternative-forced choice manner, participants are instructed to respond to both cue and probe stimuli with left or right trigger buttons on a joystick or computer keyboard. In the target AX sequence, X probes following A cues demand a 'right' trigger press; all other cues and probes are to be responded to with the left trigger. 70% of trials are composed of AX cue-probe 'target' pairs, entailing a 'left-right' cue-probe response sequence, and AY, BX, and BY cue-probe 'non-target' pairs are much more rare (10% trials of each). Habitual responses are expected for AX sequences, whereas AY cue-probe pairs demand reactive control in responding to Y. B cues are expected to elicit proactive control, as the upcoming probe response can be fully prepared. A. The delay between cue and probe stimuli is fully known, remaining at 1000 ms for 250 consecutive trials. B. The delay between cue and probe stimuli is jittered (randomly) at around 3000 ms (+/- 500 ms). C. The delay between cue and probe is randomly chosen each trial to be either 1000 ms or 3000 ms. D. DPX cue and probe stimuli corresponding to AX-CPT cues and probes. In DPX, 68.75% of trials are AX, 12.5% AY, 12.5% BX, and 6.25% BY.

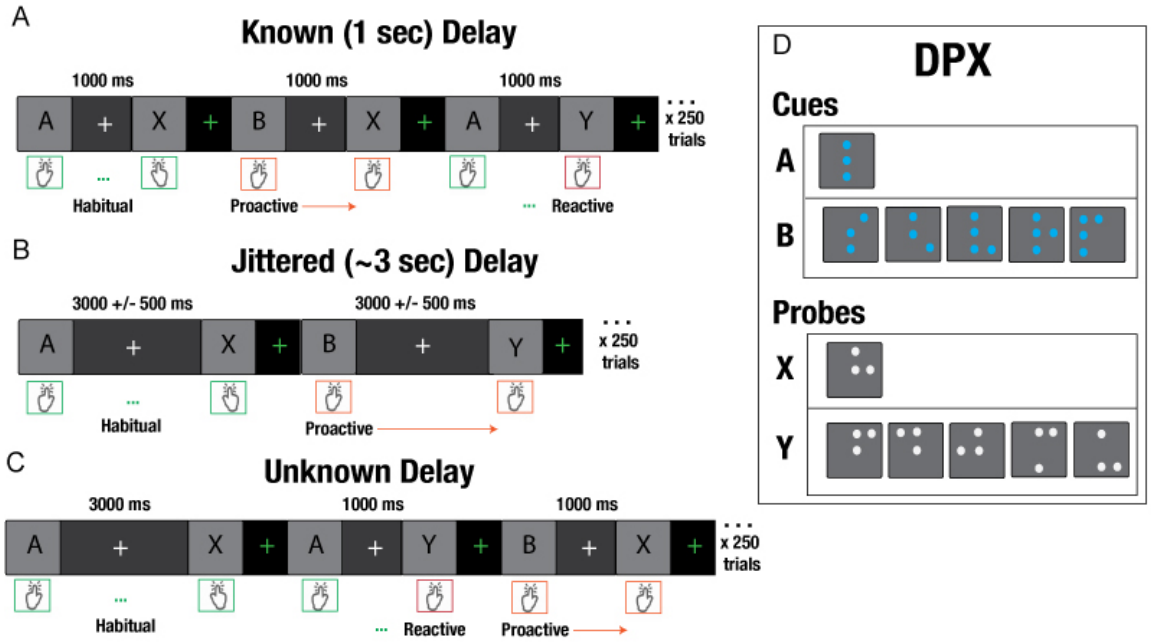
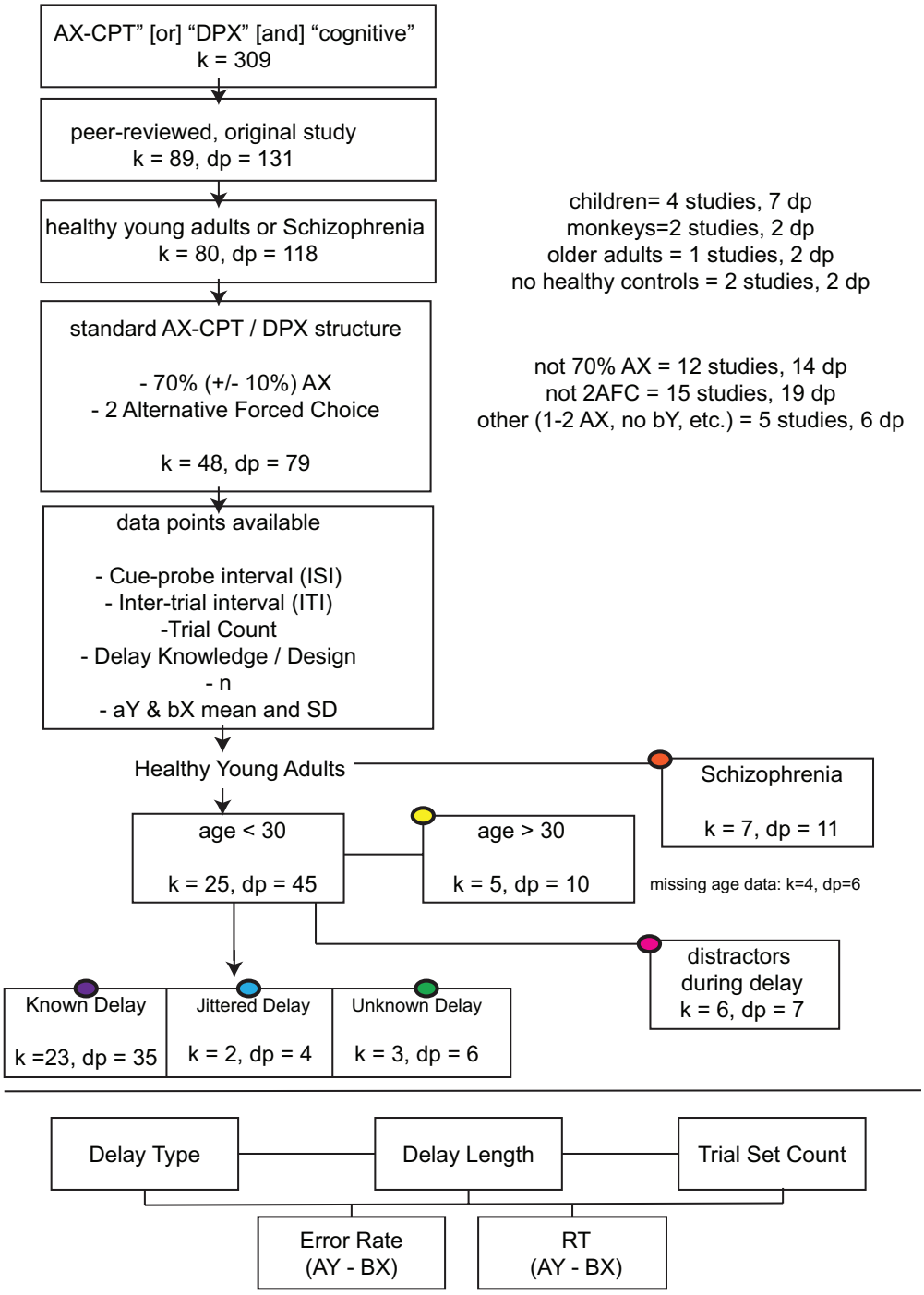


Figure 2.2: Meta-analysis Data Selection. Flow chart detailing selection of manuscripts (k) and data-points (dp) to be included in meta-analyses. For manuscripts with multiple experiments, participant sub-groups, and/or delay lengths, distinct data-points were established. Colored ovals indicate final selection for the primary (purple, blue, and green) and sub-group analyses (yellow, orange, and pink). The bottom section shows the variables assessed as moderators for our outcome control indices (AY-BX Error Rate and RT).



2.2

Outcome Measures

Error rate and reaction time data means and standard deviations for AY and BX probe stimuli were compiled. When manuscripts reported only standard error of the mean, standard deviation was computed as: SD = SEM / sqrt(n). AY and BX cue-probe combinations have been established as markers of proactive and reactive control, and their relationship has been used to assess ratios of proactive versus reactive control, with higher (AY-BX / AY + BX) scores indicating greater proactive control and lower scores indicating greater reactive control (Braver, 2012; Braver et al., 2009).

Separate outcome measures of effect size for error rate and reaction time were created with Cohen's d_av (Cumming, 2012; Lakens, 2013). Because the correlations between pairs of (AY and BX) observations (r) were not available, standardized mean differences (Borenstein, 2009; Borenstein, Hedges, Higgins, & Rothstein, 2009) were calculated using a formula designed for independent groups, with standard deviation computed as the within-groups standard deviation pooled across groups

The standardized mean difference (effect sizes) were computed by dividing the mean AY – BX difference by the within-groups standard deviation for AY and BX, pooled across groups:

$$\frac{\text{(mean AY - mean BX)}}{\text{(sqrt ((N-1)* AY stdev^2 + (N-1)* BX stdev^2)) / (2*N-2)))}}.$$

Variances were calculated separately for error rate and reaction time, using a between-subjects formula:

((2*N / N^2) + (([error rate OR reaction time d_av] ^2) / (4*N)))

Confidence intervals were estimated at 95% to assess the likelihood of a given study's results of containing the true population mean.

2.3

Methods: Meta-regression Procedures

In all analyses, more positive effect sizes indicate greater use of proactive control, whereas more negative effect sizes indicate greater use of reactive control. With our composite measures of AY-BX performance, we cannot precisely distinguish increased proactive control from decreased reactive control, but we consider the general proportional shifts in use of proactive versus reactive control on a continuous spectrum.

2.3.1

Baseline Meta-regressions

Initially, we established a baseline summary of expectancy task performance in healthy young adults using a fixed-effects model. The fixed-effects model enables only conditional inference about the existing literature (Hedges & Vevea, 1998), but is important in guiding interpretation of existing studies in light of any effect of delay or trial parameters on performance.

Following the fixed-effect model, we conducted a baseline random-effects meta-regression. A random-effects meta-analysis model was used to allow for true variance in proactive/reactive behavior between studies, in addition to sampling variance (Riley,

Higgins, & Deeks, 2011). Random-effects analyses more conservatively accounts for the variance between studies' methods and sample characteristics by treating each study's variance as purely random (Viechtbauer, 2010). As such, the random-effects model can be used to make unconditional inference about similar studies outside of the meta-analysis sample. The baseline random-effects model established the level of variance between studies, without any moderators taken into account.

For all random-effects meta-regressions, we used the Restricted Maximum Likelihood Estimation (REML) method, and computed unbiased estimates of the sampling variances (vtype="UB"). Knapp and Hartung adjustments (Knapp & Hartung, 2003) to the standard Wald-type tests tests were always applied (test="knha"). The Knapp & Hartung adjustment helps to better control for the Type I error rate in mixed-effect meta-regressions.

2.3.2

Moderators: Simple Main Effects

We then ran a series of univariate random-effects meta-regressions to understand the simple main effects of delay knowledge, delay length, and trial set count (separately) on accuracy and reaction time BSI composites. First, we conducted a set of random-effects meta-regressions assessing the moderating effect of delay knowledge on proactive/reactive accuracy and reaction time. Next, to understand the effect of delay length on expectancy task performance (both accuracy and reaction time measures), we applied a mixed-effects model with delay length as the continuous moderator hypothesized to account for variability in the true effects (Viechtbauer, 2010). A mixed

effects model assesses the effect of the moderator (delay length) at the study level, while also assuming random variance between studies, and computes the amount of variance accounted for by this moderator. Although we did not hypothesize that inter-trial interval would alter task performance, we added inter-trial interval as an additional moderator, addressing concerns that inter-trial interval – or its interaction with cue-probe delay, might account for variation in task performance. We then ran a set of mixed-effects meta-regressions with trial set count as the moderator variable.

2.3.3

Moderators: Interactions

After quantifying the simple moderating effects of delay knowledge, delay length, and trial set count separately, we conducted univariate random-effects meta-regressions to understand their interactions (delay knowledge x delay length, delay knowledge x trial set count, and delay length x trial set count). All interaction analyses included random effects for both the individual data point and the delay knowledge subgroup.

2.3.4

Sub-group Analyses

Finally, we ran a similar series of meta-regressions for our subgroups of interest: persons with Schizophrenia, slightly-older adults, and studies with mid-delay distractors. Procedures were repeated as described above for the main study sample, but did not include delay knowledge analyses, as all sub-group studies included a known delay.

3

RESULTS

All results are for the primary analyses on healthy young adults in standard AX-CPT and DPX paradigms, unless explicitly stated otherwise. Forest plots were generated to summarize between-study variation (Lewis & Clarke, 2001) in accuracy (Figure 3) and reaction time (Figure 4) metrics of proactive versus reactive control.

Figure 2.3: Forest Plot of Proactive/Reactive Control Error Rate Difference. Forest plot ordered by sub-group, delay knowledge, and trial set count. Cue-probe delay (CPD) (ms) and Intertrial Interval (ITI) (ms) are also included for reference. Scores reflect the standardized mean difference of AY-BX error rate and 95% confidence interval (CI), with more negative scores indicating greater reactive control and more positive scores indicating greater proactive control. Triangles on the CI bars indicate CIs that exceed the plotting range of standardized mean differences. Colored diamonds show the random effects model summary scores for each sub-group, and the black diamond at the base shows the overall random effects model summary for all studies combined.

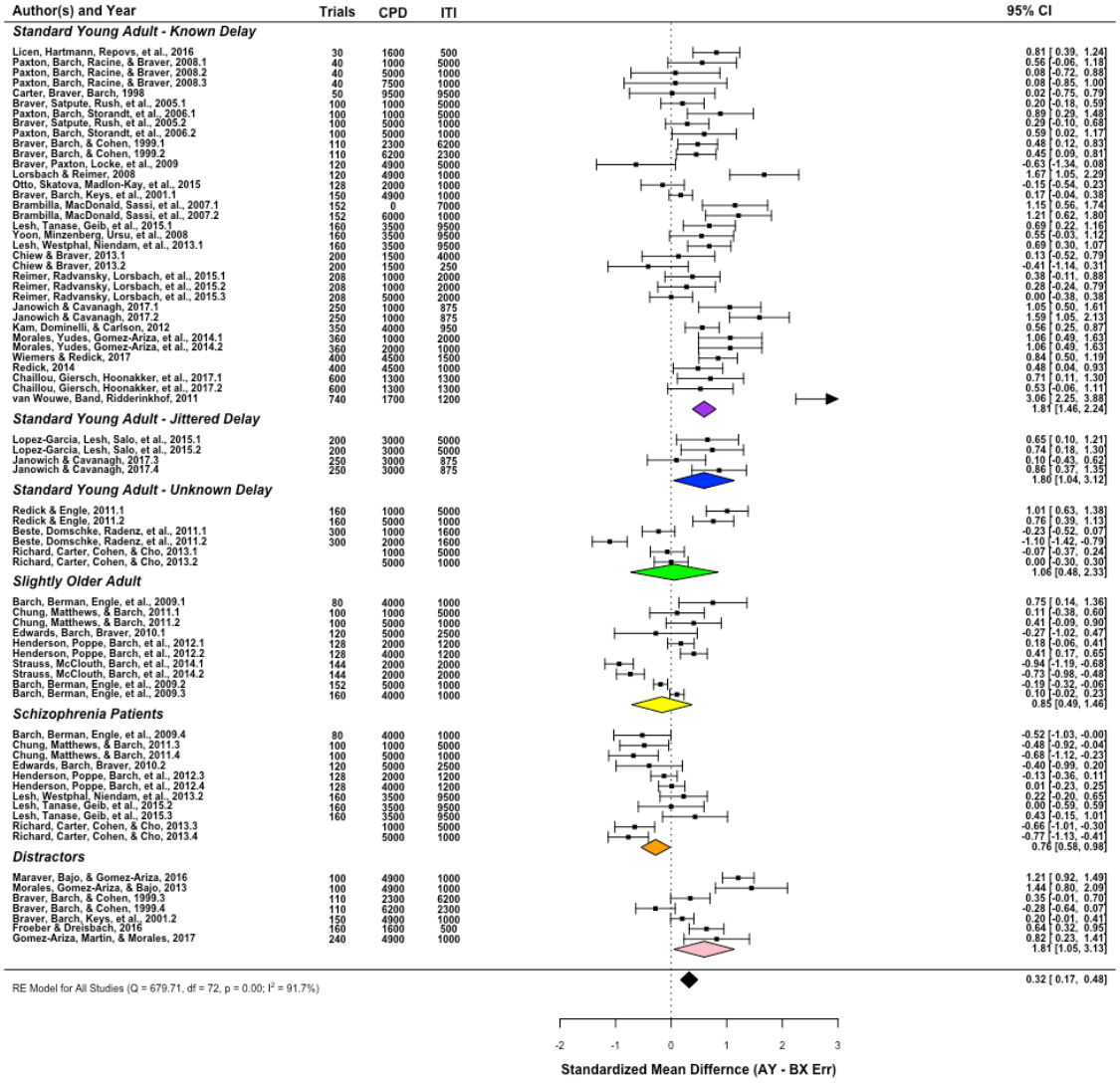
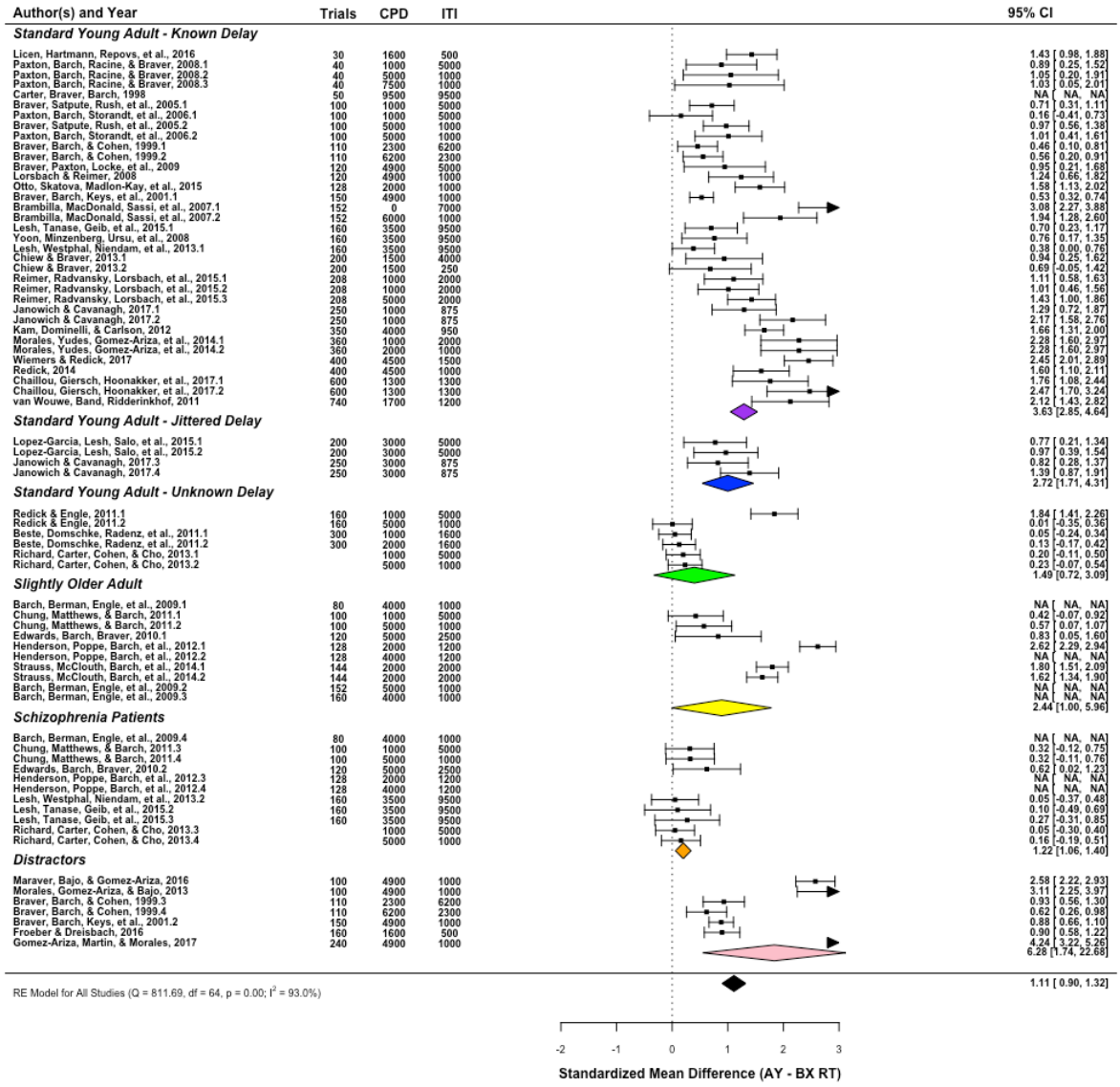


Figure 2.4: Forest Plot of Proactive/Reactive Control Reaction Time Difference. Forest plot ordered by sub-group, delay knowledge, and trial set count. Cue-probe delay (CPD) (ms) and Intertrial Interval (ITI) (ms) are also included for reference. Scores reflect the standardized mean difference of AY-BX reaction time and 95% confidence interval (CI), with more negative scores indicating greater reactive control and more positive scores indicating greater proactive control. Triangles on the CI bars indicate CIs that exceed the plotting range of standardized mean differences. Colored diamonds show the random effects model summary scores for each sub-group, and the black diamond at the base shows the overall random effects model summary for all studies combined.



3.1.1

Delay and Trial Parameters by Behavior/Imaging Modality

We first ran a set of one-way ANOVAs on all studies in our meta-analysis to understand whether delay length or trial set count differed between studies of different imaging modalities (behavior vs. EEG vs. fMRI). We found that AX-CPT and DPX delay lengths differ between imaging modalities ($F(2,70)=6.472$, $p=.003$): EEG studies use significantly shorter cue-probe delays (n=12, mean=1.86 s) than behavioral studies (n=46, 3.08 s; EEG vs. BEH $t=-3.645$, $p<.001$, Cohen's $d=-.843$) or fMRI studies (dp=15, mean= 4.44 s; EEG vs. fMRI $t=-4.146$, $p<.001$, Cohen's $d=-1.496$). In addition, cue-probe delay length was negatively correlated with trial set count ($F(1,67)=7.282$, $p=.009$, $R^2=.084$), and trial set counts were significantly different by modality ($F(2,66)=34.77$, $p<.001$), being larger in EEG studies relative to both behavioral (EEG vs. BEH $t=4.803$, $p<.001$, Cohen's $d=2.391$) and fMRI (EEG vs. fMRI $t=5.108$, $p<.001$, Cohen's $d=2.169$) studies. The outcomes of meta-analytic findings reported below should be considered in light of these systematic variations between different modalities, particularly as threats to external validity.

3.1.2

Baseline Variation in Accuracy and Reaction Time Metrics

We first tested for meaningful between-study variation in both accuracy and reaction time indices of control. In a fixed-effects univariate meta-regression, we observed significant variance in the accuracy outcome measure ($Q(df = 44) = 300.442$, p-

val < .001, z=11.591). We also observed significant variance in the reaction time outcome measure (Q(df = 43) = 400.614, p-val < .001, z=25.260).

In a random-effects univariate meta-regression, we observed significant variance in the accuracy outcome measure (Q(df = 44) = 300.442, p-val < .001, t=5.355, tau^2=.325 (SE=0.084), I^2=86.61%, H^2=7.47). We also observed significant variance in the reaction time outcome measure (Q(df = 43) = 400.614, p-val < .001, t=10.213, tau^2=.461 (SE=0.116), I^2=89.51%, H^2=9.53).

3.1.3

Differences in AX-CPT vs. DPX Paradigms

We conducted univariate random-effects meta-regressions to test the effect of stimulus type: AX-CPT letters versus DPX dots as a categorical moderator. In healthy young adults, (AX-CPT dp=41; DPX dots dp=4) there was no significant effect of paradigm on accuracy (p=.469) or reaction time (p=.266). In slightly older adults (AX-CPT dp=5; DPX dp=5), there was no significant effect of paradigm on accuracy (p=.530). Only 2 DPX data points (and 4 AX-CPT data points) in slightly-older adults included reaction time data, so we were under-powered to detect potential paradigm-evoked differences in reaction time in slightly-older adults (p=.051).

3.2.1

Main Effects: Delay Knowledge

Univariate random-effects meta-analyses for accuracy and reaction time were conducted with delay knowledge as a categorical moderator (known vs. jittered vs.

unknown). Overall, delay knowledge did not account for a significant portion of variance in accuracy (R^2=8.55%, F(1,42)=2.159, p=.128). The difference in accuracy for studies with unknown versus known delays was significant (F(1,42)=4.255, p=.045), but accuracy in studies with unknown versus jittered delays did not differ (F(1,42)=1.832, p=.183), nor did studies with known versus jittered delays (F(1,42)=.000, p=.984).

Overall, delay knowledge did account for a significant portion of variance in reaction time (R^2=19.43%, F(1,41)=4.993, p=.011). Reaction time differed significantly for studies with unknown versus known delays (F(1,41)=9.811, p=.003), but there was no difference in reaction time for studies with unknown versus jittered delays (F(1,41)=1.942, p=.171), nor for studies with known versus jittered delays (F(1,41)=.697, p=.409). In summary, delay knowledge explained significant variance in RT, with known delay driving relatively increased RT indices of proactive control.

3.2.2

Main Effects: Cue-probe Delay Length and Inter-trial Interval

We conducted univariate random-effects meta-regressions for accuracy and reaction time, with cue-probe delay length and inter-trial interval (ITI) as continuous moderators. Delay length was not a significant moderator of accuracy (F(1,41)=.049, p=.827), nor was ITI (F(1,41)=.108, p=.744). The delay-ITI interaction for accuracy was also not significant (F(1,41)=.245, p=.623).

Delay length was not a significant moderator of reaction time (F(1,40)=.205, p=.653), nor was ITI (F(1,40)=.027, p=.871). The delay-ITI interaction for reaction time was also not significant (F(1,40)=.375, p=.544). In summary, contrary to our hypothesis,

delay length did not explain meaningful variance in accuracy or RT relevant to proactive vs. reactive control. In addition, ITI also had no effect on control metrics.

3.2.3

Main Effects: Trial Set Length

We conducted univariate random-effects meta-regressions for accuracy and reaction time, with trial set length as a continuous moderator. Trial set length was a significant moderator of accuracy (R^2=5.71%, $F(1,41)$=4.562, p=.039), such that increased trial set count led to accuracy index measures of greater proactive control.

Trial set length was a significant and robust moderator of reaction time ($F(1,40)$=10.967, p=.002), accounting for 21.89% of variance (R^2=21.89%), such that increased trial count led to RT index measures of greater proactive control. In summary, both accuracy and RT measures of proactive vs. reactive control were altered by trial set length, with increased trial set length associated with greater proactive control.

3.3.1

Interactions: Delay Known x Delay Length and Inter-trial Interval

In a series of univariate mixed-effects meta-regressions, we assessed whether there was an interaction between delay knowledge and delay length or ITI in moderating accuracy or reaction time. We found no significant interaction of delay knowledge (known vs. unknown) and delay length on accuracy ($F(1,40)$=1.035, p=.315). The interaction of delay knowledge (known vs. unknown) and ITI also did not have a significant moderating effect on accuracy ($F(1,39)$=1.070, p=.307).

The interaction of delay knowledge (known vs. unknown) and delay length did not significantly moderate reaction time (F(1,39)=.106, p=.746). However, the interaction of delay knowledge (known vs. unknown) and ITI was a significant moderator of reaction time (F(1,38)=5.285, p=.027). Overall, the interaction of delay knowledge and ITI accounted for a significant amount of reaction time variance (R^2=33.68%, F(1,38)=4.054, p=.005). In summary, the interaction of ITI length and delay knowledge was a significant moderator of the RT index of proactive vs. reactive control, with longer ITIs associated with less proactive control, but the effect was only present for known delays.

3.3.2

Interactions: Delay Known x Trial Set Count

In a set of univariate mixed-effects meta-regressions, we assessed whether there was an interaction between delay knowledge (factor) and trial set count (as a continuous variable) in moderating accuracy or reaction time. We observed a significant and robust interaction of delay knowledge and trial count on moderating accuracy (F(1,37)=4.350, p=.003); these variables accounted for 38.58% of accuracy variance. Following up this significant interaction, the interaction of known vs. unknown delay studies with trial set count was strongly significant (F(1,37)=12.373, p=.001). There was no interaction involving jittered vs. known studies (F(1,37)=.292, p=.592) nor jittered vs. unknown studies (F(1,37)=.353, p=.556).

The interaction of delay knowledge and trial set count was a significant and robust moderator of reaction time (F(1,36)=5.412, p<.001), accounting for 42.28% of

variance. Following up this significant interaction, we found that the interaction of known vs. unknown delay studies with trial set count was significant ($F(1,36)=4.586$, $p=.039$), whereas the interactions with jittered vs. known ($F(1,36)=.038$, $p=.846$) and jittered vs. unknown ($F(1,36)=.750$, $p=.392$) studies were not significant. In summary, the interaction of delay knowledge and trial set count was a robust and significant predictor of control metrics for accuracy and reaction time, with known delay studies of high trial count associated with the highest rates of proactive control.

3.3.3

Interactions: Trial Set Count x Delay Length and Inter-trial Interval

A series of univariate mixed-effects meta-regressions were run to understand whether there was an interaction between trial set count and delay length or ITI on accuracy or reaction time. The interaction between trial set count and delay length did not moderate accuracy ($F(1,39)=.000$, $p=.995$), nor did the interaction between trial set count and ITI ($F(1,39)=.046$, $p=.831$).

Trial set count and delay length did not show a significant interaction for reaction time ($F(1,38)=.310$, $p=.581$), nor did trial count and ITI ($F(1,38)=.121$, $p=.730$). In summary, neither trial count nor ITI interacted with trial set count to moderate accuracy or RT control indices.

3.4.1

Sub-group: Mid-Delay Distractors

Healthy young adult accuracy in standard expectancy paradigms did not differ from that in paradigms with mid-delay distractors (dp=7) (F(1,69)=.122, p=.728), but reaction time was marginally different (F(1,61)=3.548, p=.064). All studies with distractor paradigms were run with fully known delay lengths, so delay knowledge is not included in any analyses for this sub-group. Accuracy was not moderated by delay length (F(1,5)=.056, p=.823), nor ITI (F(1,5)=.733, p=.431), nor trial set count (F(1,5)=.002, p=.964). Reaction time was not moderated by delay length (F(1,5)=.453, p=.531), nor ITI (F(1,5)=.731, p=.431), nor trial set count (F(1,5)=1.131, p=.336).In summary, paradigms with mid-delay distractors did not show significant control biases, relative to standard paradigms. Distractor paradigm control metrics were not modified by delay length nor ITI nor trial set count.

3.4.2

Sub-group: Healthy Slightly-Older Adults

Healthy slightly-older adults (mean age >30; k=5, dp=10, mean age = 37.8, range= 31.6-43.6) differed significantly from healthy young adults (mean age < 30; k=31, dp=46, mean age = 22.2 +/- 2.14 SD, range 19.4-26.0) in accuracy (F(1,69)=7.392, p=.008), but not reaction time (F(1,61)=.388, p=.536) indices of control. All studies with slightly-older adults were run with fully known delay lengths, so delay knowledge was not included in any analyses for this sub-group. We used univariate meta-regressions to assess the effects of delay length, ITI, and trial set count in slightly-older adults (dp=10). Delay length did not moderate accuracy (F(1,8)=1.345, p=.280), nor did ITI (F(1,8)=.444, p=.524). Trial set count conferred a marginally significantly effect on

accuracy accounting for 24.80% of variance ($F(1,8)=4.319$, $p=.071$). Increasing trial set count was associated with a trend toward decreased accuracy index of proactive control, which is the opposite direction from the trial set effects in healthy young adults. This effect of trial set count between younger and slightly-older adults was marginally significant ($F(1,47)=3.246$, $p=.078$). Reaction time was not moderated by delay length ($F(1,4)=.664$, $p=.461$) nor ITI ($F(1,4)=1.550$, $p=.281$), nor trial set count ($F(1,4)=4.543$, $p=.100$).

In post-hoc analyses, older (elderly) adult accuracy and reaction time was compared with that of slightly-older and young adults. Accuracy did not differ between slightly-older adults and older (elderly) adults ($F(1,58)=.298$, $p=.587$), whereas reaction time metrics of control did differ between slightly-older and older (elderly) adults ($F(1,53)=7.715$, $p=.008$), with older (elderly) adults showing greater reactive control. As expected, both accuracy ($F(1,58)=7.334$, $p=.009$) and reaction time ($F(1,53)=8.773$, $p=.005$) differed between older (elderly) adults and young adults.

In summary, slightly-older adults showed accuracy performance that was similar to that in older (elderly) adults and significantly less proactive than that in young adults. Conversely, slightly-older adult reaction time metrics were similar to that in younger adults, and more proactive than those shown in older (elderly) adults. Slightly-older adults also showed a marginally-significant effect of trial set length on accuracy. Interestingly, increasing trial set count tended to decrease proactive control, which was an opposite pattern from that in young adults. This effect was marginally different between groups, where more trials led to a greater effect size differentiation between healthy young and slightly-older adult participants.

3.4.3

Sub-group: Schizophrenia

Studies in persons with schizophrenia included four studies sampling young adults with schizophrenia (k=4, mean age=22.0), six studies sampling slightly-older adults with schizophrenia (dp=6, mean age=37.7), and one study with unreported sample age. When compared to their age-matched controls, young adults with schizophrenia did not differ in accuracy (dp=7, F(1,5)=1.620, p=.259) nor reaction time (dp=7, F(1,5)=1.786, p=.239) from healthy young adults. In contrast, slightly-older adults with Schizophrenia showed significantly different (more reactive) accuracy than their age-matched healthy (slightly-older) adults (dp=12, F(1,10)=12.744, p=.005). Reaction time metrics did not differ between slightly-older adults with Schizophrenia and healthy slightly-older adults (dp=7, F(1,5)=1.350, p=.298).

All data points with these samples were run with fully known delay lengths, so delay knowledge was not included in any analyses for this sub-group. We used univariate meta-regressions to assess the effects of delay length, ITI, and trial set count in participants with Schizophrenia. We collapsed across age for moderator analyses due to the small number of studies in each age range. Accuracy was not moderated by delay length (F(1,9)=.011, p=.920), but ITI showed a marginally significant effect (F(1,9)=4.721, p=.058, R^2=21.39%). Trial set count was a very strong moderator of accuracy (F(1,7)=25.969, p=.001, R^2=100.00%), such that increasing trial set count was associated with increased proactive control. This effect of trial set count on accuracy was similar to that found in healthy young adults (F(1,46)=2.233, p=.142). Reaction time was

not moderated by delay length ($F(1,6)=.778$, $p=.412$) nor ITI ($F(1,6)=1.035$, $p=.348$), nor trial set count ($F(1,4)=2.825$, $p=.168$).

In summary, slightly-older adults with Schizophrenia showed more reactive accuracy performance compared to healthy slightly-older adults, but there were no differences in performance between young adults with Schizophrenia and their healthy young adult controls. Collapsing across age, trial set count was the only moderator to bias performance in schizophrenic patients, enhancing proactive control accuracy indices in a similar manner as in healthy young adults.

4

4.1

DISCUSSION

In this series of meta-regressions, we quantified the moderating influence of several experimental parameters that vary throughout the AX-CPT and DPX literature. In healthy young adults, we found that delay knowledge and trial set count, but not delay length or ITI, were significant moderators of behavior. Delay knowledge increased the reaction time index of proactive control, and comparison of known vs. unknown delay type revealed differences in reaction time as well as accuracy, such that known delays were associated with increased indices of proactive control. Trial set count moderated both accuracy and reaction time, with increasing trial count associated with increased proactive control. Finally, the interaction of trial count and delay type conferred

significant additional predictive benefits for accuracy and reaction time, such that the effects of trial set count were stronger in studies with a known delay.

Importantly, we observed that delay parameters and trial set count differs between imaging modalities, such that EEG studies use significantly shorter cue-probe delays and have higher trial set counts than behavioral or fMRI studies. Although the choices of delay length may be incidental to the need for a longer delay time in fMRI and practical benefits to shortened trial length, these systematic differences in delay length render comparison across AX-CPT and DPX studies problematic. Even though we do not find that delay length moderates AY-BX behavioral metrics of control, delay length may still be an important variable in studies examining neural correlates of control. Further, EEG-measured neural correlates of control may not be directly generalizable to those observed during fMRI due to different cognitive processes evoked by larger versus smaller trial set counts.

Beyond highlighting the methodological importance of parameter selection in continuous performance tasks, these meta-analytic findings help us understand more generally how cognitive control might work. We observed that knowledge of delay duration biases performance toward proactive control, suggesting that the ability to plan to execute a task at a precise time increases the amount or robustness of preparation. Alternatively, the lack of temporal knowledge might bias toward a "choice" to not activate proactive preparation systems, saving valuable cognitive resources. As AX-CPT and DPX tasks are commonly used to study working memory performance, it is important to consider that distinct working memory processes might be elicited when different proactive/reactive strategies are utilized.

As trial count increases, both accuracy and reaction time metrics of proactive control increase, suggesting that preparatory control processes become more automatic or habitual as they are repeatedly executed. Intriguingly, this effect becomes much stronger (explaining ~40% of variance in performance) when delay length is known (versus unknown). This finding suggests that it is not just the repetition of a process that habituates control, but even moreso the rhythmic, temporally predictable repetition of that process. In support of the importance of rhythmic predictability for habituation of control, we found that studies with mid-delay distractors did not differ significantly from standard expectancy studies, but failed to show moderating effects of delay knowledge or trial set count (as observed in standard studies). Whether this rhythmic predictability also facilitates different mechanisms for proactive context maintenance or reactive inhibition is a pressing question for future work.

In contrast to the robust increase in proactive control with trial count observed in healthy young adults, slightly-older adults do not show this effect, and in fact greater trial set count here is associated with an opposite trend toward greater reactive control. Importantly, slightly-older adults showed reactive accuracy performance similar to that in older (elderly) adults, and significantly less proactive than that in young adults. However, slightly-older adult reaction time metrics were similar to that in younger adults, and more proactive than those shown in older (elderly) adults. These findings are important because slightly-older adults are typically compared with participants with Schizophrenia without addressing potential changes in control preferences in from healthy young adulthood to healthy middle age. More aging studies are needed to test how proactive and

reactive changes in slightly-older adulthood facilitate this shift from proactive to reactive accuracy performance.

In studies of persons with Schizophrenia, we observed an interesting distinction between young adults with Schizophrenia and slightly-older adults with Schizophrenia. Young adults with Schizophrenia showed similar control ratios compared to their age-matched controls, whereas slightly-older adults with Schizophrenia showed more reactive accuracy than their age-matched controls. This may suggest that over time, the disease limits the efficacy of proactive control systems or biases toward reactive control processes. However, these age-based findings are based on analysis of only 4 (young) and 6 (slightly-older) Schizophrenia data-points, and should be interpreted with caution. Collapsing across age, there is a strong effect of trial count in persons with Schizophrenia, with greater trial repetition associated with greater proactive control. This effect of trial count, similar to that observed in healthy young adults, is interesting because it suggests that the context maintenance deficits (failures in rare cue BX trials) long observed in this population could be altered in part by extended rhythmic task repetition.

The lack of significant influence of either cue-probe delay length or ITI was surprising, and contrary to our hypotheses. One possible explanation is that although specific timing intervals do not alter the ratio of proactive versus reactive control (with delay knowledge already instantiating proactive control), timing demands may vary the instantiation and type of proactive control. Supporting this hypothesis, an EEG experiment examining AX-CPT and DPX instantiation at different cue-probe delay intervals does show distinct neural signatures during the cue-probe delay based on delay

length (Janowich & Cavanagh, under review). It is possible that manifest behavioral indicators are too crude to reveal subtle delay-induced changes on the relative influence of difference control systems. A prior meta-analysis (Lee & Park, 2005) surveyed the relative impact of increasing delay length on overall working memory performance in persons with Schizophrenia versus healthy controls, and also found no significant relationship.

4.2

Limitations and Future Directions

Our study focused on understanding the effects of delay knowledge, delay length, and trial set length in the AX-CPT and DPX literature. There are several limitations to this meta analysis, as well as many potential confounding factors that should be considered in its interpretation. First, although we limited our selection of studies to those with standard ~70% AX proportions, we included studies within a 10% range of the standard. We were underpowered to detect changes as a result of slightly-varying expectancy, but this factor may play a role in explain some residual between-study variance. The expectancy studies included in the meta-regression sample did vary in several aspects that are beyond the scope of this paper, but may be influential, including behavioral/imaging modality, overall task session length, response time-out speed, or cultural differences in the populations from which study samples were gathered.

In our meta-analysis, we collapsed across AX-CPT and DPX studies, which varied only in stimulus type (letters versus dots). Only one prior study has directly compared these paradigms (with otherwise identical parameters) in the same sample of

healthy young adults, and found similar behavioral performance, as well as general engagement of the same brain networks (Lopez-Garcia et al., 2015). However, in slightly-older adults, a large-scale study (n=131) did show a general decrease in performance for DPX relative to AX-CPT (Strauss et al., 2014). A post-hoc test of our meta-analysis data showed that there were no significant differences in accuracy nor reaction time control metrics based on use of AX-CPT versus DPX paradigms, but future work may be needed to understand how differences in paradigm could alter other aspects of control processing.

Finally, our study used the standardized mean differences of AY-BX for accuracy and RT as our outcome measures. Although we discuss results in terms of changes toward proactive or reactive control, composite measures of AY-BX performance cannot fully disentangle whether a composite shift toward proactive control is due specifically to enhancement of proactive control (improvement on BX trials), a weakening of reactive control (worsening performance on AY trials), or a combination of both. Detailed statistical analysis of specific AY and BX differences is beyond the scope and data available for this meta-analysis. However, we observed trends in healthy young adults showing increasing AY errors and in persons with Schizophrenia showing decreasing BX errors with increasing trials, allowing us to speculate that healthy young adults exhibit a relative weakening of reactive control with increasing trial count, whereas persons with Schizophrenia exhibit a strengthening of proactive control.

A major limitation to the calculation of our AY-BX outcome measures is that individual correlations between AY and BX were not available from the literature. As such, we were forced to rely on between-subject formulas to calculate effect size and

variance. If more complete data were to come available, a follow-up analysis should be conducted, estimating r (the correlation between AY and BX) from related studies, and performing a sensitivity using a range of plausible correlations (Borenstein et al., 2009).

Although a AY-BX subtraction measure is similar to the commonly-used Behavioral Shift Index (Braver et al., 2009), which has been useful in parsing proactive versus reactive control, other task performance measures (ie: BX-AX) may better capture important aspects of cognition. Different cue-probe pairs in the AX-CPT and DPX paradigms have been shown to reflect distinct aspects of cognitive processing. In a large-scale confirmatory factor analysis, context processing was strongly correlated with BX cue-probe performance, and this relationship showed convergent validity across AX-CPT and DPX tasks (MacDonald et al., 2005). Context processing shared significant variance with both intellectual functioning and working memory. AY trials, in contrast, loaded onto the preparatory factor (and shared more variance with preparatory factor in DPX than in AX-CPT). Preparatory factor shared significant variance with working memory, but not intellectual functioning. Overall, behavioral response to AY-BX probes does seem to capture a convergence of context processing and preparation, but other outcome measures should be considered in future analyses.

Future studies should advance these meta-analytic findings by methodically assessing the parameters tested in this study. For instance, a future study could compare participants' performance on an expectancy task with known delay and unknown delay blocks, to directly understand the varied processes evoked by delay knowledge. In addition, an large-scale experiment could be run on Amazon Mechanical Turk, testing trial set counts ranging from 50 to 500 (in intervals of 25), to understand the exact nature

of the relationship between trial set count and control. Finally, neuroimaging studies (and meta-analyses) could be conducted to investigate neural differences based on delay knowledge, trial count, as well as parameters not explicitly associated with behavior, like delay length.

4.3

Conclusions

The present series of meta-regressions revealed significant and robust effects of delay knowledge and trial set count on error rate and reaction time metrics of proactive vs. reactive control. In healthy young adults, studies with full knowledge of upcoming delay length shifted both accuracy and reaction time measures toward an increased use of proactive control, relative to studies in which the upcoming delay was unknown. Increasing trial set count also increased the use of proactive control in both healthy young adults and persons with Schizophrenia, whereas it increased the use of reactive control in healthy slightly-older adults. These results demonstrate that delay knowledge and trial set count are critical parameters in expectancy studies, guiding distinct cognitive control behaviors reflected in both error rate and reaction time measures. Researchers using the AX-CPT or DPX paradigms should no longer consider delay knowledge or trial set count as incidental parameters, and should select these parameters intentionally in accordance with the control type(s) of experimental interest. More broadly, this meta-regression advances our knowledge of cognitive control instantiation, providing strong evidence that cognitive control becomes more reactive when timing demands are not known, and more

proactive when timing demands are known. Further, our finding that healthy young adults (and persons with Schizophrenia) shift toward proactive control with increasing repetitions of a task set gives quantitative evidence that proactive systems are preferentially activated by increasingly regular patterns of expectancy.

CHAPTER 3

Immediate vs. delayed control demands elicit distinct mechanisms for instantiating proactive control

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ABSTRACT:

Proactive preparation for an upcoming goal differs from last-minute reactive adaptation, but it is unclear how preparatory mechanisms change based on *when* in the future a goal needs to be executed. To assess how timing information is integrated into preparatory control, we designed a novel variant of the Dot Pattern Expectancy task, where each cue signaled both task rule and delay duration (known short, known long, or unknown) between cue and probe. We recorded EEG while healthy young adult participants (n=36) performed this task, and found that delay demands elicited distinct prefrontal preparatory activities. Medial prefrontal amplitude was sensitive to delay knowledge and delay length. In addition, inter-site theta phase consistency between mid-frontal and right pre-frontal sites was strengthened for known short delays. These results show that different prefrontal preparatory control processes are elicited depending on goal timing demands, and highlight the need to consider timing dynamics in control preparation.

INTRODUCTION

As one must not only plan "what", but also *"when"*, we expect processes underlying proactive control to be sensitive to temporal information. To better understand the mechanisms facilitating proactive control, we evaluate the hypothesis that proactive control may comprise distinguishable sub-sets of processes that are elicited differently in accordance with the temporal dynamics of goal demands. We propose that updating vs. retention processes may be conducted differently and thereby express dissociable signals based on *when* the goal is to be acted upon.

Prior research (Janowich, 2016) has demonstrated dissociations in behavioral (neurocognitive task) performance and neural signals based on the duration of a well-known delay in the AX-CPT paradigm. Considering the potential importance of these findings and the merit of replication (especially with small sample sizes in neuroimaging studies), we sought to replicate and extend these findings in a similar (but non-identical) task.

In the present set of experiments, we investigate the hypothesis that the features contributing to proactive control vary systematically with the temporal delay over which goals need to be held in mind, and can be at least partly dissociated into separable neural processes. This approach does not posit that proactive processes are necessarily binary nor mutually exclusive, but instead tests whether some sub-processes may be more strongly elicited in the context of particular delay dynamics. We hypothesized that short temporal delays will require more of a goal-updating process (comparable to task-switching), where transient control processes immediately drive the rapid instantiation of a new state representation at the expense of the previous state (Medalla & Barbas, 2009;

Stanley, Roy, Aoi, Kopell, & Miller, 2018). In contrast, we expect that long temporal delays will utilize more of an active maintenance process (comparable to working memory), where control processes elicit persistent activity patterns to maintain a sustained representation (Barak & Tsodyks, 2014; Jensen & Lisman, 2005; Vogel & Machizawa, 2004; Wang, 2010; Wasmuht, Spaak, Buschman, Miller, & Stokes, 2017; although also see Spaak, Watanabe, Funahashi, & Stokes, 2017; Stokes et al., 2013).

To interrogate the effects of temporal demands on proactive control processes, we manipulated delay length in a second common cued control task that is also known to evoke proactive and reactive cognitive control. Like the AX- Continuous Performance Task (AX-CPT) (Barch et al., 1997; Cohen et al., 1997) analyzed in Janowich (2016), the Dot Probe Expectancy (DPX) task (Henderson et al., 2012b; MacDonald et al., 2005) (Figure 1) presents a cue informing the participant of the common or rare (control-demanding) task to be performed after the cue-probe delay. By manipulating shorter versus longer cue-probe delays, we aimed to elucidate how proactive control processes during the delay differ based on temporal demands. To maximize differences between the short and long delay conditions and the cognitive processes being tested, we used a static 1-second delay in the short delay condition and a jittered 3-second delay (+/- 0.5 seconds) in the long delay condition. In addition to eliciting distinct timing processes across these different temporal delays (Buhusi & Meck, 2005; Morillon, Schroeder, Wyart, & Arnal, 2016), the predictability of a static vs. jittered delay may further alter anticipatory processes, optimizing the ability for precise temporal preparation in the short condition while making temporal preparation more difficult in the long condition. Experimental procedures were replicated precisely from our prior AX-CPT analysis (Janowich, 2016).

Applying a label to proactive control sub-processes is fraught with inevitable disagreement over semantics and operational definitions of the likely role of frontal cortex, but here we attempt to dissociate proactive processes by their neural mechanisms and subsequent behavioral consequences. In order to define the most likely candidate processes, we quantified neural signals chosen *a priori* from well-established literatures in task switching and working memory maintenance. Critically, we are not inferring the existence of these exact constructs based on their neural signatures (e.g. reverse inference), but we aim to utilize these signals as a foundation for dissociating between delay conditions. This is a more conservative form of inference and should be considered as the first step within a broader research program that will aim to ultimately distill invariant features associated with distinct psychological processes. Task-switching has been characterized in the EEG literature with three well-replicated event-related potential (ERP) components during pre-stimulus preparation: an early anterior positivity, a differential switch positivity and a sustained frontal negativity (Capizzi, Feher, Penolazzi, & Vallesi, 2015; Jamadar, Hughes, Fulham, Michie, & Karayanidis, 2010; Karayanidis, Provost, Brown, Paton, & Heathcote, 2011; Lenartowicz, Escobedo-Quiroz, & Cohen, 2010; Li, Wang, Zhao, & Fogelson, 2012; Nicholson, Karayanidis, Poboka, Heathcote, & Michie, 2005; Rushworth, Passingham, & Nobre, 2005).

The early anterior positivity is evoked early in the cue-probe interval during switch trials, primarily during N1 and P2 periods (Capizzi et al., 2015; Collins, Cavanagh, & Frank, 2014; Karayanidis et al., 2009) over anterior and mid-frontal electrodes (Astle, Jackson, & Swainson, 2008; Lavric, Mizon, & Monsell, 2008; Manzi, Nessler, Czernochowski, & Friedman, 2011). The early anterior positivity is suggested to

reflect early context updating in the prefrontal cortex, prior to task-set reconfiguration. Task goal reconfiguration is also associated with the mid-frontal N2 ERP component (Di Russo et al., 2016; Gajewski, Kleinsorge, & Falkenstein, 2010), which is modulated by the need for cognitive control (for review, see (Folstein & Van Petten, 2008). Together, these multiphasic aspects of the midfrontal ERP complex may reflect the operations of a generic mediofrontal theta-band process (Harper, Malone, & Bernat, 2014) that appears to be a marker of the need for control (Cavanagh & Frank, 2014). Notably, recent task switching investigations have described how switching is associated with enhanced frontal midline theta power (Cooper et al., 2015b; Cooper, Darriba, Karayanidis, & Barceló, 2016; Cunillera et al., 2012).

The differential switch positivity is a positive-going waveform observed primarily at centro-parietal sites, emerging as early as 200 ms post-cue and peaking between 300-700 ms post-cue, greater for switch- relative to stay- trials (Capizzi et al., 2015; Cunillera et al., 2012; Karayanidis et al., 2009; Li et al., 2012; Manzi et al., 2011; Nicholson, Karayanidis, Davies, & Michie, 2006; Nicholson et al., 2005). This component has also been referred to as a P3b (Kieffaber & Hetrick, 2005) and a late parietal positivity (Astle, Jackson, & Swainson, 2006; Gajewski & Falkenstein, 2011). The switch positivity is widely thought to be associated with anticipatory task-set reconfiguration that is normally specific to switch-to trials, in which the participant knows the exact task for which to prepare a response (Karayanidis et al., 2011; Nicholson et al., 2006).

The sustained frontal negativity, also referred to as the frontal contingent negative variation (Astle et al., 2008; Lavric et al., 2008; Nicholson et al., 2005; Poljac & Yeung, 2014) is a late component associated with proactive preparation of overt response

processes (i.e., with motor output) (Astle et al., 2008; Capizzi et al., 2015; Karayanidis et al., 2010). This sustained frontal negativity is often observed at centro-frontal electrodes (Barcelo, Escera, Corral, & Periáñez, 2006) including AFz, (Astle et al., 2008), Fz, and FCz (Capizzi et al., 2015).

Although the task-switching literature is rich with work comparing short (< 200 ms) and longer (up to 1000 ms) switch intervals, it is important to note that this literature does not sufficiently address how task switching differs over multi-second delays. In addition, prior work, to our knowledge has not comprehensively analyzed task-switching components in the AX-CPT or DPX paradigms. Based on our prior experiment in AX-CPT comparing activity over short (1 second) and long (~3 second) delays, we hypothesize that similar results will be observed in the DPX paradigm. First, that rare (control-demanding) cues in the short delay will instantiate increased amplitude of mid-frontal early anterior positivity, as well as corresponding increases in mid-frontal theta power. Similarly, we expect to replicate selective increases in differential switch positivity and sustained frontal negativity for short and rare cues.

The AX-CPT and DPX paradigms have most often been presumed to assess working memory (Barch et al., 2009; Cohen, Barch, Carter, & Servan-Schreiber, 1999; Kessler, Baruchin, & Bouhsira-Sabag, 2015; Redick, 2014), and this construct has been associated with distinct neural processes from those implicated in switching task sets. Activation in both posterior parietal (Kikumoto & Mayr, 2017) and lateral prefrontal regions has been implicated in working memory maintenance (for review, see Eriksson, Vogel, Lansner, Bergström, & Nyberg, 2015). However, the electrophysiological signatures of working memory are not yet well defined. Recent findings have suggested

that working memory can be instantiated with short term synaptic plasticity (Christophel, Klink, Spitzer, Roelfsema, & Haynes, 2017; Polanía, Paulus, & Nitsche, 2011), and there is ample evidence that slow wave activities are also associated with active maintenance (Freunberger, Werkle-Bergner, Griesmayr, Lindenberger, & Klimesch, 2011; Schmitt, Ferdinand, & Kray, 2014; Unsworth, Fukada, Awh, & Vogel, 2015; Vogel & Machizawa, 2004). As reliable, generic EEG signatures of working memory have not been established, we hypothesize only that we will observe increased sustained, slow-wave activity for rare (control-demanding) cues during the long delay condition.

In summary, we hypothesized that proactive control is not a unitary construct, and that the influence of distinct sub-processes could be parsed based on temporal demands. This is an important idea, since the AX-CPT and DPX paradigms have been run in healthy and patient populations, with delay length often treated as a trivial parameter. Cue-probe delay length varies widely between studies in the AX-CPT/DPX literature, with mixed behavioral (for a meta-analytic review, see Janowich & Cavanagh, 2018 (Dissertation Chapter 2) and neural findings. As the literature fails to substantively address the role of delay in proactive control processes, here we set forth to empirically examine the behavioral consequences and neural manifestations of temporal delay. We tested our delay manipulation in two experiments using the AX-CPT or DPX paradigms, similar cued control tasks differing only on their use of verbalizable letter (AX-CPT) versus non-verbalizable dot stimuli (DPX) cues. By utilizing each of these widely-used paradigms in separate within-subjects experiments, we aim to establish a strong initial report on the generalizability and reliability of temporal effects on control. If delay dynamics do reliably alter behavior and/or neural mechanisms of proactive control, the

field will need to re-evaluate the findings and implications of cued control studies in light of their respective timing demands.

METHODS

Participants:

Forty undergraduate students at the University of New Mexico (26 women, ages 18-41 years, mean 21.3 +/- SD 5.0 years) participated in this experiment. Demographic information is displayed in Table 1. Participants reported no current use of psychiatric or neurological medication, no history of head injury or epilepsy, and normal or corrected-to-normal vision. All participants were right handed. Participants provided written informed consent and received course credit for their participation. The University of New Mexico Institutional Review Board approved these experiments. Data from three participants were excluded for excessive noise in the EEG data, and two participants were excluded for sub-par behavioral performance (below 50% accuracy averaged between all conditions, or any one condition less than 25% accuracy). This left a total of 35 participants.

Cognitive/Behavioral Tasks:

The AX-Continuous Performance Task (AX-CPT) (Carter et al., 1998; Cohen et al., 1999; Cohen et al., 1997) is a standard cue-probe cognitive task in which variance in cue and probe expectancy are used to assess the impact of (cue-derived) context on cognitive control. The task flow and parameters are depicted in Figure 1. In this task, a probe stimulus (X or Y) was presented following a paired cue stimulus (A or B) in target

and non-target combinations. In a two-alternative-forced choice manner, participants were instructed to respond to both cue and probe stimuli with left or right trigger buttons on a joystick. In the target AX sequence, X probes following A cues demanded a right trigger press; all other cues and probes were to be responded to with the left trigger. Because 70% of trials were composed of A-X cue-probe target pairs, entailing a left-right cue-probe response sequence, and A-Y, B-X, and B-Y cue-probe non-target pairs were much more rare (10% trials of each), a strong expectancy was generated to respond according to the 'A-X' rule (Servan-Schreiber et al., 1996). Feedback was given for incorrect ("ERROR!") and non-response ("Too Slow!") trials, for 500 ms. Trials were separated by a jittered inter-trial interval of 750-1000 ms.

A key feature of our variant of the AX-CPT paradigm is the block-wise manipulation of short vs. long delays between cue ('A' or 'B') and probe ('X' or 'Y') stimuli. In the short delay condition, a static 1000 ms delay separated the cue and probe stimulus. In the long delay condition, the probe was presented ~3000 ms after the cue (randomly jittered between 2500-3500 ms in intervals of 50 ms). All participants completed both short and long delay blocks, with block order randomly counterbalanced between participants.

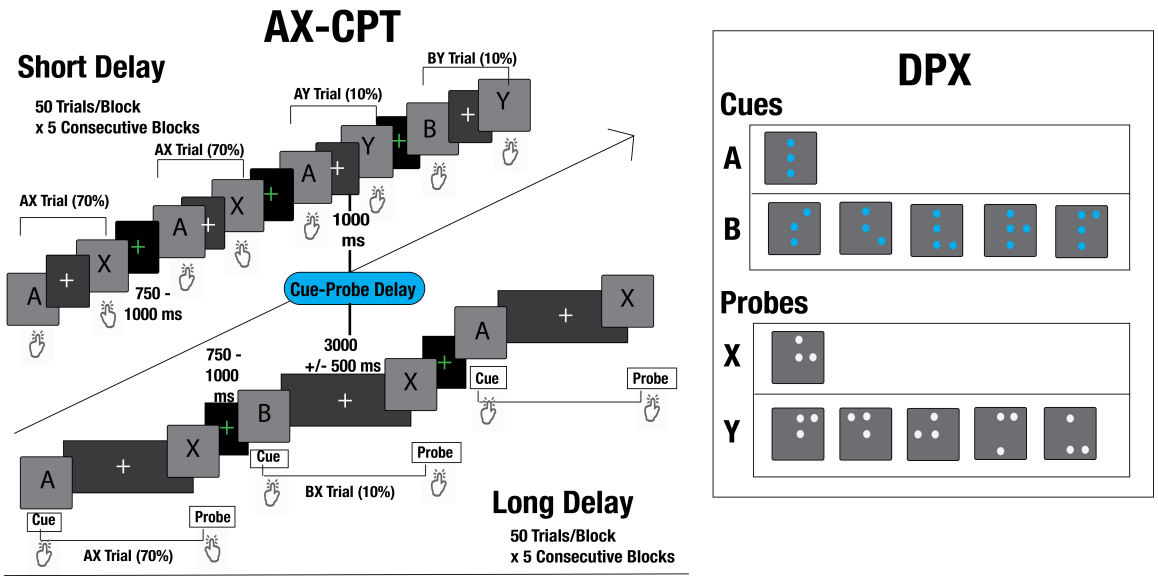
After being instructed in AX-CPT task rules by the experimenter, participants completed a practice session of 25 (short delay) trials. Participants were then given delay-specific instructions for the first delay condition, and completed five blocks of 50 trials (total 250 trials) with short breaks offered between each block. Instructions for the second delay condition were then presented, followed by five blocks of 50 trials (total 250 trials), with short breaks offered between each block. Total task duration was 41.7

minutes (+/- 3.4 mins). This task was written in Matlab using the Psychophysics Toolbox extensions (Brainard, 1997; Kleiner, Brainard, & Pelli, 2007; Pelli, 1997).

While the AX-CPT continues to be used in many studies, more recent investigations have adapted a number of subtle alterations to the perceptive and probabilistic features of the original AX-CPT, engendering the emergence of the Dot Pattern Expectancy Task (DPX) (Barch et al., 2009; MacDonald et al., 2005). DPX follows similar experimental design and logic as AX-CPT, but differs in the stimuli used as "A/B" cues and "X/Y" probes, as well as using slightly different proportions of cue-probe combinations (MacDonald et al., 2005). Here we aimed to replicate our prior AX-CPT findings with the DPX task, which shares the same general structure of proactive control and hypothesized dependence on timing manipulation, even in the context of lower-level parameter changes.

In the present experiment, there were three differences from the AX-CPT. First, in DPX, cues and probes were depicted as dot combinations instead of letters (Figure 1 inset). Second, 5 unique "B" cues and 5 unique "Y" probes were used. Third, the cue/probe proportions were altered: A-X: 70%, A-Y: 12.5%, B-X: 12.5%, B-Y: 5%. The different cue-probe proportions in DPX were chosen due to the predominant use of these proportions in the DPX literature (MacDonald et al., 2005). All other timing, trial/block, and feedback parameters used in the AX-CPT experiment were replicated in the DPX experiment. To ease discussion of the DPX study, terms "A/B" and "X/Y" will be used throughout this manuscript.

Figure 3.1: AX-CPT (from Janowich, 2016) and DPX Task designs. Participants performed the AX-CPT for 10 blocks of 50 trials each, in which cue-probe delay varied by block set. Five blocks of short (1 sec) cue-probe delay were followed by five blocks of long (3 +/- .5 sec) cue-probe delay, *or vice versa*, with delay order counter-balanced between participants. Participants responded to all cues by pressing the left index finger. Only X probes following A cues demanded a right index finger button press; this A-X combination occurred on 70% of trials. All other cue-probe combinations (A-Y, B-X, B-Y) demanded a left index finger button press to the probe; these combinations were rare, each only occurring on 10% of trials. [Inset:] In DPX, the task design was identical, except the cue and probe stimuli were dot combinations (see inset) instead of letters, and the cue-probe frequencies differed slightly from those used in AX-CPT (AX=68.75%, AY=12.5%, BX=12.5%, BY=5%).



Cue-Based Analyses:

We compared behavioral and neural responses for A vs. B cues in order to distinguish instantiation of common vs. rare rule sets between delay lengths. Trials were divided into four conditions for each set of comparisons: short A, short B, long A, and long B. Two-way repeated measures ANOVAs were used to calculate main effects of cue type and delay length, and cue-delay interactions; only the interactions are of theoretical interest for inferring different neural proactive control processes due to delay.

Non-parametric correlations between neural and behavioral variables were computed with Spearman's rho. To assess statistical differences in correlations between short and long delay lengths, within-sample rho-to-z tests (Lee & Preacher, 2013; Steiger, 1980) were conducted; these tests incorporate a variable describing how the two tests are themselves correlated (Meng, Rosenthal, & Rubin, 1992), and are preferred for non-independent correlations. In order to facilitate direct comparison of preparatory activity for short versus long delay, analyses and visualizations were conducted for only the first 1000 ms post-cue (the length of the short delay).

Behavioral Analyses:

Context activation/updating was quantified with the Behavioral Shift Index (BSI) (Braver et al., 2009) (used in (Chiew & Braver, 2013; Edwards, Barch, & Braver, 2010; Lamm et al., 2013; Lucenet & Blaye, 2014; Morales et al., 2014; Schmitt et al., 2015)), which indexes the proportional use of proactive versus reactive control based on task error rate or reaction time to "AY" relative to "BX" cue-probe pairs. The following formula generates a single proactive/reactive BSI value:

$$(aY - bX) / (aY + bX)$$

Higher BSI scores are associated with a greater use of proactive control, whereas lower BSI scores are associated with a greater use of reactive control. If context activation/updating abilities are intact, proactive control should bias responses based on context (Braver, Barch, & Cohen, 1999) and manifest in impaired performance on 'AY' trials (Braver et al., 2005), during which a robust pre-potent response must be inhibited. BSI operationalizes proactive control as a unitary construct. By considering the

relationship between BSI and cue-locked neural activity, we can resolve whether different neural responses to cued task demands bias behavior toward proactive or reactive control.

EEG Data Acquisition:

EEG data were acquired with a BrainVision 64-channel amp, with standard 10-20 configuration, and recorded with PyCorder software. Data were recorded continuously across 0.1-100 Hz and sampled at 500 Hz. VEOG was recorded above and below the right eye. FPz was utilized as online ground, and CPz was the online reference.

EEG Data Pre-Processing:

Epochs were created surrounding cue onset (-2000: 7000 ms), from which associated cue and cue-probe delay activity were isolated. CPz was re-created by re-referencing the data to an average reference. Very ventral channels (FT9, FT10, TP9, TP10) were removed due to unreliability. Bad channels were identified using a combination of FASTER (Nolan, Whelan, & Reilly, 2010) and EEGlab's pop_rejchan (Delorme & Makeig, 2004), and were then interpolated. Bad epochs were identified by FASTER and then rejected. Independent components analysis (runica.m) was run and VEOG activity and a Gaussian template around frontopolar channels were compared with components to help identify and remove blink activity.

After pre-processing, data were transformed to surface Laplacian *(laplacian_perrinX.m)* (Cohen, 2014; Perrin, Pernier, Bertrand, & Echallier, 1989). As a high-pass spatial filter, the Laplacian filters out spatially broad features thereby

minimizing effects of volume-conduction, and highlights local topographical features. The surface Laplacian is reference-free, and as such avoids confounds with the choice of reference electrode (Cohen, 2014; Kayser & Tenke, 2006).

ERP & Time-Frequency Analyses

Event-related potentials (ERPs) were created to assess the early post-cue activity involved in instantiating proactive control. Cue-locked activity for each condition (see above) was calculated as an average of all trials with correct responses to both cue and probe, ensuring attention to the task and successful context processing. To equalize the signal to noise ratio, trial count was equated between conditions by randomly drawing A trials equal to the count of B trials. This resulted in approximately 40-50 trials for each cue x delay condition (48 +/- 4 trials). Data were low-pass filtered at 20 Hz (eegfilt.m). Epochs for ERP analyses were created from -200:1000 ms peri-cue, and activity was baseline-corrected to -200:0 ms pre-cue.

The ERP and time-frequency components chosen for analysis were selected based on prior literature suggesting their involvement in task-switching or working memory processes, and were evaluated at a priori regions and time windows of interest, as detailed below. Grand averages were collapsed between all conditions in order to derive analytic windows of interest (Cohen, 2014). For each ERP component of interest at each electrode of interest, individual peaks were identified from the across-condition time windows. For early components, windows were centered at 20 ms around the component peak. For later sustained components, average activity was computed across the entire window of interest. Early anterior potential was computed at FCz as the P2-N2 difference for each

participant, in which the minimum (trough) of the N2 was subtracted from the maximum (peak) of the P2. The differential switch positivity was quantified at Cz from 400-600 ms. The sustained frontal negativity was quantified at an average of mid-frontal electrodes (AFz, Fz, and FCz) from 400-600 ms. To investigate working memory related sustained activity during the delay, two exploratory analyses were conducted based on a history of prefrontal and posterior parietal activations in the working memory literature, in conjunction with observations of our data. First, a left pre-frontal cluster (AF3, AF7, F3, F5, F7) of electrodes was evaluated from 150-400 ms post-cue. In addition, a cluster of bilateral posterior-parietal (PO3,PO4,PO7,PO8) electrodes was evaluated from 400-800 ms post-cue.

We conducted time-frequency analyses to follow up the ERP findings, investigating only spectral phenomena immediately seen in ERPs. For time-frequency analyses, wavelet transforms (Cavanagh, Cohen, & Allen, 2009) were applied to cue-locked EEG data in the original -2000:7000 ms epochs. Utilization of these longer epochs allowed us to extract and analyze low frequency bands. As temporal smoothing from time-frequency decomposition may introduce temporal leakage of trial-related activity into the pretrial period (Cohen, 2014), all time-frequency analyses were conducted with a baseline time period of -300 to -100 ms pre-cue. Main and interaction effects were tested in two ways. First, for display, paired-samples t-tests were computed over the entire time-frequency spectrograph. Second, time-frequency regions of interest (tf-ROIs) were run in ANOVAs for direct comparison to the ERP activities. As time-frequency activities are smeared by wavelet convolution, time-frequency and ERP windows will not precisely overlap, but they are nonetheless reflective of frequency-related information underlying

the ERPs (Cohen, 2014). In light of the relative prominence of theta (4-7 Hz) and delta (1-4 Hz) activity corresponding to early and later/ sustained ERP activities, respectively (Harper, Malone, Bachman, & Bernat, 2016), theta was used to assess spectral phenomena seen in early delay periods (200-400 ms), and low-frequency delta-theta (1-7 Hz) power was used to investigate spectral properties of activities in later delay periods (200-600 ms). Thus, full spectra plots and band-specific topoplots are displayed in figures for visualization purposes only, and do not represent hypothesis testing for all points shown.

RESULTS

Accuracy

A repeated-measures 2 (Delay: short, long) * 2 (Cue: A,B) * 2 (Probe: X, Y) ANOVA was run for behavioral accuracy in the DPX task (see Figure 2 and Tables 2-3). All main and interaction effects were significant (see Table 3). Most critically, participants showed robust deficits in accuracy on aY trials in Short Delay relative to Long Delay.

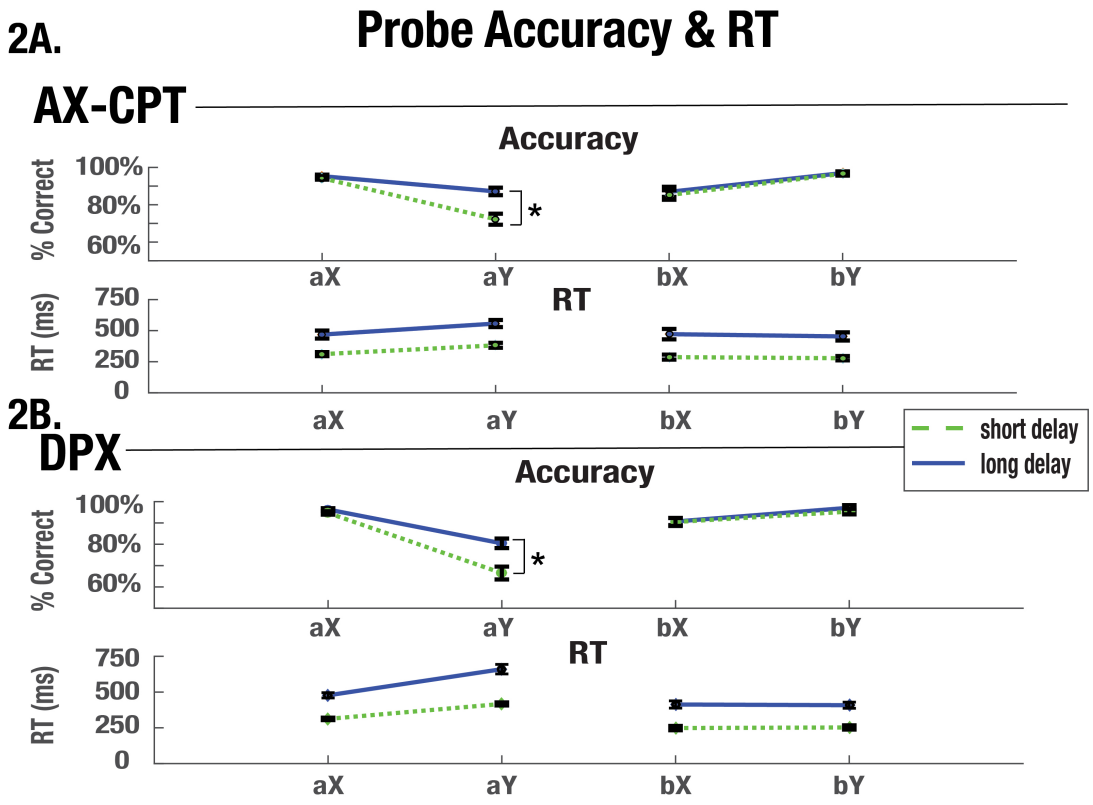
As detailed in the methods, we are only interested in control-related interactions with delay. Motivated by the 3-way interaction and a priori hypotheses on the relevance of aY and bX trials in the AX-CPT/DPX paradigms, we investigated delay effects on aY and bX trials specifically. A repeated-measures 2 (Delay: short, long) by 2 (Cue-Probe: aY, bX) ANOVA revealed main effects of delay, cue-probe combination, and delay*probe interaction. To follow up this significant interaction, we ran paired t-tests

for delay on aY and bX separately. aY accuracy was significantly different between delay lengths , whereas bX was not different (see Tables 2-3).

Response Time

A 2 (Delay: short, long) * 2 (Cue: A,B) * 2 (Probe: X, Y) repeated-measures ANOVA was also run for probe RTs (Table 3). All major main effects were significant, and delay*cue, delay*probe, and cue*delay*probe interactions were also significant.

Figure 3.2: AX-CPT (from Janowich, 2016) and DPX Accuracy and Reaction Time to probe stimuli. Error bars represent standard error. Asterisks indicate significant Cue-Probe x Delay interactions ($p<.05$). aY accuracy was significantly worse in short delay blocks relative to long delay blocks for both AX-CPT (2A) and DPX (2B) experiments. Main effects of delay on reaction time were found for all Cue-Probe pairs, but no delay x cue-probe type interactions were observed.



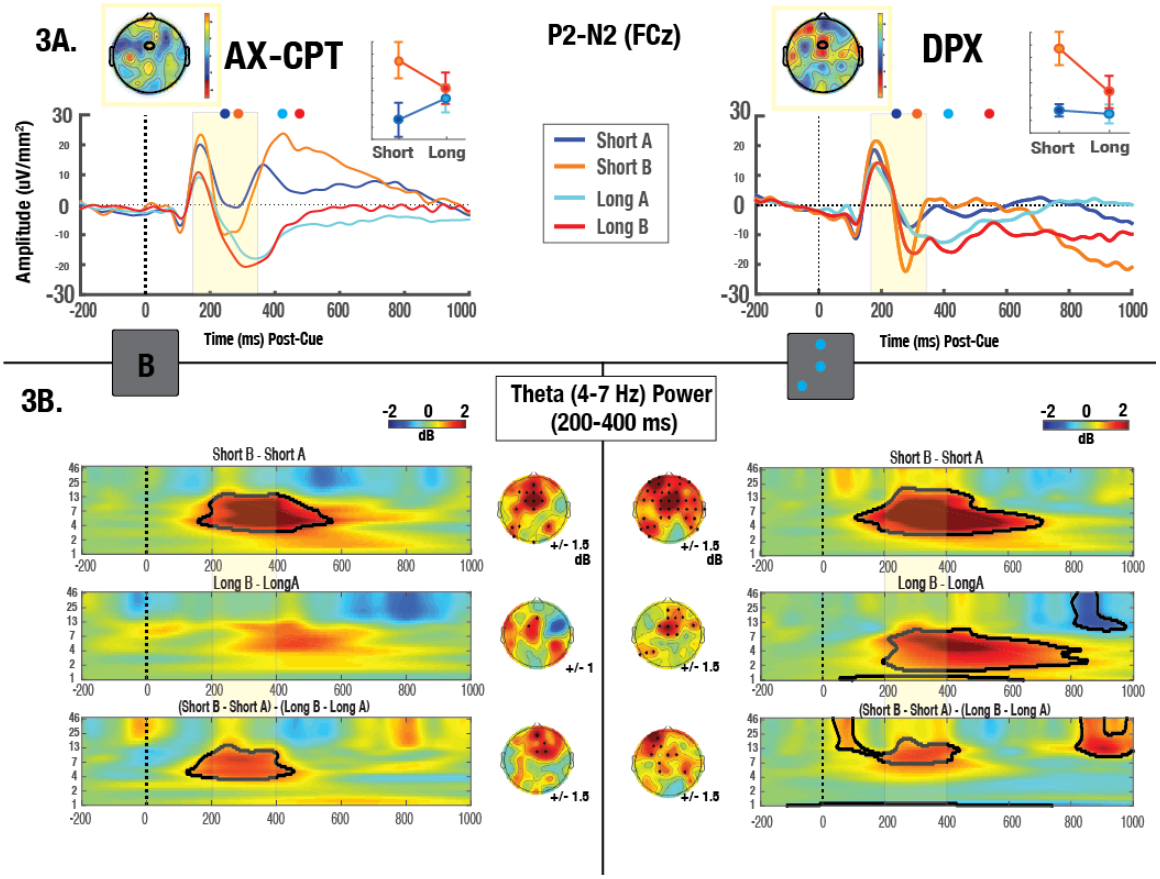
Early Anterior Potential following cues

In DPX, the Early Anterior Potential at FCz (see Figure 3A) showed a simple main effect of cue (B>A; $F(1,34)=11.24$, $p=.002$), a main effect of delay (S>L; $F(1,34)=7.27$, $p=.011$), and a critical significant interaction between cue and delay length ($F(1,34)=13.86$, $p<.001$).

Time-frequency power was evaluated at FCz (see Figure 3B); these findings indicate statistically significant main effects in the *a priori* theta band TF-ROI (as well as extending in both later time and broader frequency) from cue type as well as a cue*delay interaction, shown as the difference of differences plot. Topoplots (Figure 3B inside) depict un-corrected statistical differences between conditions. Theta (4-7 Hz) tf-ROI power was calculated from 200-400 ms at FCz with 2x2 repeated-measures ANOVAs.

There was a significant main effect of cue (B>A; $F(1,34)=46.18$, $p<.001$), a significant main effect of delay, (S>L; $F(1,34)=31.73$, $p<.001$) and a significant cue*delay interaction ($F(1,34)=4.90$, $p=.034$), in which the greatest power was observed for Short B cues. These findings suggest that early mid-frontal activities during proactive control can be differentiated by delay length, in particular activities previously associated with task switching during short delay.

Figure 3.3: Early anterior potential and early theta power at FCz. 3A. Cue-locked ERPs at by delay length and cue type, for AX-CPT (left, Janowich 2016) and DPX (right) experiments. Vertical lines indicate average cue RT for each color-coded condition; a priori region of interest indicated by yellow highlight. Insets display the P2-N2 cross-over interaction for each cue by delay type. B. Time-frequency main effects displayed as subtractions of short and long delay, and the interaction displayed as the difference of differences. Outlined time-frequency areas highlight statistically significant differences. Topoplots show theta (4-7 Hz) power differences 200-400 ms post-cue at each delay length between cue types. Black dots indicate statistically significant differences between cue types at that delay length for that electrode.

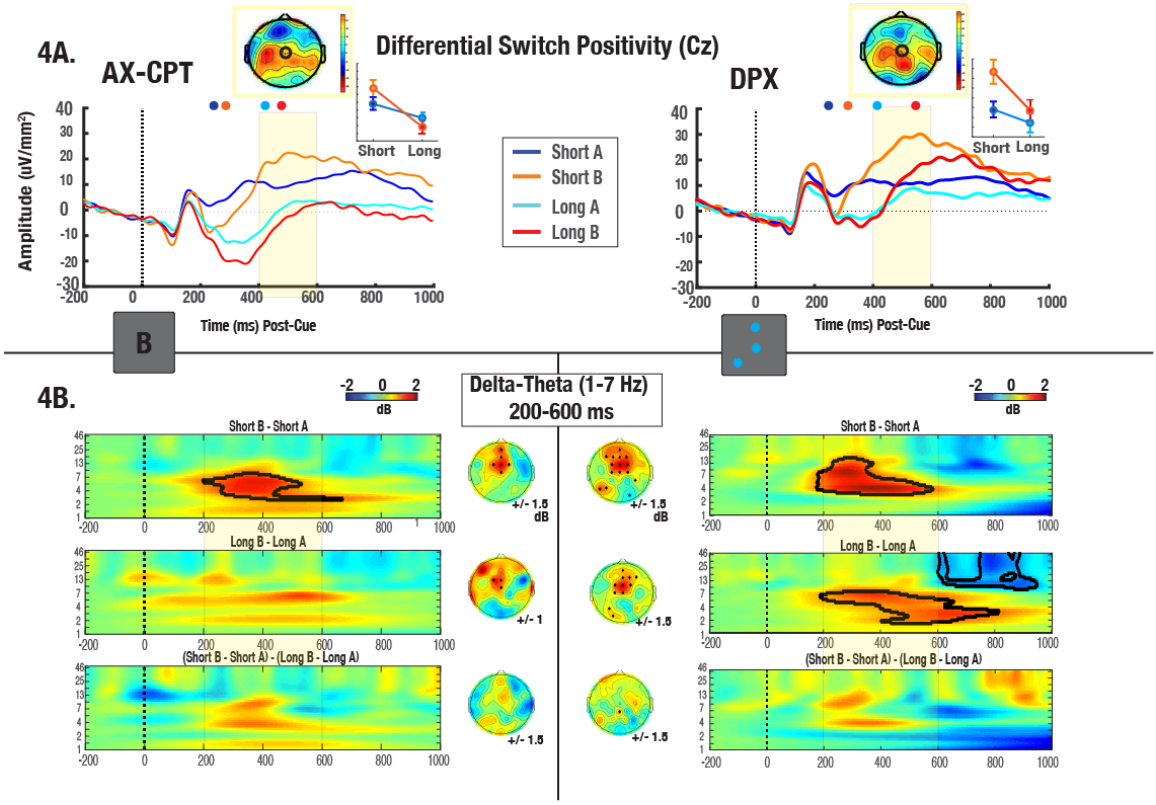


Differential Switch Positivity following cues

The differential switch positivity (Figure 4) was quantified as the average amplitude at Cz between 400-600 ms. We observed a significant main effect of cue (B>A; $F(1,34)=11.60$, $p=.002$), a significant main effect of delay (S>L; $F(1,34)=6.44$, $p=.016$), and a cue*delay interaction ($F(1,34)=6.04$, $p=.019$) with greater amplitudes following Short B cues.

To follow up these ERP findings, time-frequency power was evaluated at Cz, and statistics were computed on low-frequency delta-theta (1-7 Hz) band activity at Cz (Figure 4B outside). Topoplots (Figure 4B inside) depict un-corrected delta-theta band differences between conditions to demonstrate the spatial selectivity of these findings. There was a significant main effect of cue (B>A; $F(1,34)=19.87$, $p<.001$), but no main effect of delay ($F(1,34)=.29$,$p=.596$) or cue*delay interaction ($F(1,34)=.29$, $p=.592$). These findings suggest that later midline activities during proactive control can be differentiated by cue rarity and delay length, at least in ERP amplitudes. The preferential finding of differential switch positivity for short rare cues lends further support to the hypothesis that short delays during proactive control are most similar to this established task switching component.

Figure 3.4: Differential switch positivity and early-mid delta-theta power at Cz. 3A. Cue-locked ERPs by delay length and cue type, for AX-CPT (left, Janowich 2016) and DPX (right) experiments. Vertical lines indicate average cue RT for each color-coded condition; a priori region of interest indicated by yellow highlight Insets display the mean 400-600 ms cross-over interaction for each cue by delay type. 3B. Time-frequency main effects displayed as subtractions of short and long delay, and the interaction displayed as the difference of differences. Outlined time-frequency areas highlight statistically significant differences. Topoplots show delta-theta (1-7 Hz) power differences 200-600 ms post-cue at each delay length between cue types. Black dots indicate statistically significant differences between cue types at that delay length for that electrode.



Sustained Frontal Negativity following cues

The sustained frontal negativity was assessed as the average amplitude at midline frontal electrodes AFz, Fz, and FCz between 400-600 ms. There was no main effect of delay ($F(1,34)=.57$, $p=.455$), no main effect of cue ($F(1,34)<.01$, $p=.955$), and no delay*cue interaction ($F(1,34)=.25$, $p=.624$).

Sustained Posterior-Parietal Activity following cues.

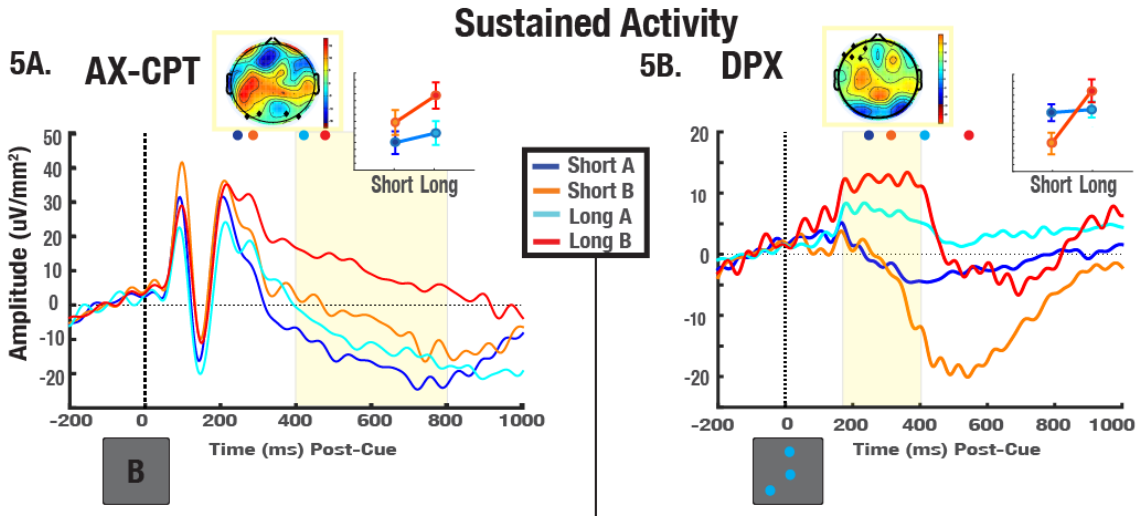
Late sustained activity at posterior parietal electrodes was computed by averaging amplitude from 400-800 ms post-cue at an average of bilateral posterior-parietal electrodes (PO3,PO4,PO7,PO8). This ERP effect was non-significant in DPX (Cue $F(1,34)=.30$, $p=.586$); Delay $F(1,34)=.19$, $p=.671$; Cue*Delay Interaction $F(1,34)=2.26$, $p=.146$). Since this ERP feature was slow and sustained, we did not investigate it with time-frequency methods due to limited resolution of sub-1 Hz activity.

Left Prefrontal Activity following cues.

In an exploratory analysis, we observed a different interaction of delay*cue in left prefrontal areas. Left prefrontal activity was computed by averaging amplitude from 150-400 ms post-cue at an average of left frontal electrodes (AF3, AF7, F3, F5, F7) (Figure 5B). We observed a significant main effect of delay (L>S; $F(1,34)=5.52$, $p=.027$), no main effect of cue type ($F(1,34)=.43$, $p=.517$), and a critical significant delay*cue interaction ($F(1,34)=9.13$, $p=.006$), where the greatest amplitude was observed following Long B cues. These findings suggest that late, slow activities that may be reflective of active maintenance can differentiate proactive control specifically during long delays.

However, the lack of specificity in working memory signatures suggests that this hypothesis remains incompletely resolved.

Figure 3.5: Posterior-parietal and left frontal sustained activity. Cue-locked ERPs by delay length and cue type. Vertical lines indicate average cue RT for each color-coded condition; time region of interest indicated by yellow highlight. 5A: AX-CPT (Janowich 2016) average of posterior parietal electrodes (PO3, PO4, PO7, PO8) Insets display the mean 400-800 ms cross-over interaction for each cue by delay type. 5B: DPX average of left frontal electrodes (AF3, AF7, F3, F5, F7). Insets display the mean 150-400 ms cross-over interaction for each cue by delay type.



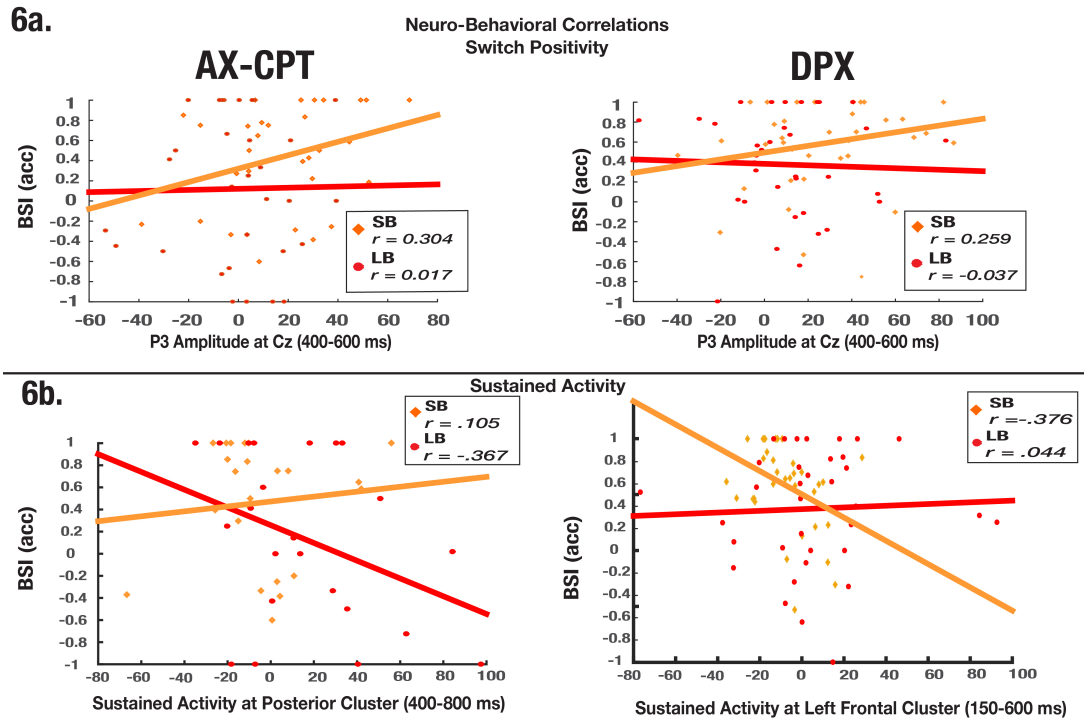
Brain-Behavior Correlations

While delay effects on behavior were robust, and several neural features were enhanced differentially in short or long delay, it is not clear whether these cue-locked EEG features are intimately related to probe behavior. We tested whether the behavioral shift index accuracy metric was differently correlated with our EEG measures for short versus long delay (Supplemental Figure 1). In DPX, correlations between differential

switch positivity and BSI were trending but non-significant for short versus long delay (DPX z-score= 1.722, p=.085). BSI did not correlate with short versus long differences in sustained left frontal activity.

In sum, weak statistical differentiation of BSI by delay-related neural activity suggests that these cue-locked components offer only modest evidence of brain-behavior associations.

Figure 3.6: Brain-behavior correlations between Behavioral Shift Index (BSI) for accuracy and neural measures for AX-CPT (left, Janowich 2016) and DPX (right). Pearson's r for each condition in inset boxes. 6A. Differential switch positivity at Cz (400-600 ms) correlations with BSI (Acc). These correlations show marginally significant positive correlations between differential switch positivity to rare 'B' cues and BSI, which is greater for short vs long delay. 6B. (Left) AX-CPT sustained posterior-parietal activity (PO3, PO4, PO7, PO8) and (Right) DPX left frontal (AF3, AF7, F3, F5, F7) correlations with BSI (Acc). AX-CPT correlations show a trend of negative correlation between long B cue-locked and BSI accuracy. DPX correlations show an unexpected (negative) relationship between short B cue-locked activity and BSI accuracy.



DISCUSSION

To understand how upcoming temporal demands modulate proactive control, we manipulated timing-related task demands in a cued control task, and compared within-subjects behavior and electrophysiological signals associated with goal updating and active maintenance. Critically, our findings suggest a temporally-guided fractionation in the construct of proactive control, which has typically been evaluated as a unitary construct. Two specific major findings emerged from this experiment. First, within-subjects accuracy to rare aY probes was selectively impaired during short delay, implicating specific difficulty in inhibiting a pre-potent aX response. Second, we observed significant within-subjects differences in ERP and time-frequency signatures associated with task-switching, cognitive control, and active maintenance based on delay length and cue type. Both of these major findings were previously observed in the AX-CPT (Janowich, 2016) and replicated in a separate sample in the present study. This serves as the first study to attempt to dissociate different sub-types of proactive control, and provides novel evidence that temporal demands can elicit behavioral differences and neurophysiological distinctions in proactive processes. Again, we operationalized these distinct features as 1) a goal updating process in which transient control immediately drives the rapid instantiation of a new state at the expense of a previous state, in contrast to 2) an active maintenance process where control processes elicit persistent activity patterns to maintain a sustained representation (Barak & Tsodyks, 2014; Jensen & Lisman, 2005; Vogel & Machizawa, 2004; Wang, 2010; Wasmuht, Spaak, Buschman, Miller, & Stokes, 2017; although also see Spaak, Watanabe, Funahashi, & Stokes, 2017; Stokes et al., 2013). Of course, we do not expect that active maintenance would occur in

isolation; even a distant goal must be updated at some point in time. We posit that this active maintenance process stores one's new goals, preceding a later or more gradual reconfiguration to the new state (Frohlich, Bazhenov, Timofeev, Steriade, & Sejnowski, 2006).

Dissociating Proactive Control

For the last several years, the dual mechanisms of control framework has divided cognitive control into proactive and reactive cognitive control (Braver, 2012), with proactive control instantiated to actively maintain goal-relevant information ahead of cognitively demanding events (Miller & Cohen, 2001), and reactive control called upon as a late correction mechanism utilized as needed, and only after a high-interference event occurs (Jacoby et al., 1999). Proactive control has been described and studied as a unitary construct, but this present work attempts to highlight how different sub-processes within proactive control are utilized based on known temporal differences as to when the cognitively demanding event will occur.

In the current study, within-subjects EEG activity was analyzed during the cue-probe delay to reveal how cues were processed to proactively (ahead of the probe) instantiate cognitive control. If there are dissociable neural processes underlying different types of control instantiation ("A" vs "B" rules) during different known delay durations, it is reasonable to deduce that participants are using different "types" (or sub-processes) of proactive control according to temporal demands.

Accuracy was impaired specifically to rare aY probes in the short cue-probe delay condition (Figure 2). This finding not only indicates difficulty in inhibiting the aX

response that is demanded on 80% of A trials, but highlights that this pre-potency is significantly stronger and/or more difficult to overcome with a predictable, short cue-probe delay.

Dissociating Proactive Control: "Goal-Updating" or "Active Maintenance" Sub-Types

We expected short delay demands to evoke a rapid, goal-updating type of cognitive control to B cues, where control is needed to immediately alter task goals. Neural differences were observed for short B over long B cues in early evaluative components (early anterior positivity), and later preparatory components (differential switch positivity). Due to the specificity to goal updating trials and short-delay context, this post-cue neural activity can be characterized as a delay-sensitive marker of goal updating (Cacioppo & Tassinary, 1990).

In the task-switching literature, it has been observed that participants often fail to proactively reconfigure task sets when there is a long cue-probe interval (de Jong, 2000). In these long delay scenarios where proactive task set reconfiguration is not triggered, it is likely that a different process is used to maintain changing task goals. We expected long delay cues to evoke a slower active maintenance process following rare B cues, in order to hold the new stimulus-response mappings over a long and uncertain delay. We observed a sustained increase in left pre-frontal electrodes selectively for rare cues during long delay, providing a plausible mechanism for maintenance of the rare cued rule in long, but not short delay. However, the current experiment is not suited to definitely declare this sustained activity as working memory maintenance. First, the characterization of electrophysiological markers of working memory is widely variable

(Brookes et al., 2011; Jensen & Tesche, 2002; Polanía et al., 2011; Vogel & Machizawa, 2004). Furthermore, the working memory literature has predominantly focused on maintenance of concrete visuo-spatial or auditory items, as opposed to retention of abstract rules. To better understand how rule retention might relate to item maintenance, it will be important for future work to more directly compare these constructs and their underlying mechanisms.

Differences between AX-CPT and DPX Paradigms

Despite the procedural differences between studies (cue type, single vs. multiple stimuli, cue-probe percentages) nearly all brain and behavioral effects were replicated between experiments, demonstrating generalizability. Prior studies comparing AX-CPT and DPX paradigms in health young adults have also observed similar behavioral performance between the two studies (Barch et al., 2009), as well as many common areas of fMRI activation for goal maintenance (Lopez-Garcia et al., 2015). This generalizability is important because both AX-CPT and DPX tasks are widely used to assess working memory in various patient and healthy control groups, as well as in translational work (Blackman et al., 2016; Blackman, Macdonald, & Chafee, 2013).

Yet, several subtle but potentially important distinctions between the AX-CPT and DPX paradigms must be noted, as these distinctions may evoke different strategies for proactive control. First, AX-CPT utilizes verbalizable letters as cues, whereas DPX uses non-verbalizable dot combinations. The need for intermediate translation from dot stimuli to task identity may impose at least some additional cognitive demand. It is unclear how proactive control instantiation might differ with these greater demands on

working memory and/or task switching in the Dot Pattern Expectancy (Henderson et al., 2012a; MacDonald et al., 2005; Otto, Skatova, Madlon-kay, & Daw, 2015). Since these tasks were run in separate samples, we are unable to provide a formal (within-subjects) test of potential task differences.

Limitations and Future Directions

The current study has several limitations, each of which invite questions to be addressed by future research. First, this study assessed two cue-probe delay lengths: 1000 ms and 3000 +/- 500 ms. Although a 1000 ms cue-probe delay is commonly used in AX-CPT and DPX studies, the next most common delay frequency in the published literature is between 4500 and 6000 ms (Janowich & Cavanagh, 2018). It is unclear whether delay-related differences in control instantiation would change significantly with an increase in delay from ie: 3 to 5 seconds; future studies could explore the full range of AX-CPT/DPX delay lengths used (5 seconds – 10 seconds). In addition, this short delay was fixed at 1000 ms, while the long delay was jittered between 2500 and 3500 ms, conflating expectancy and delay. The increased reaction times in long delay, for instance, may be due in part to the cue-probe jitter. These parameters were set in the present experiment in order to maximize the chance of generating a maximal pre-potent response in the short delay, but future replications could systematically parse these parametric choices.

With the current set-up of the DPX task, remembering the A or B cue involves a relatively low working memory load, especially for our sample of healthy college students, which may explain the limited individual differences in accuracy and reaction

time. As such, our brain-behavior correlations trended in the expected direction, but were non-significant. Finally, the ability to infer cognitive processes based on different neural activities is limited by the lack of specificity between common EEG activities and presumably distinct cognitive processes. The centro-parietal P3, for instance, has been associated with task-switching (Gajewski & Falkenstein, 2011) as well as working memory (Polich, 2007). Consequently, it is difficult for correlations with any one brain signal to definitively characterize a certain type of behavior. Moreover, any psychological definition of an ERP or time-frequency component is likely imprecise, as the actual neural operation it indexes is unlikely to directly map onto a large-scale construct such as "task-switching" or "working memory". To reiterate our earlier point, we did not aim to use abductive (reverse) inference to definitively parse distinct cognitive processes in this study; we aimed for a more modest approach that provides suggestive cognitive labels for our observed dissociations in neural activity. We hope to use experimental and quantitative constraints in the future to provide more definitive labels for these processes (Cavanagh & Castellanos, 2016a; Hutzler, 2014; Poldrack, 2006; Yarkoni, Poldrack, Nichols, Van Essen, & Wager, 2011); however that is clearly outside the scope of the current report.

CONCLUSIONS

In this report, we describe how temporal delay, an otherwise arbitrarily controlled parameter in a popular assessment of cognitive control, has an important influence over of the type of cognitive control utilized. We suggest that timing demands may tap into distinct mechanisms for goal updating versus active maintenance. This proactive adaptation to temporal context is likely useful to optimally balance the costs of sustained

control with the need to successfully execute behavior. Given the prevalence of this task for assessing cognition in psychiatric samples, it is critical to consider whether a given group is deficient in one or both of these dissociated aspects of control. Accordingly, researchers must preemptively weigh whether short and/or long delays best tax the cognitive constructs under consideration. Compounding this issue, fMRI studies tend to use long delays to facilitate the hemodynamic response function, whereas behavioral and EEG studies tend to use shorter delays (Janowich & Cavanagh, 2018). This pattern of differences in delay parameters suggests that there is a previously unappreciated problem generalizing findings between these techniques.

The temporal dissociation of two sub-types of proactive control merits further critical discussion of the common conceptualization of proactive control as a unitary construct. Altogether, our results suggest that cued continuous performance tasks tap into different cognitive features depending on seemingly arbitrary timing parameterization choices.

CHAPTER 4

Temporal information and trait impulsivity guide prefrontal preparatory activity

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ABSTRACT:

Proactive preparation for an upcoming goal differs from last-minute reactive adaptation, but it is unclear how preparatory mechanisms change based on *when* in the future a goal needs to be executed. To assess how timing information is integrated into preparatory control, we designed a novel variant of the Dot Pattern Expectancy task, where each cue signaled both task rule and delay duration (known short, known long, or unknown) between cue and probe. We recorded EEG while healthy young adult participants (n=36) performed this task, and found that delay demands elicited distinct prefrontal preparatory activities. Medial prefrontal amplitude was sensitive to delay knowledge and delay length. In addition, inter-site theta phase consistency between mid-frontal and right pre-frontal sites was strengthened for known short delays. These results show that different prefrontal preparatory control processes are elicited depending on goal timing demands, and highlight the need to consider timing dynamics in control preparation.

1
INTRODUCTION

1.1

When we need to deviate from our routine, we exert effort to synchronize different systems and facilitate goal-directed behavior; this process is often referred to as cognitive control. However, it is unknown how inherent constraints of timing influence the orchestration of control. In the present study, we tested how people integrate known and unknown timing demands into the preparation of cognitive control.

When a situation arises that may require cognitive control, the dorsal anterior cingulate cortex (dACC) (Botvinick et al., 2001; Shenhav et al., 2013) is thought to assess the identity and intensity of the control signals that are needed. The dACC communicates these control needs to lateral PFC (Botvinick et al., 2001; Kerns et al., 2004), and the lateral PFC and subcortical structures (Braver & Cohen, 2000; Shenhav et al., 2013) represent, maintain, and exert appropriate control procedures. Increased cognitive control demands have been shown in EEG to robustly upregulate theta (4-8 Hz) power (Cavanagh & Frank, 2014; Janowich 2016; Janowich & Cavanagh (under review); van Driel, Swart, Egner, Ridderinkhof, & Cohen, 2015). In line with the pre-frontal medial to lateral communication described in the Expected Value of Control model (Botvinick et al., 2001; Shenhav et al., 2013), mid-frontal theta activity has also been shown to synchronize with lateral frontal PFC during increased control needs (reviewed in Cavanagh & Frank, 2014). However, most studies have not addressed how different timing demands alter the proactive communication, representation, and maintenance of control goals. A meta-analytic review of the cued control literature shows that delay *knowledge* biases performance toward proactive (vs. reactive) control (Janowich &

Cavanagh, 2018), although the mechanisms underlying this shift are unclear. We have previously hypothesized that mid-frontal theta power signals a general need for control, whereas lateral prefrontal theta dynamics may communicate the specific information contained in control demands (Cavanagh & Frank, 2014). The current study will allow us to differentiate the signaling of a general need for control versus communication of specific control information, in particular *when* control is needed.

While the role of timing demands in cognitive control remain largely unaccounted for, a robust timing literature has identified candidate mechanisms in prefrontal cortex for predicting temporal durations (Durstewitz, 2004; Mento et al., 2015; Niki & Watanabe, 1979; Pfeuty et al., 2005; Quintana & Fuster, 1999; Rainer et al., 1999). Intriguingly, several human EEG studies suggest that the slope of medial frontal ERP activity may differentiate timing-related dynamics (Gupta & Merchant, 2017; Macar & Vidal, 2003; Pfeuty et al., 2003, 2005; Praamstra, 2006), but it is not known how these late sloping activities are modified by the intersection of timing demands and control demands, nor as a function of individual differences in preparation.

To summarize, this study tested the novel hypothesis that temporal prediction is integrated in the specification, communication, and/or maintenance of cognitive control. We manipulated delay demands and control demands (goal rarity) on a trial-by-trial basis and compared prefrontal neural activities during the cue-probe delay interval. Our first aim was to dissociate preparation ahead of different known delay durations, and understand whether there was an interaction between known delay length and goal rarity. We included an unknown delay condition to examine the role of temporal uncertainty in preparation. Finally, in light of individual differences in preparation and impulsivity

(Patton, Stanford, & Barratt, 1995; Stanford et al., 2009), and the known interactions between impulsivity and frontal processes (Cools, Sheridan, Jacobs, & D'Esposito, 2007; Correa, Triviño, Pérez-Dueñas, Acosta, & Lupiáñez, 2010; Kam, Dominelli, & Carlson, 2012), we investigated whether trait impulsivity moderates these preparation processes.

2
METHODS

2.1

Participants

Forty-four undergraduate students at the University of New Mexico (13 male, ages 21.1 +/- 4.5 years) participated in this experiment. Data from 8 participants were excluded from analyses: 3 due to technical problems with the EEG equipment and 5 due to failure to understand and/or perform the task (below 50% accuracy averaged between all conditions, or any one condition less than 25% accuracy). This left a total of 36 participants (12 male, ages 18-38, mean 21.5 +/- 4.8 years). Participants reported no current use of psychiatric or neurological medication, no history of head injury or epilepsy, and normal or corrected-to-normal vision. All participants were right handed. Participants provided written informed consent and received course credit for their participation. The University of New Mexico Institutional Review Board approved this experiment.

2.2

Data Collection and Processing Procedures

2.2.1

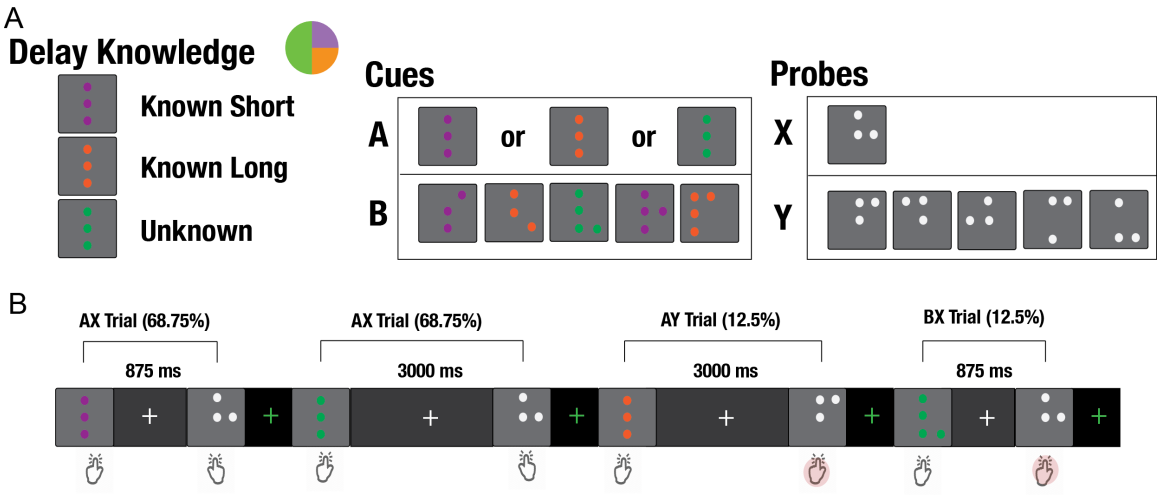
Cognitive Task: Color Cue Dot Pattern Expectancy

We devised a novel variant of the Dot Pattern Expectancy (DPX) task to study the effect of cue-probe delay length on processes for instantiating cognitive control. Task flow and parameters are depicted in Figure 1. The DPX task (Barch et al., 2009; MacDonald et al., 2005) is a variant of the AX-CPT cue-probe task, following similar experimental design and logic as the AX-CPT, but using dot combinations (instead of letters) as the cue and probe stimuli. In the standard DPX, a cue stimulus (dots representing a common "A" cue or rare "B" cue) is presented briefly, followed by a delay (blank screen), and then by a probe stimulus (dots representing a common "X" or a rare "Y" probe). "B" and "Y" stimuli are any dot combinations other than the "A" and "X" dots, respectively. A cues appeared on 81.25% of trials and B cues on 18.75% of trials, preceding the following cue-probe proportions: 68.75% AX trials, 12.5% AY trials, 12.5% BX trials, and 6.25% BY trials.

Our novel variant of the DPX manipulated delay length and delay knowledge in a trial-wise manner. The color of the cue indicated whether the cue-probe delay was to be short, long, or of an unknown duration (either short or long). Delay was known on 50% of trials and unknown on 50% of trials. Of the unknown trials, 50% were short and 50% were long. Short delays were chosen randomly from a uniform distribution of 750 to 1000 ms in 50 ms increments. Long delays were chosen randomly from a uniform distribution of 2500 to 3500 ms in 50 ms increments. Cue-probe delay time began immediately after participants responded (left button press) to the cue, ensuring attention

to the task. Participants performed 500 trials, split into 10 blocks of 50 trials each. Color mappings were counterbalanced between participants. Prior to recording, experimenters explained the task and monitored participants through practice until successful performance in all conditions was observed. Experiment duration (including instructions and practice) was 42 minutes.

Figure 4.1: DPX Color Dots Task Design and Flow.
1A. DPX Color Dots Task Design. The color of cue dots indicated the trial's cue-probe delay length, with one color (purple) informing a known short delay (average 875 ms), another color (orange) informing a known long delay (average 3000 ms), and another color (green) indicating that delay could be either short or long. 50% of trials were known (half short and half long), and 50% of trials were unknown (half short and half long). Cue dot shape/arrangement indicated the task set, with one shape signaling an A task set, and five shapes signaling a B task set. Probe (white) shape/arrangement indicated the probe identity (X or Y). The response to the probe is dependent on whether it is preceded by an A or B. 1B. DPX Color Dots Task Flow. Each trial, participants saw a cue stimulus indicating both the task set and upcoming delay, and pressed 'left'. After the cue-probe delay (short or long distributions), a probe stimulus appeared. Participants responded based on the cue-probe combination (aX=right; aY=left; bX=left; bY=left). Rare responses are highlighted in red. Participants performed 500 trials, split into 10 blocks of 50 trials each.



2.2.2

Barratt Impulsiveness Scale (BIS-11)

The Barratt Impulsiveness Scale (BIS-11) (Patton et al., 1995) is the prevalent questionnaire used to measure trait impulsiveness (Stanford et al., 2009), and has been used to differentiate behavioral and electrophysiological variance in the AX-CPT (Kam et al., 2012). To understand whether people with high or low impulsivity differ in preparatory control, we administered the BIS-11 prior to the cognitive task, and spilt participants with high and low impulsiveness total scores (top and bottom third) for analysis as "high" and "low" impulsivity groups (Cools et al., 2007).

2.2.3

EEG Data Acquisition

EEG data were acquired with a BrainVision 64-channel amp, with standard 10-20 configuration, and recorded with PyCorder software. Data were recorded continuously across 0.1-100 Hz and sampled at 500 Hz. VEOG was recorded above and below the right eye. FPz was utilized as online ground, and CPz was the online reference.

2.3

Data Analysis

2.3.1

Behavioral Analysis of Color Cue Dot Pattern Expectancy

We tested accuracy and reaction time for the critical AY and BX cue-probe pairs to examine if either individual measure was sensitive to the manipulation of delay

parameters. These particular cue-probe pairs are critical in the AX-CPT and DPX paradigms because they rely on distinct cognitive control demands. For AY pairs, A cues signal a common task set that is then disrupted with a rare Y probe, requiring a habitual response to be inhibited with reactive control. For BX pairs, the B cue requires context updating to the rare B task set, and then demands proactive control to maintain the rare task set to respond correctly to the common X probe.

We used the Behavioral Shift Index (BSI) (Braver et al., 2009) (used in (Chiew & Braver, 2013; Edwards, Barch, & Braver, 2010; Lamm et al., 2013; Lucenet & Blaye, 2014; Morales et al., 2014; Schmitt et al., 2015)), to index the proportional use of proactive versus reactive control based on task error rate or reaction time to AY relative to BX cue-probe pairs (see Supplemental Methods). One-way repeated-measures ANOVAs were used to evaluate overall differences between cue-probe combinations. Two-way repeated measures ANOVAs were conducted to evaluate the effects of known vs. unknown and short vs. long delays on AY, BX, and BSI performance.

2.3.2 EEG Processing

Epochs were initially created surrounding cue onset (-2000: 7000 ms), from which associated cue and cue-probe delay activity were isolated. CPz was re-created by re-referencing the data to an average reference. Very ventral channels (FT9, FT10, TP9, TP10) were removed due to unreliability. Bad channels were identified using a combination of FASTER (Nolan et al., 2010) and EEGlab's pop_rejchan (Delorme & Makeig, 2004), and were then interpolated. Bad epochs were identified by FASTER and

then rejected. Independent components analysis (runica.m) was performed and VEOG activity and a Gaussian template around frontopolar channels were compared with components to help identify blink activity, which was then removed following ICA back-projection.

After pre-processing, data were transformed to surface Laplacian *(laplacian_perrinX.m)* (M. X. Cohen, 2014; Perrin et al., 1989). As a high-pass spatial filter, the Laplacian filters out spatially broad features thereby minimizing effects of volume-conduction, and highlights local topographical features. The surface Laplacian is reference-free, and as such avoids confounds with the choice of reference electrode (M. X. Cohen, 2014; Kayser & Tenke, 2006). Importantly, the surface Laplacian has been shown in recent work to provide better temporal and spatial resolution in resolving the rapid temporal adjustments involved in cognitive control, compared to alternative spatial filtering techniques (Wong et al., 2018).

2.3.3

Event-related potentials and component selection with PCA

Event-related potentials (ERPs) were created to assess the early post-cue activity involved in instantiating proactive control. Epochs were trimmed to -200:874 ms peri-cue, and activity was baseline-corrected to -200:0 ms pre-cue. Analyses and visualizations were conducted for only the first 874 ms post-cue (the length from cue onset through the duration of the earliest short cue-probe delay) in order to facilitate direct comparison of preparatory activity for short versus long delay. Because the focus

of this manuscript is on temporal preparation and its interaction with control, we report but do not elaborate on main effects of cue type.

Cue-locked activity for each condition (cue x delay) was calculated as an average of all trials with correct responses to both cue and probe, ensuring attention to the task and successful context processing. To equalize the signal to noise ratio, trial count was equated between conditions by randomly drawing A trials (from a pool of 128.759 +/- 10.286 trials) equal to the count of B trials (23.194 +/- 4.152). This resulted in analysis of approximately 23 trials for each cue x delay condition (see Supplement). Data were low-pass filtered at 20 Hz (eegfilt.m).

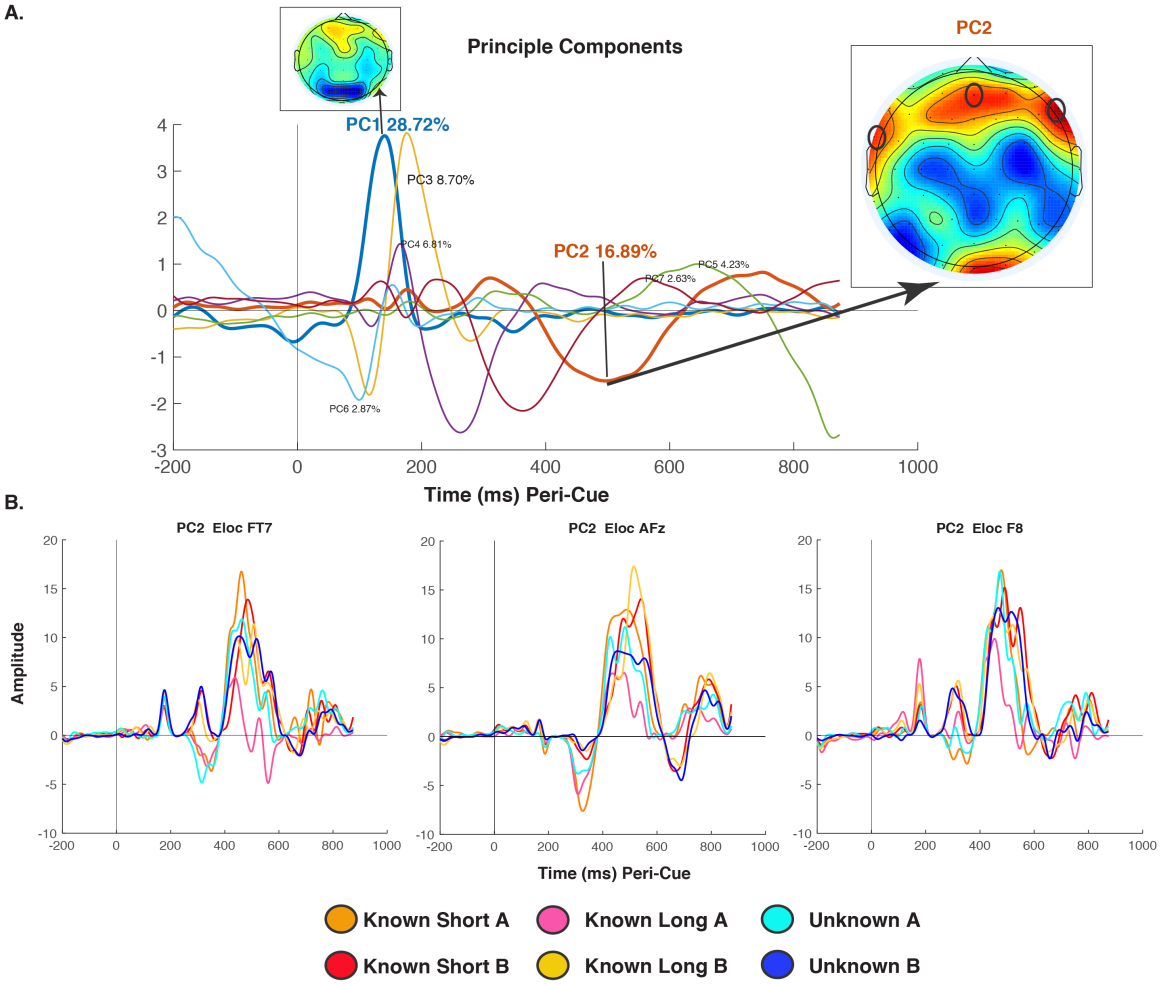
Principal Component Analysis (PCA) (Abdi & Williams, 2010) was used to extract the most important components and structure of the ERP waveforms in an unbiased, data-driven manner (Kayser & Tenke, 2003). We ran temporal PCA on the -200:874 ms surrounding the cue with conditions, electrodes, and participants as concatenated observations. We determined the number of components to extract and rotate by iterating through factor numbers until the component structure stabilized. The outcome of this temporal PCA identified 7 components that accounted for common variance in the six experimental conditions (all cue (A,B) and delay (known short, known long, and unknown) combinations) (Figure 2). Components were rotated with an oblique Promax rotation (Hendrickson & White, 1964), in which the strict orthogonality constraint is relaxed and factors are allowed to share variance (Abdi & Williams, 2010). Promax rotations have been found to give the best overall results for temporal PCA (Dien, 2010; Dien, Beal, & Berg, 2005), and oblique rotation in general has been argued

to be more physiologically plausible (Andresen, 1993; Thurstone, 1947), as ERP components and their underlying generators are likely correlated.

We observed that the first component (154 ms post-cue) explained 28.72% of variance between conditions, and was maximal at PO3, PO4, and FCz. This component highlighted a main effect of cue type (B>A). As the main effect of control was not of interest in this experiment, we did not utilize this component further. PC2 explained 16.89% of the variance, and was maximal between 400-600 ms post-cue at AFz, F8, FT7. All other principal components explained less than 10% of variance, and were not utilized further. Because PC2 explained a large degree of variance and was not dominated by a simple main effect of control, we selected its temporal peak (400-600 ms) and regions of maximal activity (AFz, F8, and FT7) as our spatio-temporal regions of interest in this manuscript.

To ensure that our component selection was not dominated by variance due to the unknown delay condition, we also derived the PCs for the four known conditions (cue (A,B) x known delay (known short, known long)), and found that the principal components were nearly identical (see Supplemental Figure 2 and Supplemental Methods).

Figure 4.2: Principal Component Analysis of Cue-Probe Delay (-200-874 ms post-cue) from all conditions. 2A. The top 7 temporal principle components are plotted, along with the percent of variance attributed to that component. Topoplots (inset) depict the maximal regions of activation for the top two components at their respective peaks. Circles overlaid on inset PC2 reflect frontal electrodes with maximal activity, which are plotted individually in 2B. 2B. Principal component 2 is plotted at the frontal electrodes for which it is maximal. Each line represents the mean for all participants across a particular delay x cue condition.



At the spatial and temporal regions of interest as established by PCA, we examined mean amplitude at each electrode of interest by computing the average amplitude between 400 ms and 600 ms post-cue. As late sloping activity has been found to be meaningful for temporal preparation, we computed slope at our main window of interest (400-600 ms) by subtracting the final from the first timepoint to obtain a measure of amplitude change, and then dividing this difference by the amount of time in the window.

2.3.4 Time-frequency Analyses

We conducted time-frequency analyses to follow up the ERP findings, investigating only spectral phenomena at spatio-temporal ROIs identified in the ERP PCA. For time-frequency analyses, wavelet transforms (Cavanagh et al., 2009) were applied to cue-locked EEG data in the original -2000:7000 ms epochs. Utilization of these longer epochs allowed us to extract and analyze low frequency bands.

Power and intertrial phase consistency (ITPC) were computed at electrodes of interest, using the Laplacian-transformed EEG epochs. The EEG time series in each epoch was convolved with a series of complex Morlet wavelets, defined as a Gaussian-windowed complex sine wave. In these wavelets, frequency increased from .01 to 50 Hz in 30 logarithmically spaced steps, and width/cycles of each frequency band were set according to 4.0/(2*pi*frequency). From the resulting signal, we obtained estimates of instantaneous power and phase for each epoch. We then cut each epoch to -300 to 874 ms peri-cue and applied a baseline-correction to each epoch by subtracting out the average

frequency power -300 to -200 ms pre-cue. This baseline period was chosen because temporal smoothing from time-frequency decomposition may introduce temporal leakage of trial-related activity into the pretrial period (M. X. Cohen, 2014). Such a baseline is common in the field since a small time sample reflects the wavelet-weighted influence of longer time and frequency periods (M. X. Cohen, 2014). Power was normalized by conversion to decibel (dB) scale, which allows direct comparison across frequency bands.

Phase coherence was computed both within-site (intertrial phase consistency - ITPC) and between sites (interchannel phase consistency - ICPC). ITPC quantifies the consistency of phase (angles) at a particular time and frequency at a single site (e.g.: AFz) across trials. ITPC varies from 0 (random) to 1 (identical), and is a useful metric for comparing whether an experimental condition consistently evokes some time-frequency processes, thereby implicating those time-frequency processes in the neurocognitive processing of that condition.

ICPC quantifies the similarity of phase consistency across different electrodes in a particular time-frequency space. ICPC is computed by extracting phase from each of two electrodes and subtracting them, thus observing whether the phase clustering of these electrodes fluctuates randomly (ICPC values near 0) or synchronously (ICPC values near 1). Since previous studies have usually used FCz as a seed region in ICPC (Cavanagh et al., 2009; Cavanagh, Meyer, & Hajcak, 2017), we used this mid-frontal lead as a pair for each of our PCA-defined *a priori* lateral sites of interest, FT7 (left PFC) and F8 (right PFC). For more detail on the equations from which our power and phase calculations were derived, please see (Cavanagh et al., 2009).

To establish appropriate ROIs for time-frequency analyses, we computed the peak time and frequency windows over all conditions. Power and ITPC were maximal in delta and/or theta frequencies (see Supplement for more details). At each site, ICPC was maximal between 3-7 Hz). Because the ICPC ROIs were very long (400 or 600 ms in duration), we computed inter-channel phase consistency at early (first half) and late (second half) windows of the maximal ICPC ROI across conditions (see Supplement for precise ICPC temporal ROIs at each electrode).

2.3.5

Statistical Testing of ERP and Time-Frequency Components

Using the electrodes (AFz, F8, FT7) and time-window (400-600 ms) established by PCA, we used separate 2x2 repeated-measures ANOVAs to test for the effects of cue type (Cue: Common A vs. Rare B) with either delay length (Delay: known short vs. known long) or delay knowledge (Knowledge: unknown vs. known short OR unknown vs. known long). This was the most appropriate setup to address our separate *a priori* questions regarding delay length and delay knowledge (see Supplemental Methods)

To resolve the effects of delay *length*, we used 2 (Cue: A vs. B) x 2 (Delay *Length*: known short vs. known long) repeated measures ANOVAs. Next, we tested the effects of delay *knowledge*. Because known delay lengths were hypothesized to elicit distinct mechanisms from one another, we did not collapse across known delay lengths, but used separate repeated-measures 2 (Cue: A vs. B) x 2 (Delay *Knowledge*: unknown vs. known short OR known long) ANOVAs for each known delay length. Because 3 non-neighboring electrodes (AFz, F8, FT7) and 3 delay comparisons (known short vs. known

long; unknown vs. known short; unknown vs. known long) were analyzed using separate ANOVAs, we applied Bonferroni correction (critical p value=.05/6 = .0083) to control for Type I errors.

To understand whether preparatory neural activity varied based on individual differences in impulsivity (and thus, general preparation strategy), we compared neural components of interest with 3-way mixed effects ANOVAs, with impulsivity (Impulsivity: top third versus bottom third), cue type (Cue: A vs. B), and either delay length (Delay: known short vs. known long) or delay knowledge (Knowledge: unknown vs. known short OR unknown vs. known long).

RESULTS

3.1
Dot Pattern Expectancy Behavioral Results

3.1.1

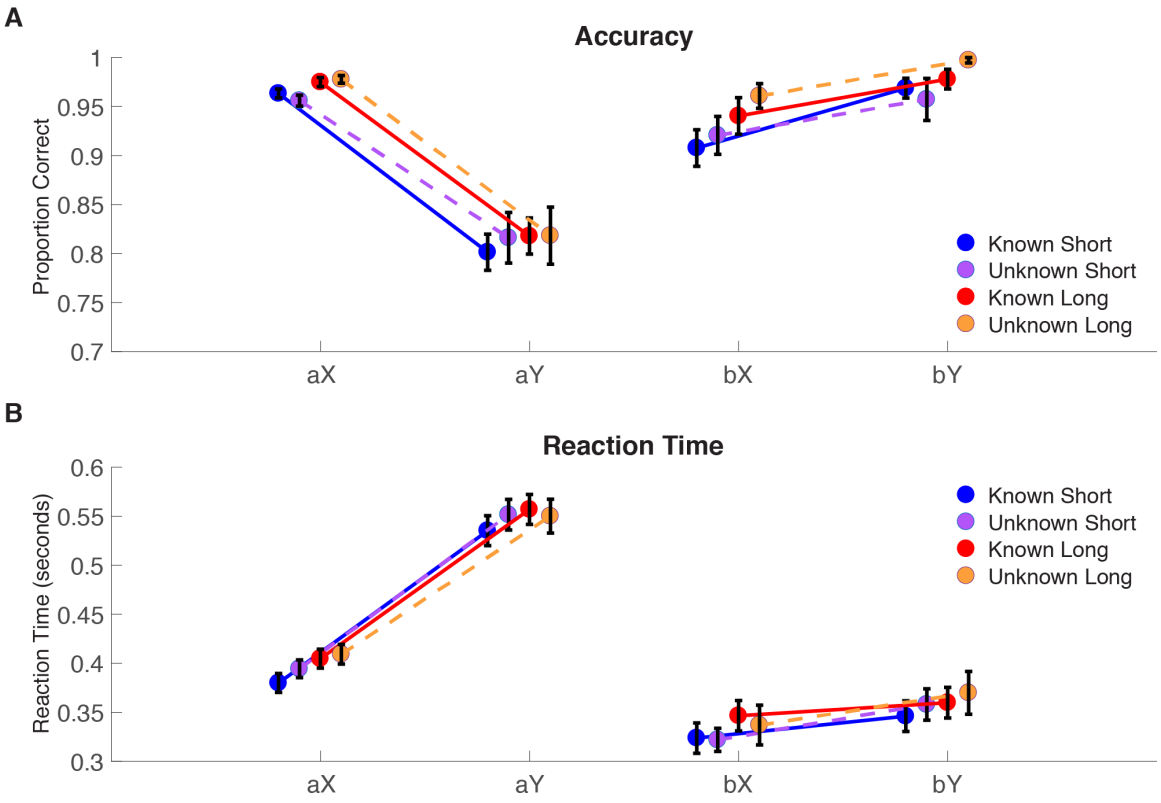
DPX Accuracy and Reaction Time

Behavioral results are depicted in Figure 3 and detailed in Table 1. Across delay conditions, participants performed very accurately on the task. There was a strong overall main effect of cue-probe combination on accuracy ($F(3,35)=67.01$, $p<.001$). Post-hoc t-tests confirmed that AY accuracy was lower than that for each other cue-probe type (all p's <.0001). BX accuracy was significantly moderated by delay length ($F(1,35)=8.470$, $p=.006$), where BX accuracy was increased for long delays (mean=95.06%, SD=7.80%) relative to short delays (mean=90.75%, SD=12.33%). We tested for main effects and interactions of delay knowledge and delay length on AY and BX accuracy, as well as

BSI-Error Rate, but all results failed to reveal any significant differences (see Supplement). In summary, the only effect of our delay knowledge and length manipulations on accuracy was an increase in BX accuracy for long relative to short delay trials.

Across delay conditions, cue-probe combination conferred a significant effect on reaction time ($F(3,35)=123.82$, $p<.001$). Post-hoc t-tests confirmed that AY reaction time was slower than that for each other cue-probe type (all p's <.001). We then evaluated how delay knowledge and delay length modulate reaction time for AY, BX, and BSI-Reaction Time, but all outcomes failed to reveal any significant differences (See Supplement). In summary, neither our delay knowledge nor delay length manipulations resulted any significant changes in reaction time.

Figure 4.3: Probe Behavior. Accuracy (3A) and Reaction time (3B) means (and standard deviations) by cue-probe type and delay condition.



3.1.2

Barratt Impulsiveness Scale (BIS-11)

A total summary score was computed from the BIS-11 (Supplemental Figure 1). Total scores ranged from 45 to 85 (mean=65.1 +/- 9.5). A Lilliefors test (Lilliefors, 1967) (lillietest.m) showed that the BIS Total scores follow a normal distribution.

3.2

EEG Results

3.2.1

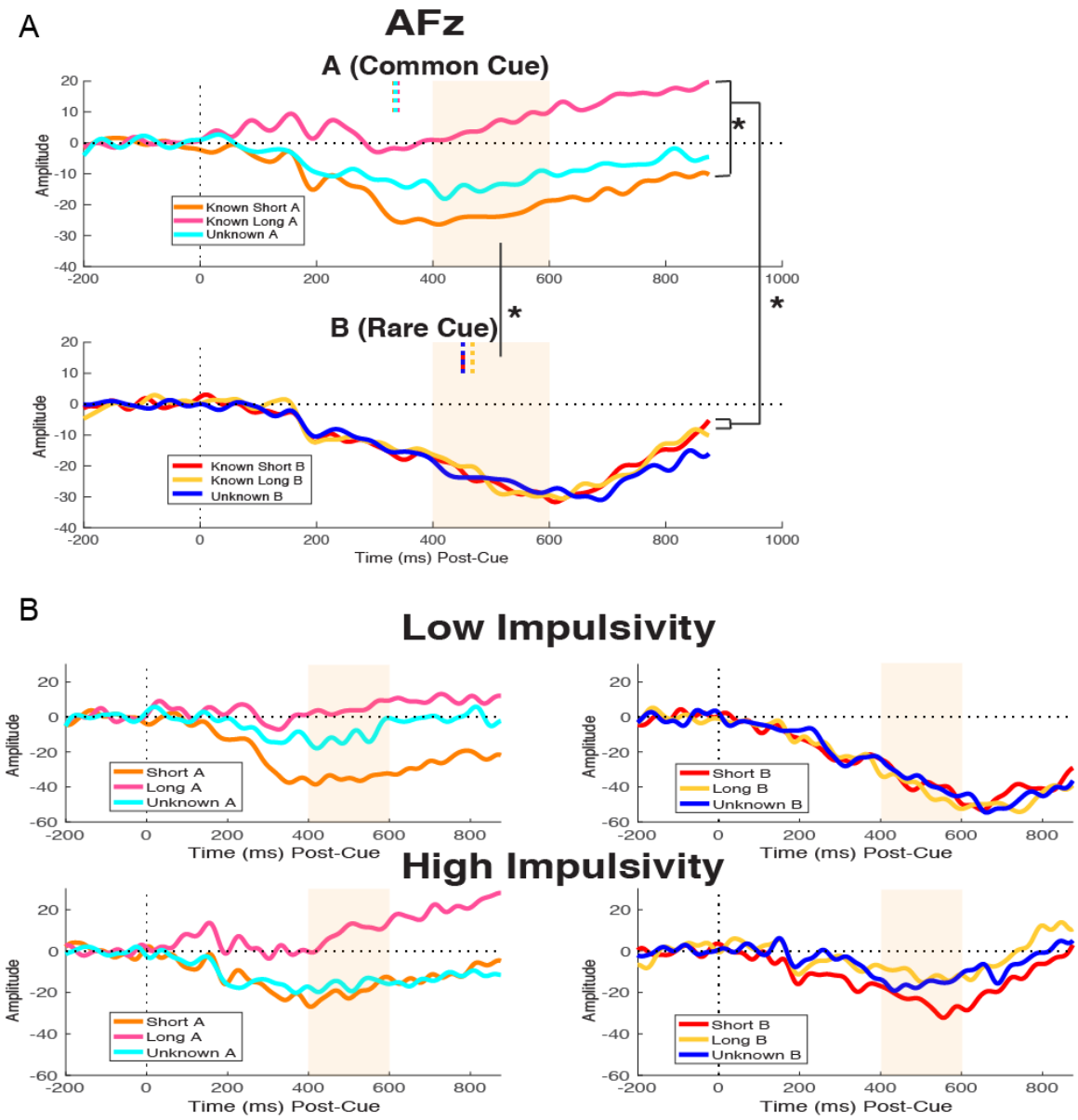
ERP Results: Fixed Effects of Delay and Control Demands

Fixed effects of delay and cue type at medial pre-frontal AFz are depicted in Figure 4A. To assess differences in AFz amplitude based on known delay *length*, we used a 2 (Delay Length: known short vs. known long) x 2 (Cue: A vs. B) repeated measures ANOVA, and found a main effect of cue type ($F(1,35)=11.200$, $p=.002$), a main effect of delay length ($F(1,35)=19.093$, $p<.001$), and an interaction between cue and delay length ($F(1,35)=8.223$, $p=.007$). Long delay amplitude was greater than short delay amplitude, although this delay-related difference was driven almost entirely by increased sustained activity to Long A cues.

We then tested effects of delay *knowledge* on AFz amplitude. A 2 (Delay Knowledge: known long vs. unknown) x 2 (Cue: A vs. B) repeated-measures ANOVA revealed a main effect of delay knowledge ($F(1,35)=10.823$, $p=.002$) and a main effect of cue type ($F(1,35)=13.371$, $p<.001$). This effect was driven by increased amplitude for known long A cues relative to unknown A cues ($t=3.531$, $df=35$, $p=.001$). Post-hoc tests revealed that delay knowledge and delay length effects observed at AFz were not replicated at more posterior mid-frontal electrodes Fz and FCz (Supplemental Results).

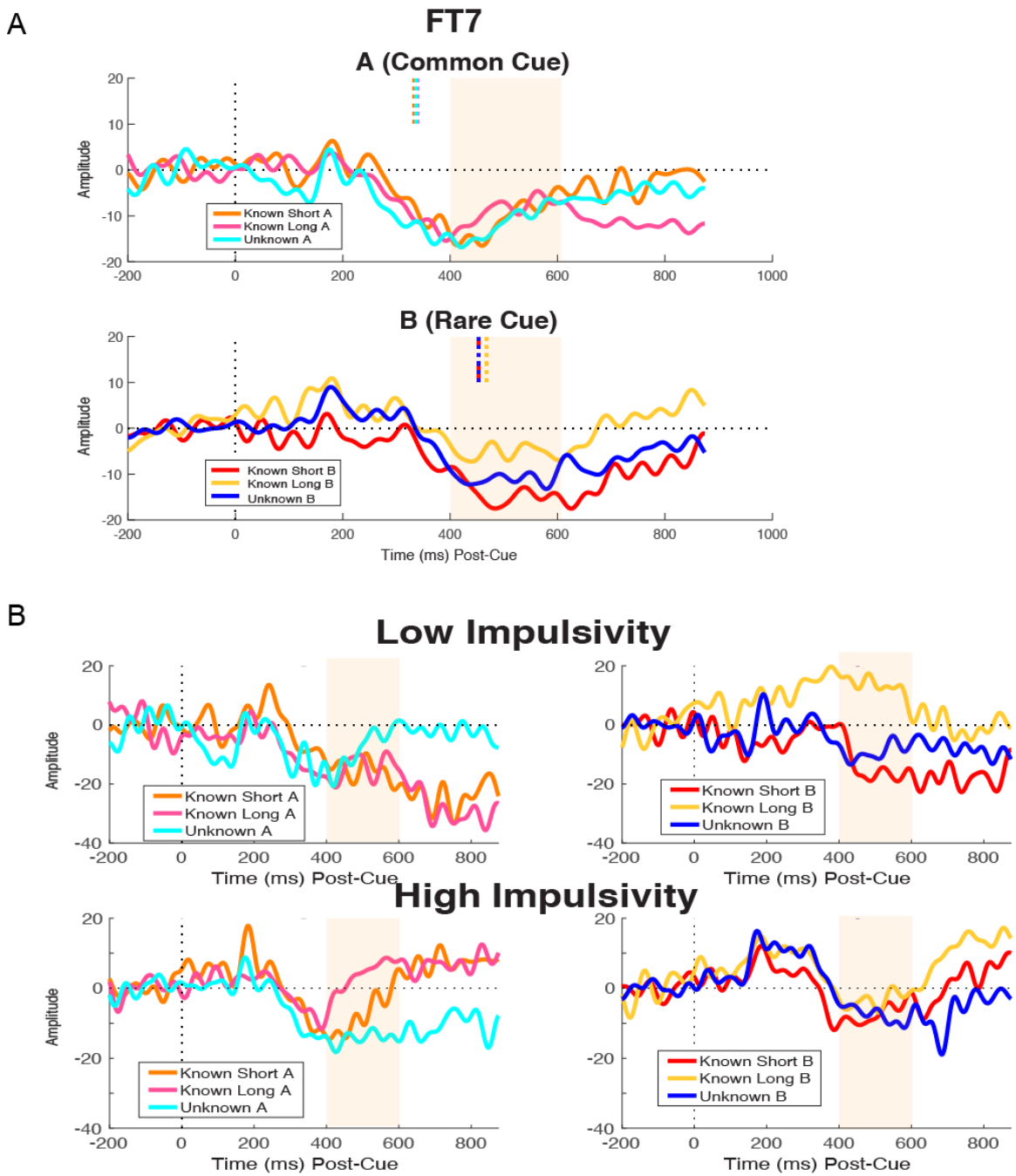
In summary, at medial pre-frontal AFz we observe significant differences in mean amplitude (400-600 ms) as a function of delay length, delay length x cue, as well as delay knowledge, with maximal amplitude for known long delay A cues.

Figure 4.4: Cue-locked Laplacian ERPs at medial prefrontal AFz. 4A. ERPs to A cue (upper plot) and B cue (lower plot) by delay condition. Short dot segments are average RT for each cue x delay condition.
4B. ERPs to A cue (left plots) and B cue (right plots) by trait impulsivity. Groups derived from bottom third and top third of impulsivity scores (BIS-11 Total).



Fixed effects of delay and cue type at right prefrontal F8 and left prefrontal FT7 are depicted in Figures 5A and 6A, respectively. No main effects of delay nor delay x cue interactions survived Bonferroni correction (see Supplemental Results in Appendix 2).

Figure 4.5: Cue-locked Laplacian ERPs at left frontal FT7.
5A. ERPs to A cue (upper plot) and B cue (lower plot) by delay condition. Short dot segments are average RT for each cue x delay condition.
5B. ERPs to A cue (left plots) and B cue (right plots) by trait impulsivity. Groups derived from bottom third and top third of impulsivity scores (BIS-11 Total)



ERP Fixed Effects Summary

The significant main effects of delay length, delay knowledge, and the delay length x cue interaction at medial prefrontal AFz amplitude (400-600 ms) were the only fixed effects comparisons of interest to survive Bonferroni correction. Slope differed by cue type at all selected electrodes (A>B), but showed no effect of delay. All other statistical tests were non-significant (see Appendix 2).

3.2.2

ERP Results: Mixed Effects of Impulsivity x Delay and Control Demands

Cue-locked activities split by low and high impulsivity groups are depicted in Figures 4B (AFz), 5B (F8), and 6B (FT7). At left frontal FT7, a 2 (Impulsivity: high vs. low) x 2 (Knowledge: unknown vs. known *short*) x 2 (Cue: A vs. B) ANOVA revealed a significant impulsivity x delay knowledge interaction on slope ($F(1,24)=13.900$, $p=.001$). Similarly, a 2 (Impulsivity: high vs. low) x 2 (Knowledge: unknown vs. known *long*) x 2 (Cue: A vs. B) ANOVA also revealed a significant impulsivity x delay knowledge interaction on slope ($F(1,24)=10.375$, $p=.004$). For low impulsivity participants, unknown duration A cues elicited greater slope than for known short or known long delays, whereas for high impulsivity participants, unknown duration A cues elicited a lesser slope than for known short or known long delays.

All other statistical tests were non-significant (see Supplement). Post-hoc tests revealed that delay knowledge effects observed at FT7 were not observed at other motor nor pre-motor electrodes.

3.2.3

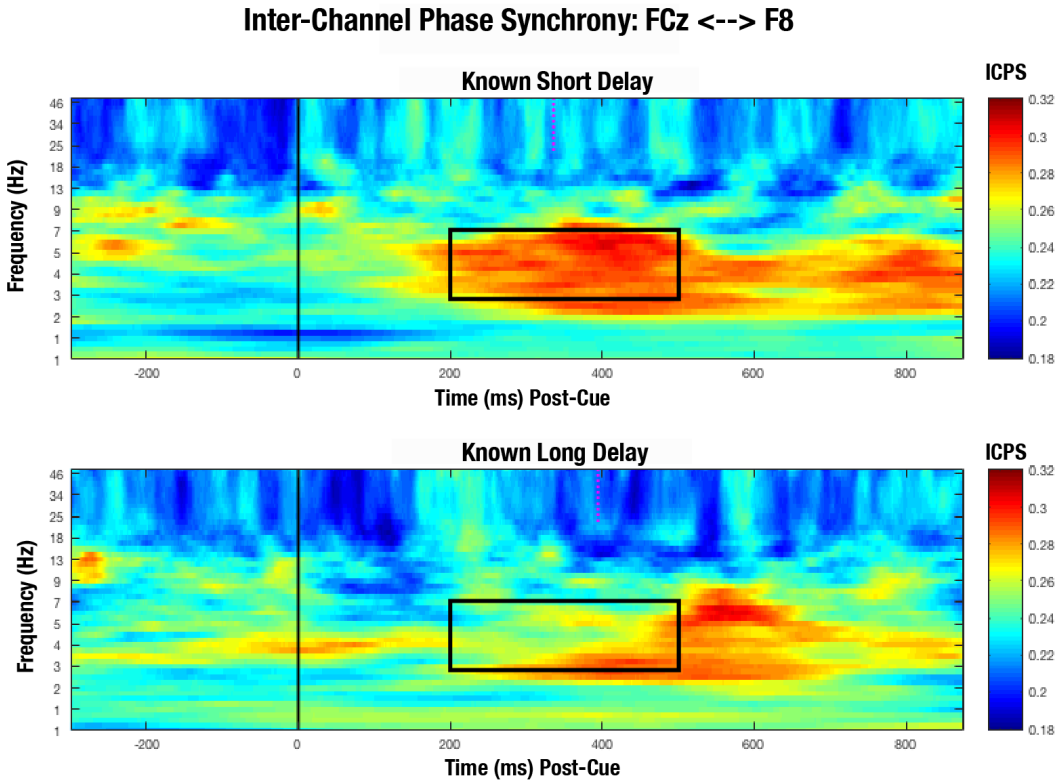
Time-Frequency Results

Delta/theta power (3-7 Hz) shows robust main effects of cue type (B>A) at AFz (Supplemental Figure 4 in Appendix 2) and F8. ITPC (Supplemental Figures 5 (F8) and 6 (FT7) in Appendix 2) also shows robust main effects of cue type (B>A).

Inter-channel phase consistency (ICPC) from mid-frontal FCz to right prefrontal F8 (Figure 6) in the early window (200-500 ms) showed a strong significant main effect of delay length, such that known short delay exhibited greater FCz:F8 phase consistency than known long delay ($F(1,35)=14.034$, $p<.001$).

All other main effects and interactions did not survive Bonferroni correction (see Supplemental Results in Appendix 2).

Figure 4.6: Cue-locked Interchannel Phase Consistency (ICPC) between mid-frontal FCz and right prefrontal F8 for known short (top) and known long (bottom) delay conditions. Box inset depicts early ROI (200-500 ms) used in analysis.



In summary, low-frequency inter-channel phase consistency between mid-frontal and right lateral frontal F8 was differentiated by delay length demands, with greater ICPC for known short delay than known long delay. In addition, delta/theta power was significantly increased at AFz for control demanding B cues (vs. common A cues), but showed no effect of delay.

3.2.5

Results Summary

While manipulations in temporal delay did not elicit changes in task accuracy or reaction time, preparatory neural mechanisms were robustly differentiated by delay condition. Critically, different frontal electrodes as elucidated by PCA were sensitive to distinct processes in proactive control. Medial prefrontal AFz was shown to index many parameters of task demands, including cue type, delay knowledge, delay length, and the interaction between delay length and cue type. In contrast, right prefrontal F8 was sensitive to delay length demands, as shown by a robust increase in inter-channel phase consistency with mid-frontal FCz for known short relative to known long delays. At left frontal FT7, trait impulsivity appeared to modulate a difference in processing based on delay knowledge, with sloping activities strongly differentiated in persons with high versus low impulsivity.

4

DISCUSSION

4.1

General Summary

To address the lack of understanding on how temporal demands influence goal preparation, we manipulated delay length and delay knowledge in a trial-wise manner to elicit proactive preparation processes ahead near-immediate, more temporally distant, or unknown duration common or rare goals. This manipulation revealed that both delay length and delay knowledge altered proactive goal preparation, with different regions of prefrontal cortex orchestrating different elements involved in the use of temporal

information. In particular, alterations in known delay length instantiated significant changes to ERP amplitude at AFz (Long > Short), as well as inter-channel phase consistency between mid-frontal FCz and right prefrontal F8 (Short > Long). We also found that delay knowledge altered medial prefrontal (AFz) amplitude (known long > unknown), and that unknown delay trials elicited distinct slope patterns at left prefrontal (FT7) slope as a function of impulsivity. These results show that preparatory neural dynamics are sensitive to timing information, and that timing-related neural dynamics vary within the prefrontal cortex. Whereas medial prefrontal AFz was sensitive to a broad array of information, including cue identity / task control demands and timing demands, right lateral prefrontal F8 was sensitive to delay length, and left prefrontal FT7 was sensitive to delay knowledge.

The localization of timing and goal-related processing in most-anterior AFz – but not immediately posterior mid-frontal electrodes Fz or FCz (post-hoc analyses) – is important because it suggests that this computation is specific to anterior AFz, reflecting the processing of very high level (temporal planning) information. It has been suggested that information is organized in an increasingly abstracted manner within a rostro-caudal frontal hierarchy (Badre, 2008; Badre & Nee, 2017; Koechlin & Summerfield, 2007), and that more abstract rules may instantiate greater frontal theta phase dynamics (Voytek et al., 2015). However, to our knowledge, neither experimental nor theoretical work on frontal hierarchies has addressed how timing demands are integrated as a type of abstract rule. The results reported in this manuscript add to the hierarchical control literature by suggesting that timing information is a high-level demand reflected in sustained activity at the very prefrontal AFz. However, in contrast to our finding of heightened activity for

known over unknown delay durations, other work has shown sustained anterior prefrontal activity greater for unknown delay (internally guided) than known delay (explicitly instructed) (Mento et al., 2015). This divergence may be due to the difference in goal demands between the two studies; while the present manuscript requires maintenance of goal rules over time, Mento (2015) investigates temporal preparation ahead of a simple target response. To directly test whether temporal preparation interacts with goal maintenance or task difficulty, a future study could manipulate the difficulty of task demands ahead of known and unknown delays.

As an alternative to integration and maintenance of timing information, the persistent prefrontal activity observed in this experiment could be characterized as a mechanism for sustained working memory of the task rule over several seconds (Sigala, Arnsten, Martinez-Trujillo, Constantinidis, & Riley, 2016). Future work is needed to carefully dissociate whether this sustained prefrontal activity is instantiated for integrating timing information as a high-level abstract rule, and/or is responsible for the "working-memory" -like maintenance of an abstract rule over longer periods of time. If this medial anterior prefrontal activity is critical for one or both functions, it will help to parse the convergence or divergence of timing, rule maintenance, and working memory processes in frontal cortex.

The dissociation between a mid-frontal "alarm bell" for control (theta power) and a mid-frontal to lateral communication of control timing (inter-channel phase consistency) has important implications for understanding how control is successfully implemented over different time-courses. Early delta/theta inter-channel phase consistency from mid-frontal FCz to right prefrontal F8 was sensitive to known delay

length, confirming prior suggestion that this processes reflects a candidate mechanism for communication of control information. Importantly, this synchrony was not sensitive to differentiating common versus rare rules, suggesting that task novelty is not necessary for this process. Future work in clinical populations could investigate whether differences in control timing help to explain deficits in maintaining sustained control (e.g. ADHD, traumatic brain injury) vs. enhanced or deficient responses to novelty (e.g. anxiety disorders vs. schizophrenia).

Finally, our study demonstrated that left prefrontal FT7, but not other motor/pre-motor regions, was sensitive to delay knowledge as a function of impulsivity. The current study cannot definitively resolve whether these processes reflect pre-motor preparation or higher-order planning processes, but nonetheless, this region appears to compute and/or consider whether a goal requires near-immediate or more delayed execution. Extending these findings to persons with clinical levels of impulsivity, or studying/manipulating dopamine levels, would help to more fully understand the neural mechanisms for judging and using temporal information in goal preparation.

Contrary to our hypotheses, most timing-related differences were found to be similar for both common and rare (control-demanding) trials. This may indicate that trial-by-trial changes in task demand required a constant exertion of control, and this continuous demand was more important for task performance than standard approaches which leverage novelty as a rare imperative event.

4.2

Limitations and Future Directions

One important limitation of our study is that our delay manipulation did not meaningfully alter accuracy, reaction time, or BSI (indexing proportional use of proactive versus reactive control). This is likely due to ceiling-level performance in the task. Future studies should utilize a more demanding task or calibrate the task individually to equally tax participants' cognitive resources. However, the lack of significant behavioral differences suggests that these strong neural differences are indeed tied to differential cognitive processing, and are not unduly influenced by differences in task difficulty or motor processing. . The difference in preparation for unknown delays based on trait impulsivity (within a sub-clinical range) suggests that patients with extreme differences in impulsivity should show further exaggerated differences in utilizing delay knowledge during preparation.

This study does not show evidence to support an interaction between rare control demands and timing demands. We used rare control demands as a common procedure for eliciting elevated proactive control (Braver et al., 2009). The lack of interaction bolsters our suggestion that these processes are separate mechanisms involved in gauging and/or communicating the type versus the timing of control. Further, as stated above, the amount of control needed to process trial-by-trial changes in task demands may have outweighed the increased control needs to process rare task cues. Future studies could utilize different manipulations to increase cognitive control, and thereby further our understanding of the interaction between control needs and control timing.

Our study focused on the influence of delay duration and delay knowledge on proactive preparation, but it is important to be reminded that many other factors may contribute to variance in preparation, and many other neural processes beyond those

tested in our study may play an important role in temporal planning. For instance, phase-amplitude coupling of low and high frequencies has been observed in cued (spatial) attention tasks (Chacko et al., 2018). Other work theorizes that alpha frequency (Kononowicz & van Wassenhove, 2016) and beta oscillatory dynamics (Kononowicz & van Rijn, 2015; Meijer, te Woerd, & Praamstra, 2016) are important in temporal prediction. Although alpha and beta differences were not readily apparent in this study, this is likely due a key difference in paradigms. In particular, our study did not demand a button press (motor activity) at the end of the to-be-timed interval. Future work should continue to explore the relationship of phase-amplitude coupling and other time-frequency dynamics in the timing of control.

4.3

Conclusions

In a novel variant of the Dot Pattern Expectancy (DPX) task, we manipulated control and timing demands on a trial-wise basis, and observed several prefrontal differences elicited by variation in delay length and delay knowledge. These neural features were differently sensitive to dynamics of goal preparation, including processes underlying judgment, communication, and maintenance of the temporal delay before goal execution. Together, these study results provide novel evidence that dynamic goal timing information is communicated through several distinct pre-frontal mechanisms, largely separate from (common versus rare) goal identity. Further, the influence of trait impulsivity on preparation for unknown versus known timing demands suggests that individual differences may be important in understanding how preparation strategies are

shaped. To further our understanding of top-down goal preparation, we must consider the influence of timing on separable aspects of proactive control, as well as individual differences in each of these aspects.

CHAPTER 5:

Mechanisms for retention of cognitive control versus working memory

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ABSTRACT:

To cross a busy street, we use cognitive control not only to plan an action, but also to execute that action at the appropriate time in the future. However, it remains unknown how we retain control-demanding, abstract goal information for future use. Do we engage active maintenance processes as if holding the goal like a sensory item in working memory (WM), or do we employ goal-updating processes to efficiently activate the new goal state? In this study, we aimed to elucidate the electrophysiological mechanisms differentially elicited to retain visuo-spatial WM information vs. abstract rules. We developed a novel EEG paradigm in which participants (n=50) were tasked each trial to retain either a common rule, a rare, control-demanding rule, or a visuo-spatial WM stimulus. We applied LASSO classification to identify retention-period EEG activities that dissociated visuo-spatial stimuli (active maintenance) from common rules, and then applied those classification weights to determine if the processing of rare, control-demanding rules (i.e. goal-updating) differed significantly from active maintenance. Regression analysis demonstrated that individual differences in complex span (trait WM) score was significantly predictive of out-of-sample (transfer) classification of the control-demanding retention activity (p=.019). In participants with higher trait WM, control-demanding goals were processed more similarly to common goals than to visuo-spatial WM stimuli (goal-updating ~= WM). In participants with lower trait WM, control-demanding goals were processed like visuo-spatial WM stimuli (goal-updating == WM). In conclusion, electrophysiological activities underlying goal retention differ based on control demands, and vary based on individual WM abilities.

INTRODUCTION

To cross a busy street, take a highway exit, or swing a baseball bat, we are tasked not only to plan an (goal-directed) action, but also to execute that action at the appropriate time in the future. This goal-directed preparation is ubiquitous in human life, enabling us to efficiently ready neural resources and optimize behavior for when it is needed. Critically, however, it is unknown *how* we retain abstract rule/goal information ahead of near-future use. Do we engage active maintenance processes as if holding the rule/goal as a sensory item in working memory, or do we employ different processes and networks that may be less resource-demanding (Shenhav et al., 2013)?

It is well known that sensory item information is maintained in working memory (WM) for near-future processing (Oberauer & Hein, 2012) (phonological (A. Baddeley, 2003) and visuo-spatial (Klauer & Zhao, 2004; Vergauwe, Barrouillet, & Camos, 2009)), although the basic mechanisms underlying item maintenance are widely debated. Many studies have provided evidence for item maintenance through active, stable representation of the to-be-remembered item (Adam, Robison, & Vogel, 2018; Unsworth et al., 2015). Further, evidence from Unsworth and colleagues (2015) suggests that trait working memory capacity is associated with electrophysiolgical mechanisms of stable maintenance. However, one must note that a growing surge of recent work suggests that items may be maintained through "activity-silent" or non-stable bursting activity (Lundqvist et al., 2016; Spaak et al., 2017; Stokes, 2015; Trübutschek, Marti, Ueberschär, & Dehaene, 2018). Irrespective of specific signal characteristics, electrophysiological activities observed during several-second (item) WM maintenance have been used effectively (within-studies) to discriminate memory performance and in some cases,

decode item content (Bae & Luck, 2017; Siegel, Warden, & Miller, 2009; Wolff, Ding, Myers, & Stokes, 2015) (however, see also (Berggren & Eimer, 2016).

Sub-second mechanisms underlying abstract goal retention are less understood. Prior empirical and computational modeling work has shown that when the need for cognitive control is signaled ahead of its execution, mid-frontal theta power (Cooper et al., 2016; van Driel et al., 2015; Verguts, 2017) and frontoparietal delta power (Cooper et al., 2016) increase. Still, it is not understood how these initial need-for-control signals relate to the retention and ultimate instantiation of the control-demanding rule. In a task with more complex, well-practiced cued rules, fMRI revealed the loading of goal representations (from long-term memory) from anterior prefrontal cortex in a top-down manner. These representations were then activated in lower-level working memory in dorsolateral prefrontal cortex (Cole, Bagic, Kass, & Schneider, 2010). However, the sluggish BOLD response in fMRI cannot differentiate the sub-second processes by which a rule biases processing over the loading and activation periods.

Here, our primary aim is to address the gap in knowledge as to how cognitive control (rule information) is retained over time, quantifying on a sub-second timescale how rules bias neural processing throughout their initiation and retention. To achieve this aim, we have developed a novel neuro-cognitive paradigm that allows us to directly compare rule retention with item WM maintenance within healthy human participants. Although there is currently no agreed-upon electrophysiological "signature" of item WM, electrophysiological activities over a retention (delay) period provide a strong platform enabling comparison between rule and item retention. To ensure that we best characterize the retention of cognitive control, we compare retention of common versus rare (control-

demanding) goals. Prior work (Janowich & Cavanagh, under review A & B) shows that rules are processed differently depending on the rule rarity, with rare rules eliciting greater pre-frontal power and amplitude dynamics.

To address the behavioral importance of these neural markers of retention, we tested the relationship between each marker and individuals' scores on a well-established suite of complex span (trait working memory) tasks (Operation Span, Symmetry Span, and Rotation Span). We hypothesized that complex span scores would correlate (equally) strongly with neural activities during both rule preparation and item maintenance. Overall, this study will enhance our understanding of the fundamental nature(s) of retention, and shed light on how and precisely when high-level control processes distinguish and/or guide information retention.

2

Methods

2.1

Participants

Sixty-four healthy undergraduate students at the University of New Mexico participated in this experiment (19.98 +/- 2.08 years old; 66% female). Data from 13 participants was excluded from analysis: 10 due to failure to understand and/or perform the task (below 50% accuracy averaged between all conditions, or any one condition less than 25% accuracy), and 3 due to failures in the EEG equipment. This left a total of 50 participants (20.04 +/- 2.15 years old; 58% female). Participants with good data were invited to return for a second session to complete a series of complex SPAN tasks; 35/50

participants (70.0%) returned (19.833 years old; 17 male, 18 female, 51.4% female). Participants reported no current use of psychiatric or neurological medication, no history of head injury or epilepsy, and normal or corrected-to-normal vision. All participants were right handed. Participants provided written informed consent and received course credit for their participation. The University of New Mexico Institutional Review Board approved this experiment.

2.2

Experimental Procedures

2.2.1

Main Experiment: Working Memory Dots

To directly compare the mechanisms for abstract rule retention and visuo-spatial working memory, we designed a novel variant of the Dot Pattern Expectancy Task (DPX) (Henderson et al., 2012b; MacDonald et al., 2005), a cued cognitive control task derived from the AX – Continuous Performance Task (AX-CPT) (J. D. Cohen et al., 1999; Servan-Schreiber et al., 1996). In our novel variant, cues demanded either 1) visuo-spatial memory of an array of dots (ahead of a delayed single dot match-to-sample), or 2) preparation of an abstract task rule coded by the array of dots. We recorded EEG and compared neural activity during the post-cue delay to understand the temporally-precise mechanisms underlying rule retention vs. item maintenance.

In our experiment, we used a ~3 second cue-probe delay (jittered randomly between 2.5 seconds and 3.5 seconds) and a inter-trial interval randomly jittered between 750 ms and 1000 ms (mean= 875 ms). Cue-probe delay began immediately after participants responded to the cue, ensuring attention to task. Our novel variant of the DPX randomly interspersed traditional DPX "rule" trials with a variant of McNab (McNab & Klingberg, 2008) / "item WM" DPX trials (50% traditional "rule" trials, 50% item memory trials). Rule DPX trials began with 3 cue dots in green (arrayed on a 3x3 grid), whereas on item WM trials, participants first viewed a screen with 4 blue dot stimuli (arrayed on a 3x3 grid). Novelty of dot stimuli was equated between rule and item WM trials: trials in each condition contained one of six possible dot combinations.

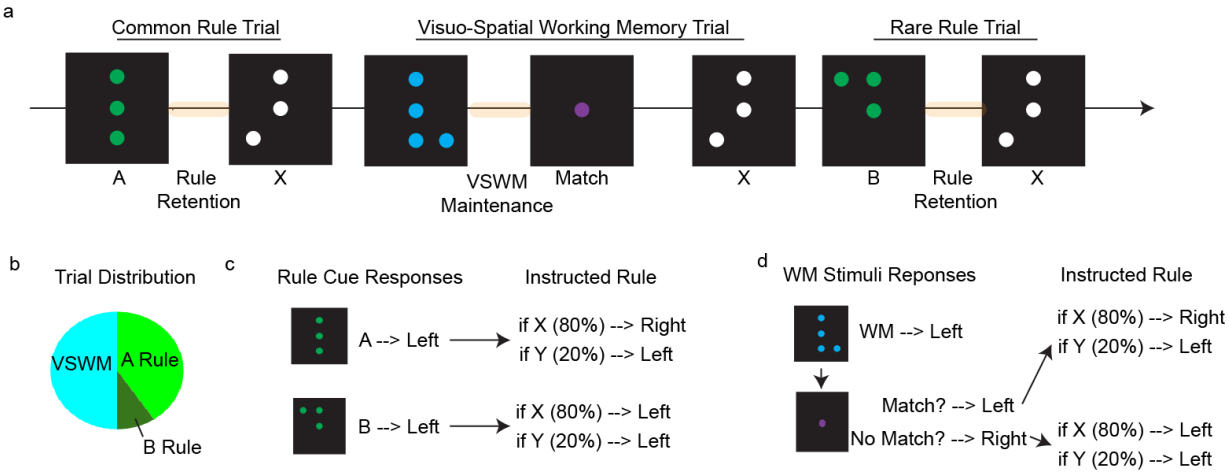
On item WM trials, after a simple left button press to demonstrate attention to the dots, the screen went "blank" for ~3 seconds (jittered randomly between 2.5 seconds and 3.5 seconds), showing only the empty grid. Then, a single purple dot appeared on the grid, and participants were asked to decide whether the purple dot matched ("press left") or did not match ("press right") one of the item memory dots. The purple dot matched on 81.25% of trials (and did not match on 18.75% of trials), which is equal to the ratio of A vs. B trials in DPX. This dot matching served two important purposes. First, it tested whether participants had maintained a successful visuo-spatial representation of the 4 item WM dots. Second, the matching/non-matching identity of the purple dot became the "A" (matching) or "B" (non-matching) cue as in the traditional DPX structure, and was maintained for 3 (+/- 0.5) seconds.

In both traditional rule and item WM trials, upon appearance of the probe (white dots), participants responded to common "AX" X probes with a "right" button press, and

to all other cue-probe combinations with a “left” button press. If participants were too slow (>1 second) or erred in responding to cue, matching dot, or probe stimuli, a message of “Too Slow!” or “ERROR”, respectively, appeared on screen.

In addition to viewing on-screen instructions, each participant was guided through task instructions by a research assistant, and repeated practice for each experiment component until successful performance was consistently obtained. Following practice for each experiment component, participants performed a final practice integrating all components until successful performance as consistently obtained. Participants were informed that the participant with the best score out of every 10 participants -- integrating accuracy and reaction time -- would win $20 cash. In the actual task, participants performed 320 total trials, split into 10 blocks of 32 trials each. After each block, participants viewed their current score (based on a combination of accuracy and reaction time) and took a self-paced break. Total time for instructions, practice, and task was 53.5 +/- 3.1 minutes.

Figure 5.1: DPX/VSWM Task Design. 1A) Flow of task trials, composed of common (A) and rare (B) rule retention trials, as well as visuo-spatial working memory (also referred to as Item maintenance) trials. 1B) Trials were divided equally between rule and visuo-spatial working memory trials, with common rules occurring on 80% of rule trials (40% of total trials). 1C) Response sequence to cued common (A) and rare (B) rules. 1D) Response sequence to visuo-spatial working memory stimuli and McNab-match portion of trial.



2.2.2
EEG Recording

EEG data were acquired during DPX task performance with a BrainVision 64-channel amp, with standard 10-20 configuration, and recorded with PyCorder software. Data were recorded continuously across 0.1-100 Hz and sampled at 500 Hz. VEOG was recorded above and below the right eye. FPz was utilized as online ground, and CPz was the online reference.

2.2.3

Complex SPAN Tasks

On a follow-up visit, participants completed a suite of shortened complex span tasks, which have been well-validated and shown to reliably measure working memory capacity (Foster et al., 2014). The tasks (Operation Span, Symmetry Span, Rotation

Span) were obtained from http://englelab.gatech.edu/tasks.html and are described in detail in Foster et al. (2014). Briefly, participants performed one block of each task (in the above order) after listening to instructions and completing practice with an experimenter. Total SPAN suite duration was ~28 minutes. Subsequent analyses were conducted based on complex span partial scores, which provide a more continuous measure of performance and have been shown to yield better test-retest reliability (Redick 2012, Friedman & Miyake 2005).

2.3

Data Analysis

2.3.1

Summary of data analytic plan

The primary aim of this project was to understand the mechanisms underlying retention of abstract rules over several seconds, relative to maintenance of visuo-spatial items. To do so, we compared within-subjects neural activity during the encoding and three-second delay periods during which the rule or visuo-spatial array was retained. To further resolve the influence of cognitive control in rule retention, we compared neural mechanisms used to retain common versus rare (control-demanding) rules.

First, we applied the LASSO (Least Absolute Shrinkage and Selection Operator) algorithm (Tibshirani, 1996), a penalized method of logistic regression, to classify the retention data. Details and parameters of our application of LASSO have been described previously (Cavanagh & Castellanos, 2016b), and are elaborated further in the methods

below. Briefly, we trained and tested (and re-tested) the classifier on spatiotemporal ERP retention data (-200:2500 ms) for common (A) rules versus VSWM stimulus trials, which generated beta weights discriminating common rule retention from active item maintenance. We then applied those beta weights to control demanding (B) rules, which allowed us to quantify for each participant whether control demanding rules were processed more similarly to common rules or more similarly to items in VSWM.

To understand if between-subjects variation in working memory capacity is differently related to mechanisms for item versus rule maintenance, we tested the correlations between well-validated working memory test scores and LASSO classification transfer activity (rare rules more similar to common rules or to VSWM stimuli).

2.3.2

Behavioral Analysis: DPX

We computed accuracy and reaction time for each cue-probe combination separately for traditional and item-memory trials, to ensure that behavioral performance was similar across conditions. We report behavioral findings but do not discuss them in depth, as this study focuses on neural mechanisms for retention.

2.3.3

Behavioral Analysis: Working Memory (Span) Tasks

Each span task (Operation Span, Symmetry Span, Rotation Span) generated an absolute score and a partial score for memory items, as well as the percentage of correct trials on the secondary task. The absolute score only gives credit for trials in which all

memory items were retained, whereas the partial score gives credit for each successful memory recall item (even if the trial was not entirely correct). Per the task guidelines to ensure that both tasks were equally attended, scores were only included if percentage of correct secondary task trials was 85% or greater. Due to the low degree of variance in absolute scores, we used partial scores for our analyses, summing (with equal weight) partial scores from each span task.

2.3.4

EEG Processing

Epochs were created surrounding cue onset (-2000: 7000 ms), from which activities locked to cue onset, cue response, matching dot onset, and matching dot response were isolated. CPz was re-created by re-referencing the data to an average reference. Very ventral channels (FT9, FT10, TP9, TP10) were removed due to unreliability. Bad channels were identified using a combination of FASTER (Nolan et al., 2010) and EEGlab's pop_rejchan (Delorme & Makeig, 2004), and were then interpolated. Bad epochs were identified by FASTER and then rejected. Independent components analysis (runica.m) was run and VEOG activity and a Gaussian template around frontopolar channels were compared with components to help identify and remove blink activity.

After pre-processing, data were transformed to surface Laplacian *(laplacian_perrinX.m)* (M. X. Cohen, 2014; Perrin et al., 1989). As a high-pass spatial filter, the Laplacian filters out spatially broad features thereby minimizing effects of volume-conduction, and highlights local topographical features. The surface Laplacian is

reference-free, and as such avoids confounds with the choice of reference electrode (M. X. Cohen, 2014; Kayser & Tenke, 2006). Importantly, the surface Laplacian has been shown in recent work to provide better temporal and spatial resolution in resolving the rapid temporal adjustments involved in cognitive control, compared to alternative spatial filtering techniques (Wong et al., 2018).

2.3.5

Event-related potentials

Event-related potentials (ERPs) were computed to investigate changes in amplitude evoked by cue stimuli and following cue responses. To ensure attention to task and successful context processing, cue-locked activity for each condition was calculated as an average of all trials with correct responses to cue, probe, and matching cue (when applicable). Data were low-pass filtered at 20 Hz (eegfilt.m). Epochs were created from -200:3000 ms peri-cue for single cue and item memory stimuli, and from -200:2500 ms peri-response for comparisons of rule maintenance following matching/non-matching response. These epoch lengths encompass (nearly) the full delay period following maintenance demands, considering the earliest possible stimulus-onset at 2500 ms post-response (mean=3000 ms post-response, max=3500 ms post-response). Whereas cue-locked epochs allow us to compare early item or rule encoding, response-locked epochs allow us to compare extended maintenance processes across the delay period, and are not confounded by overlapping activities from a motor response. All epochs were baseline-corrected by subtracting the -200:0 ms pre-cue average across all correct trials (collapsed across all conditions). To equalize the signal to noise ratio between common A (~130

trials), VSWM (~160), and rare B (~30 trials), we randomly drew A and VSWM trials equal to the count of B trials.

We analyzed ERP late period sustained amplitude (1000-2500 ms post-cue) at several regions of interest, based on prior literature. These electrodes have been shown previously to correlate with elements of cognitive control processing, working memory maintenance, or motor preparation.

Medial pre-frontal (AFz) and medial frontal (FCz) amplitudes have been shown to index cognitive control processing (Janowich, 2016; Janowich & Cavanagh under review A; Janowich & Cavanagh under review B). We also analyzed lateral pre-frontal electrodes AF7 (left) and AF8 (right); in long-delay conditions, such lateral pre-frontal electrodes have shown enhanced activity (Janowich & Cavanagh, under review B).

Central parietal (CPz) amplitude has been associated with N2 (Wang, Yang, Moreu et al., 2017) and P3 (Dias, Foxe, Javitt, 2003) components, common in cognitive control and response inhibition.

Motor preparatory activity was analyzed at C3 (left) and C4 (right), as such activity has been shown to be sustained for both common and rare rules in the AX-CPT (Bickel, Dias, Epstein et al., 2012).

Posterior parietal electrodes PO3 (left) and PO4 (right) have been shown to reflect visuo-spatial working memory delay activity (Unsworth, Kukada, Awh, et al., 2015).

2.3.6

Time-frequency Analyses

To understand the role of spectral phenomena in item and encoding maintenance, we conducted time-frequency analyses of our data. We transformed our data into time-frequency space by applying wavelet transformations (Cavanagh et al., 2009) to the original cue-locked -2000:8998 ms epochs, encompassing the full trial. Utilization of these longer epochs allowed us to extract and analyze activity from low frequency bands.

Power was computed at electrodes of interest, using the CSD-EEG epochs. The CSD-EEG time series in each epoch was convolved with a series of complex Morlet wavelets, defined as a Gaussian-windowed complex sine wave. In these wavelets, frequency increased from .01 to 50 Hz in 30 logarithmically spaced steps, and width/cycles of each frequency band were set according to 4.0/(2*pi*frequency). From the resulting CSD-EEG x wavelet signal, we obtained estimates of instantaneous power and phase for each epoch. We then cut each epoch to -300 to 2500 ms peri-cue and applied a baseline-correction to each epoch by subtracting out the average frequency power -300 to -100 ms pre-cue. This baseline period was chosen because temporal smoothing from time-frequency decomposition may introduce temporal leakage of trial-related activity into the pretrial period (M. X. Cohen, 2014). Such a baseline is common in the field since a small time sample reflects the wavelet-weighted influence of longer time and frequency periods (M. X. Cohen, 2014). Power was normalized by conversion to decibel (dB) scale, which allows direct comparison across frequency bands.

Electrodes and spectral frequencies of interest were selected based on prior literature. Temporal windows were selected based on prior literature, as well as peak across-condition activation.

Theta power (4-7 Hz) at medial (AFz- pre-frontal, FCz- frontal) and lateral frontal (AF7-left, AF8-right) regions has been implicated as a mechanism for cognitive control (for review, see Cavanagh & Frank, 2014). Centro-parietal (CPz) theta, similarly, has been shown to be a hub for proactive cognitive control (Cooper, Wong, Fulham et al., 2015).

Motor preparatory beta (13-20 Hz) power was analyzed at C3 (left) and C4 (right), as it has been shown to be sustained ahead of both common and rare rules in the AX-CPT (Bickel, Dias, Epstein et al., 2012).

Alpha (8-12 Hz) power at posterior electrodes (PO3 and PO4, 250-1000 ms) was evaluated as a potential correlate of visuo-spatial working memory maintenance (Crespo-Garcia, Pinal, Cantero, et al., 2013; Fahrenfort, Leeuwen, Foster, et al., 2017).

3
RESULTS

3.1
Behavioral Performance on Traditional/ Visuo-spatial Working Memory DPX Task

Participants made simple ("left") button presses upon appearance of the (any) cue (traditional A trials, traditional B trials), and 4-dot-WM-stim (VSWM trials). A 1x3 repeated-measures ANOVA revealed a significant difference in cue accuracy ($F(1,48)=10.599$, $p=.002$), such that rare B cues elicited lower accuracy (93.4 +/- .016 SE) than common A (98.5 +/- .003) or VSWM cues (97.9 +/- .003). RT also differed between cues ($F(1,48) = 147.352$, $p<.001$), with common A cues showing faster RT (.459 +/- .010) than rare B cues (.549 +/- .012) or VSWM cues (.531+/- .011). On VSWM trials, participants responded more accurately to matching vs. non-matching stimuli

(Figure 2) (2x1 ANOVA: $F(1,48)=70.364$, $p<.001$). Reaction time was significantly faster for matching vs. non-matching stimuli (2x1 ANOVA: $F(1,48)=141.118$, $p<.001$).

Accuracy and reaction time for each cue-probe condition and trial type (traditional vs. item working memory) are detailed in Figure 3. A 2 (traditional vs. item WM trial) x 4 (cue-probe type: AX vs. AY vs. BX vs. BY) repeated-measures ANOVA on task accuracy showed a main effect of cue-probe type ($F(3,46)=60.657$, $p<.001$) but no main effect of trial type ($F(1,48)=.748$, $p=.392$) and no cue-probe x trial type interaction ($F(3,46)=1.989$, $p=.129$). Follow-up tests showed that accuracy was significantly impaired for both BX trials and AY trials compared to baseline AX trials. Probe reaction time showed a main effect of cue-probe type ($F(3,46)=87.751$, $p<.001$), a main effect of trial type ($F(1,48)=7.416$, $p=.009$), such that VSWM trials were slower than traditional trials. There was no cue-probe x trial type interaction ($F,3,46)=.350$, $p=.789$). Follow-up tests showed that reaction time was increased for AY trials and BX trials, relative to baseline AX trials.

In summary, both accuracy and reaction time metrics showed typical DPX performance patterns including less accurate and slower performance on control-demanding BX and AY trials. Importantly, accuracy did not differ between traditional versus item working memory trials, and there was only a main effect of reaction time for item memory trials, suggesting that task difficulty was similar between the two trial types and that trial type did not differentially modify response strategies to different cue-probe pairs.

Figure 5.2: Match Behavior. Accuracy (2A) and Reaction time (2B) to Mcnab matching stimuli (purple dot). Match trials elicited greater accuracy and faster reaction time relative to non-match trials.

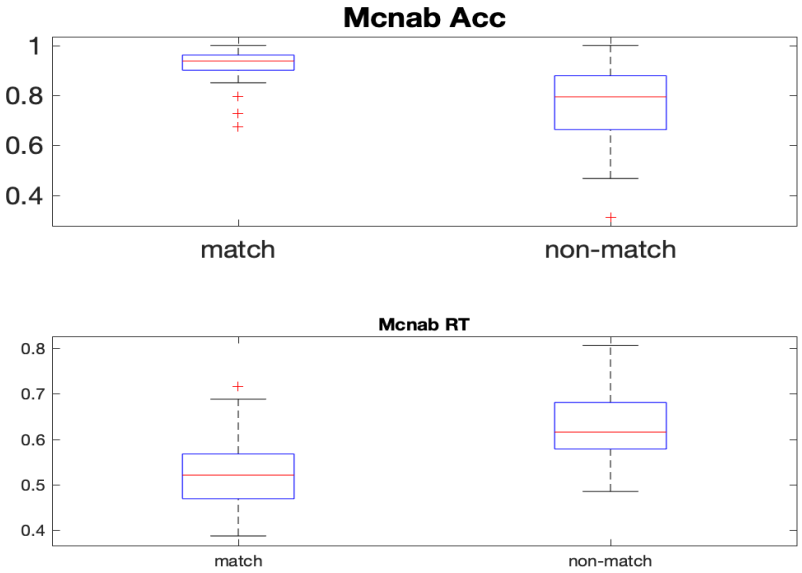
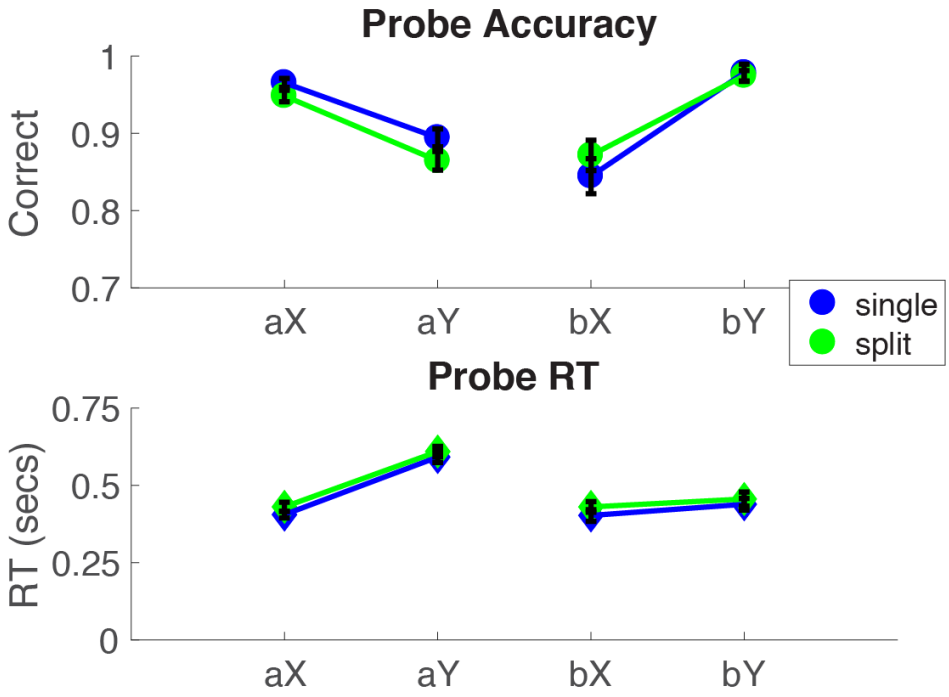


Figure 5.3: Probe Behavior. Accuracy (3A) and Reaction time (3B) to probe (X or Y) stimuli. Blue lines indicate probe performance on traditional DPX trials (+/- SD). Green lines indicate probe performance on trials with VSWM/McNab cues. There is no difference in performance between traditional and VSWM trials.



3.3.1

Fixed Effects: Event-related potentials

To test the fixed effects of retention type on delay activity, we applied 1x3 (common rule vs. rare rule vs. VSWM stimuli) repeated measures ANOVAs to *a priori* electrodes. For all ERP analyses, we compared mean amplitude 1000-2500 ms post-cue, which comprised the latter two-thirds of the retention period.

First we assessed sustained amplitudes at medial frontal, medial parietal, and lateral prefrontal electrodes. Medial pre-frontal AFz amplitude did not differ between conditions ($F(2,47)=2.266$, $p=.115$). Lateral pre-frontal amplitudes did not differ between conditions (AF7 (left) ($F(2,47)=.782$, $p=.442$) ;AF8 ($F(2,47)=.648$, $p=.506$)). Similarly, there were no differences in late amplitude at medial-frontal FCz ($F(2,47) = .031$, $p=.919$), nor at medial-parietal CPz ($F(2,47)=1.058$, $p=.335$). Next, we evaluated sustained amplitude at posterior electrodes POz, PO3, and PO4. No significant differences between retention conditions were observed (POz (center) $F(2,47)=1.911$, $p=.162$; PO3 (left) ($F(1,48)=.159$, $p=.807$; PO4 (right) $F(2,47)=.742$, $p=.444$). To assess whether motor activity was elicited differently between retention conditions, we assessed late sustained activity at left (C3) and right (C4) motor electrodes with maximal across-condition amplitude. There were no significant differences at either electrode based on retention type (C3: $F(1,48)=.213$, $p=.753$; C4 $F(1,48)=.950$, $p=.383$.

Overall, there were no fixed effects of retention condition on late sustained ERP amplitude.

3.3.2

Fixed Effects: Time-frequency Power

For time-frequency analyses, we selected each time and frequency window for analysis based on maximal across-condition power. We applied 1x3 repeated measures ANOVAs (common rule vs. rare rule vs. VSWM stimuli) to test for fixed effects of retention type in the time-frequency domain.

Early theta (250-1000 ms) power at medial-prefrontal AFz showed a main effect of retention type ($F(2,47)=3.710$, $p=.032$). Follow-up tests revealed that power was elevated for VSWM stimuli relative to common A rules ($p=.008$). We examined delta-theta (1-7 Hz) activity (750-1500 ms) at lateral prefrontal sites AF7 (left) and AF8 (right). At left prefrontal AF7, delta-theta activity differed between retention conditions ($F(2,47)=8.948$, $p=.001$), with VSWM stimuli exhibiting the greatest power (VSWM vs. A $p=.001$). At right prefrontal AF8, delta-theta activity differed between retention conditions ($F(2,47)=.347$, $p=.002$), with VSWM stimuli again exhibiting the greatest power (VSWM vs. A $p=.004$).

At medial-frontal FCz, early (200-700 ms) theta power differed between retention conditions ($F(2,47)=3.448$, $p=.040$), with rare B rules exhibiting the greatest power (B>A $p=.012$, B>VSWM $p=.019$). Medial-parietal CPz (200-500 ms) theta power also showed an effect of retention condition ($F(2,47)=4.285$, $p=.020$), with rare B rules exhibiting the greatest power (B > VSWM $p=.009$).

We examined beta power at electrodes above the left and right motor cortices (left: C3 and right: C4). Late (1000-2500 ms) C3 beta power differed between conditions ($F(2,47)=3.823$, $p=.029$), being greater for VSWM stimuli than common A cues ($p=.025$)

or rare B cues (p=.050). Similarly at C4, beta power differed between conditions (F(2,47)=3.674, p=.033), being greater for VSWM stimuli than common A cues (p=.036) or rare B cues (p=.032).

Sustained visual processing was analyzed by comparing alpha (8-12 Hz) power at posterior electrodes (PO3 (left), and PO4 (right) from 1000-2500 ms post-cue. No fixed effect differences were observed at PO3 (F(2,47)= .442, p=.646) or PO4 (F(2,47) =.248, p=.781).

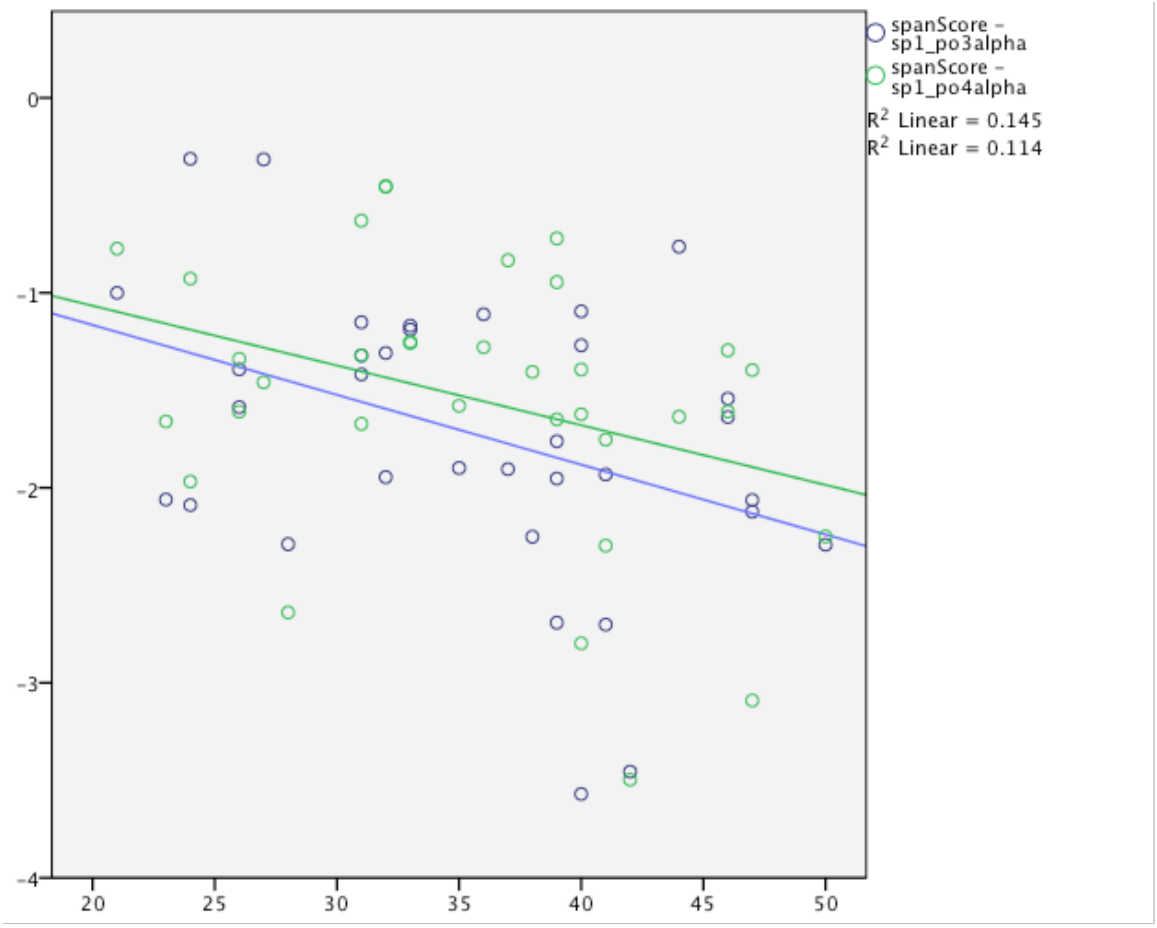
Overall, several time-frequency power differences between conditions were observed. Participants showed elevated power in response to VSWM stimuli at medial prefrontal (AFz, theta), lateral prefrontal (AF7 & AF8, delta-theta), and motor (C3 & C4, beta) sites. In response to rare B stimuli, participants showed elevated theta power at medial-frontal FCz and medial-parietal CPz.

3.4

Mixed Effects

Complex span scores were negatively correlated with sustained posterior alpha activity at PO3 (Pearson r = -.380, p=.027) and PO4 (Pearson r=-.338, p=.050), such that participants with higher trait working memory exhibited more negative alpha activity during the VSWM stimuli compared to participants with lower trait working memory.

Figure 5.4: Trait working memory and posterior alpha activity. Correlations are shown between partial complex span scores (an index of trait working memory) and alpha power at posterior electrodes PO3 (left, blue) and PO4 (right, green).



3.5

LASSO classification with *a priori* ERP and Time-frequency Power Features

To understand whether a priori hypothesized ERP or time-frequency components successfully predict transfer learning in rule retention, we classified A vs. VSWM data based on 20 a priori features (10 ERP and 10 TF, see Methods). Application of these weights to a new type of trials is referred to as 'transfer learning', or 'out-of-sample' classification. Out-of-sample classification of above 50% would suggest that rare B rules were more similar to common A rules, whereas classification below 50% would suggest that rare B rules were more similar to VSWM stimuli. Classification at 50% (chance) suggests that the electrophysiological signals being used in this out-of-sample classification cannot successfully discriminate these conditions across participants. The best model weights for each feature (across participants) are depicted in Figure 5, and transfer learning is shown in Figure 6. Transfer learning was not above chance.

Figure 5.5: Topoplots of best beta weights discriminating common rule from VSWM stimuli. Color scale indicates predictive power of that electrode for discriminating common rule (red) versus VSWM stimuli (blue).

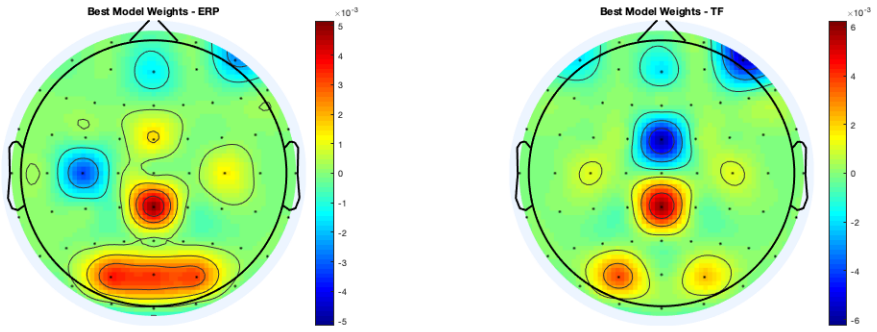
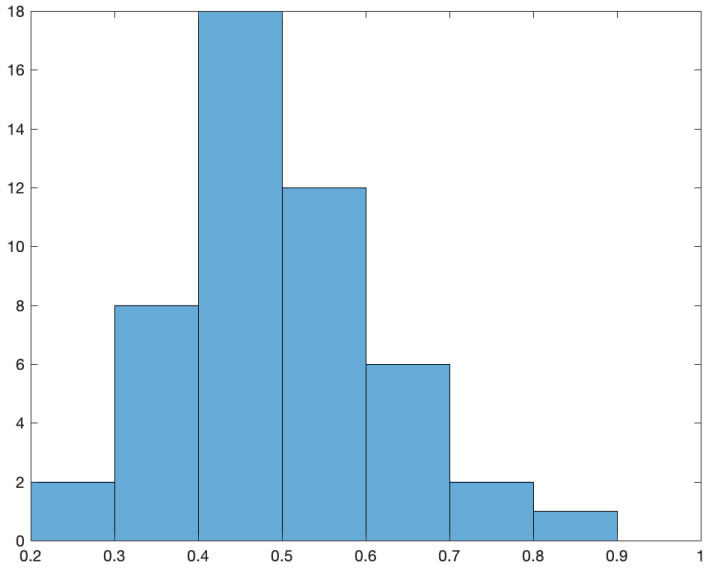


Figure 5.6: Histogram of out-of-sample classification on top 20 features.

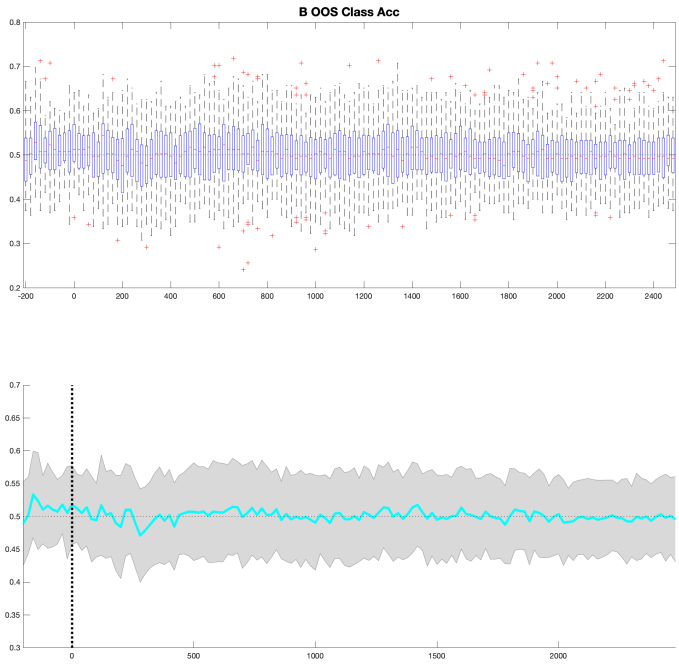


3.6

LASSO Classification of common rule vs rare rule vs. VSWM retention

To identify data-driven spatio-temporal periods of interest differentiating retention of items versus rules, we first isolated EEG activities during the encoding and retention of item working memory stimuli and common rules. We trained a classifier to discriminate between VSWM and common rule ERP activities (across the scalp, at all time-points), and then applied those classification weights to rare rule retention trials. At the group level, transfer classification of control-demanding rules (B cues) yielded overall accuracy that was not different than chance (Figure 5.7).

Figure 5.7: Out-of-sample data-driven classification of rare cues across the retention period (20ms bins). 5A) Boxplots representing classification across participants. 5B) Standard deviation of classification across participants.



However, given that retention may rely on different mechanisms across participants, we tested the correlation between trait working memory (complex span partial score) and out-of-sample classification accuracy. A correlation between trait working memory and out-of-sample classification would suggest that persons with higher working memory capacity process rare rules differently than do persons with lower working memory capacity.

We found that trait working memory correlated significantly with sustained ERP activity across the full retention period (Figures 8 and 9). Regression analysis demonstrated that individual differences in complex span (trait WM) score was significantly predictive of out-of-sample (transfer) classification of the control-demanding retention activity (p=.019). In participants with higher trait WM, control-

demanding goals were processed more similarly to common goals than to visuo-spatial WM stimuli (goal-updating ~= WM). In participants with lower trait WM, control-demanding goals were processed like visuo-spatial WM stimuli (goal-updating == WM). In conclusion, sustained ERP activities underlying goal retention differ based on control demands, and vary based on individual WM abilities.

Figure 5.8: Out-of-sample classification by complex span groups. Mean (+/- SD) classification accuracies are plotted by group, as segregated into low third, middle third, and high third span scores. Topoplots illustrate spatial (scalp) locations of classification beta weights at the timepoint of peak classification accuracy.

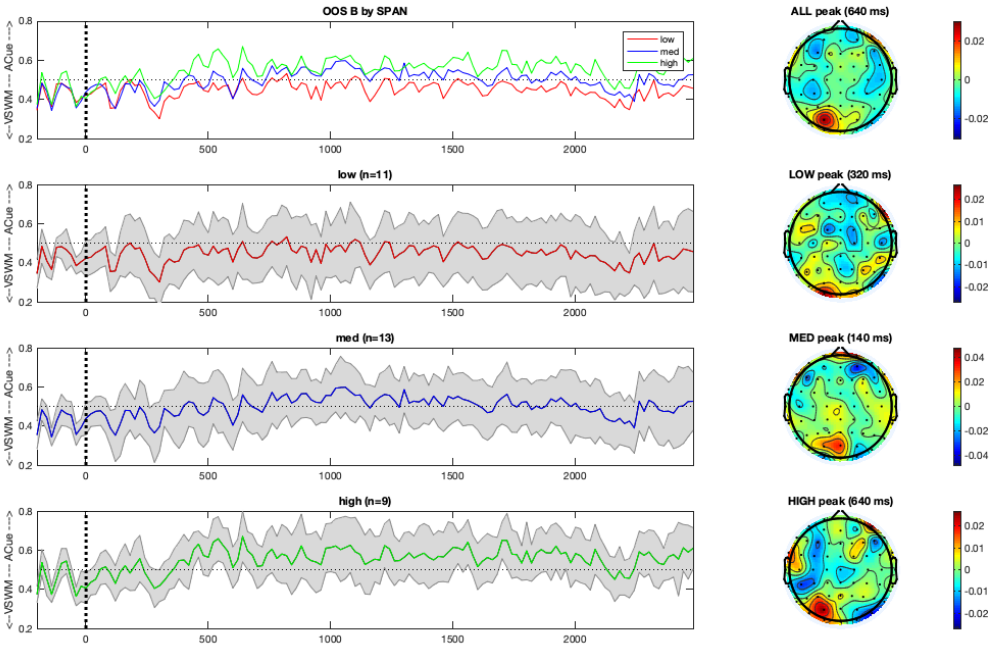
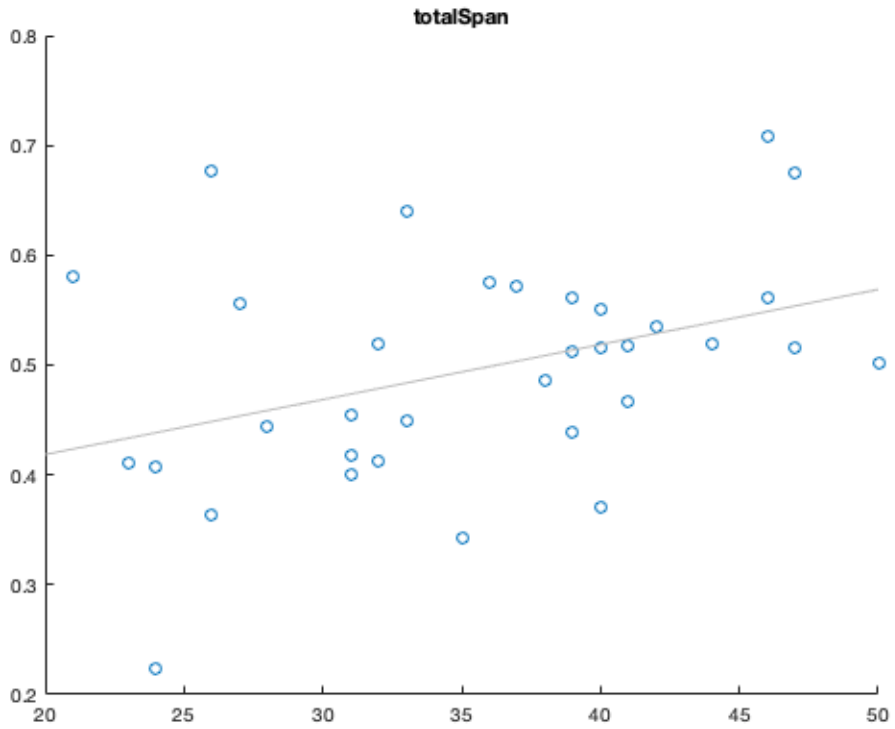


Figure 5.9: Out-of-sample rare (B) rule classification accuracy (y-axis) by complex span score (x-axis).



DISCUSSION

General Summary

This study compared mechanisms for several-second retention of common and rare rules with maintenance of a visuo-spatial working memory stimuli. We observed several electrophysiological correlates of retention processing that differed overall between retention/maintenance type (across participants), as well as sustained activities that were elicited differently depending on an individual's trait working memory.

Fixed effects were observed for several time-frequency components of a priori interest. Participants showed elevated power in response to VSWM stimuli at medial prefrontal (AFz, theta), lateral prefrontal (AF7 & AF8, delta-theta), and motor (C3 & C4, beta) sites. In response to rare B rules demanding heightened cognitive control, participants showed elevated theta power at medial-frontal FCz and medial-parietal CPz. This elevated theta power at CPz may reflect a P300-like target detection response for the rare B cues (Li, Gratton, Yao, & Knight, 2010).

Mixed effects of trait working memory (complex span score) were observed during VSWM maintenance in posterior parietal alpha activity bi-laterally. During VSWM maintenance, participants with higher trait working memory showed increased alpha suppression relative to participants with lower trait working memory. This effect was not observed for common or rare rules, suggesting that this alpha suppression may be specific to visuo-spatial working memory, at least in high working memory individuals.

To understand the interaction of many potential ERP and time-frequency components on retention, we applied classifiers to single-trial data to discriminate between retention conditions. LASSO classification using 20 a priori electrophysiological features failed to discriminate rare rule cues from common rules versus VSWM stimuli. Classifying instead with the overall time-course of ERP activity across all electrodes again yielded out-of-sample classification no greater than chance. Importantly, however, out-of-sample classification was correlated with trait working memory. Participants with higher trait working memory processed rare control-demanding rules more similarly to common rules, whereas participants with lower trait working memory processed rare control-demanding rules more similarly to visuo-spatial working memory stimuli. This

finding implies that trait working memory shapes how rare control-demanding rules are retained over long delays.

This study provides (to date) the most direct comparison between item visuo-spatial working memory maintenance and rule retention. Rule and visuo-spatial working memory were matched for stimulus characteristics, including general visual appearance, frequency/rarity, and timing dynamics. By intermingling rule and VSWM stimuli within-subjects and across trials, we ensured similar attention between rule and memory tasks. We utilized complex span scores as an out-of-task, well-validated metric of trait working memory, which provides evidence that our novel task manipulation indeed taxes these working memory abilities.

Limitations and Future Directions

Here, we assessed retention of rules and visuo-spatial stimuli in healthy college students. It is known that both cognitive control retention and visuo-spatial working memory decline with age, and in several neuropsychiatric disorders. Future studies are needed to evaluate the mechanisms of control retention in these populations.

Another limitation of our study is the relative ease of memory of the given rules and item stimuli. Participants performed very accurately on the task, successfully retaining both goal and memory stimuli on over 85% of trials. A more difficult version of the task, with more (or more complex) stimuli/rules may have elicited distinct retention processes.

Conclusions

By comparing the processing and retention of rules and VSWM stimuli in a novel variant of the DPX task, we established several frontal-parietal and posterior neural activities differentiating rule retention from item maintenance. Importantly, we also showed that much of the differentiation between retention types was sensitive to trait working memory, with different processing "strategies" being utilized for control retention. This work has important implications for the general understanding of retention and working memory. We show that rules do not necessarily rely on traditional working memory for their retention, but may utilize distinct theta signals at medial frontal and medial parietal sites. In addition, visuo-spatial maintenance appears to generally rely on lateral prefrontal theta and motor beta activities, with posterior parietal alpha being elicited more strongly in persons with high working memory.

DISCUSSION

DISCUSSION

General Summary

This dissertation was comprised of a meta-analytic review and several empirical EEG experiments evaluating the electrophysiological mechanisms faciliating the retention of cognitive control over time. In all empirical experiments, we evaluated delay/retention-related brain activity in healthy young adults, in order to understand optimal mechanisms for temporally-mediated processing of cognitive control.

In Chapter 2's meta-analytic review, we revealed significant and robust effects of delay knowledge and trial set count on error rate and reaction time metrics of proactive vs. reactive control. In healthy young adults, studies with full knowledge of upcoming delay length shifted both accuracy and reaction time measures toward an increased use of proactive control, relative to studies in which the upcoming delay was unknown. These results demonstrate that delay dynamics are critical parameters in expectancy studies, guiding distinct cognitive control behaviors reflected in both error rate and reaction time measures.

In Chapter 3, we replicated a previous empirical finding of delay-related changes in AX-CPT behavior and EEG activity (Janowich, 2016), this time in the non-verbalizable DPX task. We manipulated cue-probe delay as short or long by block, and compared within-subjects neural activity during the delay. Replicating the key behavior result, difficulty inhibiting the rare 'aY' response specfically in the short delay condition, showed that temporal delay dynamics robustly influence the development of a prepotent response. Further, we observed significant within-subjects differences in ERP and time-

frequency signatures associated with task-switching, cognitive control, and active maintenance based on delay length and cue type. Both of these major findings were previously observed in the AX-CPT (Janowich, 2016) and replicated in a separate sample in the present study. This served as the first study to attempt to dissociate different sub-types of proactive control, and provides novel evidence that temporal demands can elicit behavioral differences and neurophysiological distinctions in proactive processes. Again, we operationalized these distinct features as 1) a goal updating process in which transient control immediately drives the rapid instantiation of a new state at the expense of a previous state, in contrast to 2) an active maintenance process where control processes elicit persistent activity patterns to maintain a sustained representation (Barak & Tsodyks, 2014; Jensen & Lisman, 2005; Vogel & Machizawa, 2004; Wang, 2010; Wasmuht, Spaak, Buschman, Miller, & Stokes, 2017; although also see Spaak, Watanabe, Funahashi, & Stokes, 2017; Stokes et al., 2013). Of course, we do not expect that active maintenance would occur in isolation; even a distant goal must be updated at some point in time. We posit that this active maintenance process stores one's new goals, preceding a later or more gradual reconfiguration to the new state (Frohlich, Bazhenov, Timofeev, Steriade, & Sejnowski, 2006).

In Chapter 4, we manipulated delay length on a trial-wise basis and recorded EEG while participants performed a novel variant of the DPX. This trial-wise manipulation ensured similar baseline levels of attention across conditions. In addition, this study included a condition in which delay was unknown, to provide a baseline for comparison with temporal planning of short or long delays. We observed several prefrontal differences elicited by variation in delay length and delay knowledge. These neural

features were differently sensitive to dynamics of goal preparation, including processes underlying judgment, communication, and maintenance of the temporal delay before goal execution. Together, these study results provide novel evidence that dynamic goal timing information is communicated through several distinct pre-frontal mechanisms, largely separate from (common versus rare) goal identity. Further, the influence of trait impulsivity on preparation for unknown versus known timing demands suggests that individual differences may be important in understanding how preparation strategies are shaped.

In Chapter 5, we compared the processing and retention of rules and VSWM stimuli in a novel variant of the DPX task. We established several frontal-parietal and posterior neural activities differentiating rule retention from item maintenance. Importantly, we also showed that much of the differentiation between retention types was sensitive to trait working memory, with different processing "strategies" being utilized for control retention. This work has important implications for the general understanding of retention and working memory. We show that rules do not necessarily rely on traditional working memory for their retention, but may utilize distinct theta signals at medial frontal and medial parietal sites. In addition, visuo-spatial maintenance appears to generally rely on lateral prefrontal theta and motor beta activities, with posterior parietal alpha being elicited more strongly in persons with high working memory.

Conclusions

Through these studies, we provide evidence supporting distinct behavioral and neural mechanisms for the computation, retention, and implementation of cognitive control based on temporal dynamics. Our empirical work complements theory that distinct sub-sets of control processes are involved in immediate versus more future-oriented control needs (Koechlin & Summerfield, 2007). We repeatedly show how temporal delay, an otherwise arbitrarily controlled parameter in a popular assessment of cognitive control, has an important influence over of the cognitive control processes utilized. This impact of delay length on brain and behavior in cued control tasks highlights a major crisis in generalizing across cued continuous performance task studies, and prompts the need for further investigation of how delay information guides cognitive control. Given the prevalence of this task for assessing cognition in psychiatric samples, it is critical to consider whether a given group is deficient in one or both of these dissociated aspects of control. Researchers using the AX-CPT or DPX paradigms should no longer consider delay dynamics as incidental parameters, and should select these parameters intentionally in accordance with the control type(s) of experimental interest.

Based on our series of findings, we suggest that timing demands tap into distinct mechanisms for goal updating versus active maintenance. This proactive adaptation to temporal context is likely useful to optimally balance the costs of sustained control with the need to successfully execute behavior. Our final dissertation study (Chapter 5) complements this work, demonstrating that cognitive control is further adapted based on individual working memory capacity, with low working memory individuals relying on a

costly active maintenance strategy. This series of dissertation studies provides a major advance in understanding temporally-sensitive interactions faciliating the processing and retention of cognitive control. Following this groundwork, future studies should be well-equipped to test the temporally precise pathways facilitating successful proactive control across timing demands.

APPENDIX 1

Meta-analysis selected studies. Table listing all studies and data-points included in the meta-analysis, along with the subgroups in which each was categorized and notes regarding which study conditions were selected for inclusion. HYA=Healthy Young Adult, K=Known Delay, J=Jittered Delay, U=Unknown Delay; SOA=Slightly-Older Adults (aged 30-45); SZ=Schizophrenia patients; D=paradigm with mid-delay distractor. Further study details, including all performance and parameter data included in the meta-analysis, are available in Mendeley Data.

Authors	Study Title	Study Year	Journal	Inclusion	Notes
Licen, Hartmann, Repovs, et al.	The Impact of Social Pressure and Monetary Incentive on Cognitive Control	2016	Frontiers in Psychology	HYA-K	Baseline condition only
Paxton, Barch, Racine, & Braver	Cognitive Control, goal maintenance, and prefrontal function in healthy aging	2008	Cerebral Cortex	HYA-K	word AXCPT; Study 1
Paxton, Barch, Racine, & Braver	Cognitive Control, goal maintenance, and prefrontal function in healthy aging	2008	Cerebral Cortex	HYA-K	word AXCPT; Study 1
Paxton, Barch, Racine, & Braver	Cognitive Control, goal maintenance, and prefrontal function in healthy aging	2008	Cerebral Cortex	HYA-K	word AXCPT; Study 1
Carter, Braver, Barch	ACC, Error Detection, and the online monitoring of performance	1998	Science	HYA-K	SD converted from SEM
Braver, Satpute, Rush, et al.	Context processing and context maintenance in healthy aging and early stage dementia of the Alzheimer's type.	2005	Psychology and aging	HYA-K	YA only; SD converted from SEM
Paxton, Barch, Storandt, et al.	Effects of Environmental Support and Strategy Training on Older Adults' Use of Context	2006	Psychology and Aging	HYA-K	YA only; standard maintenance only
Braver, Satpute, Rush, et al.	Context processing and context maintenance in healthy aging and early stage dementia of the Alzheimer's type.	2005	Psychology and aging	HYA-K	YA only; SD converted from SEM
Paxton, Barch, Storandt, et al.	Effects of Environmental Support and Strategy Training on Older Adults' Use of Context	2006	Psychology and Aging	HYA-K	YA only; standard maintenance only
Braver, Barch, & Cohen	Mechanisms of cognitive control: Active Memory, Inhibition, and the prefrontal cortex	1999	Pittsburgh (PA): Carnegie Mellon University.	HYA-K	Study 5 only; SD converted from SEM
Braver, Barch, & Cohen	Mechanisms of cognitive control: Active Memory, Inhibition, and the prefrontal cortex	1999	Pittsburgh (PA): Carnegie Mellon University.	HYA-K	Study 5 only; SD converted from SEM
Braver, Paxton, Locke, et al.	Flexible neural mechanisms of cognitive control within human prefrontal cortex	2009	PNAS	HYA-K	YA only; Baseline condition only; duplicate of behavior in Paxton 2008 Study 2
Lorsbach & Reimer	Context processing and cognitive control in children and young adults.	2008	The Journal of genetic psychology	HYA-K	YA only; SD converted from SEM
Otto, Skatova, Madlon-Kay, et al.	Cognitive Control Predicts Use of Model-based Reinforcement Learning	2015	Journal of Cognitive Neuroscience	HYA-K	DPX; mechanical turk
Braver, Barch, Keys, et al.	Context processing in older adults: evidence for a theory relating cognitive control to neurobiology in healthy aging	2001	Journal of Experimental Psychology: General	HYA-K	YA only; SD converted from SEM
Brambilla, MacDonald, Sassi, et al.	Context processing performance in bipolar disorder patients	2007	Bipolar disorders	HYA-K	healthy controls only
Brambilla, MacDonald, Sassi, et al.	Context processing performance in bipolar disorder patients	2007	Bipolar disorders	HYA-K	healthy controls only
Lesh, Tanase, Geib, et al.	A Multimodal Analysis of Antipsychotic Effects on Brain Structure and Function in First-Episode Schizophrenia	2015	JAMA psychiatry	HYA-K	healthy controls only
Yoon, Minzenberg, Ursu, et al.	Association of dorsolateral prefrontal cortex dysfunction with disrupted coordinated brain activity in schizophrenia: Relationship with impaired cognition, behavioral disorganization, and global function	2008	American Journal of Psychiatry	HYA-K	healthy controls only
Lesh, Westphal, Niendam, et al.	Proactive and reactive cognitive control and dorsolateral prefrontal cortex dysfunction in first episode schizophrenia.	2013	Neuroimage: Clinical	HYA-K	healthy controls only
Chiew & Braver	Temporal dynamics of motivation-cognitive control interactions revealed by high-resolution pupillometry	2013	Frontiers in Psychology	HYA-K	Baseline condition only
Chiew & Braver	Temporal dynamics of motivation-cognitive control interactions revealed by high-resolution pupillometry	2013	Frontiers in Psychology	HYA-K	Baseline condition only
Reimer, Radvansky, Lorsbach, et al.	Event Structure and Cognitive Control	2015	Journal of Experimental Psychology: Learning, Memory, and Cognition	HYA-K	location manipulation = same; SD converted from SEM
Reimer, Radvansky, Lorsbach, et al.	Event Structure and Cognitive Control	2015	Journal of Experimental Psychology: Learning, Memory, and Cognition	HYA-K	color manipulation = same; SD converted from SEM
Reimer, Radvansky, Lorsbach, et al.	Event Structure and Cognitive Control	2015	Journal of Experimental Psychology: Learning, Memory, and Cognition	HYA-K	location manipulation = same; SD converted from SEM

Authors	Study Title	Study Year	Journal	Inclusion	Notes
Janowich & Cavanagh	Immediate vs. delayed control demands elicit distinct mechanisms for instantiating proactive control	under review	under review	HYA-K	AX-CPT
Janowich & Cavanagh	Immediate vs. delayed control demands elicit distinct mechanisms for instantiating proactive control	under review	under review	HYA-K	DPX
Kam, Dominelli, & Carlson	Differential relationships between sub-traits of BIS-11 impulsivity and executive processes: An ERP study	2012	International Journal of Psychophysiology	HYA-K	
Morales, Yudes, Gomez-Ariza, et al.	Bilingualism modulates dual mechanisms of cognitive control: Evidence from ERPs	2014	Neuropsychologia	HYA-K	collapsed across bilinguals and monolinguals
Morales, Yudes, Gomez-Ariza, et al.	Bilingualism modulates dual mechanisms of cognitive control: Evidence from ERPs	2014	Neuropsychologia	HYA-K	collapsed across bilinguals and monolinguals
Wiemers & Redick	Working memory capacity and intra-individual variability of proactive control	2017	Acta Psychologica	HYA-K	collapsed across working memory capacity
Redick	Cognitive control in context: WM capacity and proactive control	2014	Acta Psychologica	HYA-K	collapsed across working memory capacity
Chaillou, Giersch, Hoonakker, et al.	Differentiating Motivational from Affective Influence of Performance-contingent Reward on Cognitive Control: The Wanting Component Enhances Both Proactive and Reactive Control	2017	Biological Psychology	HYA-K	IAPS + monetary motivation pre-cue
Chaillou, Giersch, Hoonakker, et al.	Differentiating Motivational from Affective Influence of Performance-contingent Reward on Cognitive Control: The Wanting Component Enhances Both Proactive and Reactive Control	2017	Biological Psychology	HYA-K	IAPS mood induction pre-cue
van Wouwe, Band, Ridderinkhof	Positive affect modulates flexibility and evaluative control	2011	Journal of Cognitive Neuroscience	HYA-K	affect induction
Lopez-Garcia, Lesh, Salo, et al.	The neural circuitry supporting goal maintenance during cognitive control: a comparison of expectancy AX-CPT and dot probe expectancy paradigms	2015	CABN	HYA-J	AX-CPT
Lopez-Garcia, Lesh, Salo, et al.	The neural circuitry supporting goal maintenance during cognitive control: a comparison of expectancy AX-CPT and dot probe expectancy paradigms	2015	CABN	HYA-J	DPX
Janowich & Cavanagh	Immediate vs. delayed control demands elicit distinct mechanisms for instantiating proactive control	under review	under review	HYA-J	AX-CPT
Janowich & Cavanagh	Immediate vs. delayed control demands elicit distinct mechanisms for instantiating proactive control	under review	under review	HYA-J	DPX
Redick & Engle	Integrating working memory capacity and context-processing views of cognitive control.	2011	Quarterly journal of experimental psychology	HYA-U	collapsed across working memory capacity
Redick & Engle	Integrating working memory capacity and context-processing views of cognitive control.	2011	Quarterly journal of experimental psychology	HYA-U	collapsed across working memory capacity
Beste, Domschke, Radenz, et al.	The functional 5-HT1A receptor polymorphism affects response inhibition processes in a context-dependent manner	2011	Neuropsychologia	HYA-U	collapsed across genotype; SD converted from SEM
Beste, Domschke, Radenz, et al.	The functional 5-HT1A receptor polymorphism affects response inhibition processes in a context-dependent manner	2011	Neuropsychologia	HYA-U	collapsed across genotype; SD converted from SEM
Richard, Carter, Cohen, & Cho	Persistence, Diagnostic Specificity and genetic liability for context-processing deficits in schizophrenia	2013	Schizophrenia Research	HYA-U	healthy controls only
Richard, Carter, Cohen, & Cho	Persistence, Diagnostic Specificity and genetic liability for context-processing deficits in schizophrenia	2013	Schizophrenia Research	HYA-U	healthy controls only
MacDonald, Goghari, Hicks, et al.	A convergent-divergent approach to context processing, general intellectual functioning, and the genetic liability to schizophrenia.	2005	Neuropsychology	SOA	DPX in healthy controls; Experiment 2 Only
Chung, Matthews, & Barch	The effect of context processing on different aspects of social cognition in schizophrenia.	2011	Schizophrenia Bulletin	SOA	healthy controls only
Chung, Matthews, & Barch	The effect of context processing on different aspects of social cognition in schizophrenia.	2011	Schizophrenia Bulletin	SOA	healthy controls only

Authors	Study Title	Study Year	Journal	Inclusion	Notes
Edwards, Barch, Braver	Improving prefrontal cortex function in schizophrenia through focused training of cognitive control	2010	Frontiers in Human Neuroscience	SOA	healthy controls only
Henderson, Poppe, Barch, et al.	Optimization of a goal maintencance task for use in clinical applications	2012	Schizophrenia Bulletin	SOA	DPX; healthy controls only
Henderson, Poppe, Barch, et al.	Optimization of a goal maintencance task for use in clinical applications	2012	Schizophrenia Bulletin	SOA	DPX; healthy controls only; no RT data available
Strauss, McClouth, Barch, et al.	Temporal Stability and Moderating Effects of Age and Sex on CNTRaCS Task Performance	2014	Schizophrenia Bulletin	SOA	DPX for healthy controls only; Time 1 only
Strauss, McClouth, Barch, et al.	Temporal Stability and Moderating Effects of Age and Sex on CNTRaCS Task Performance	2014	Schizophrenia Bulletin	SOA	AX-CPT for healthy controls only; Time 1 only
MacDonald, Goghari, Hicks, et al.	A convergent-divergent approach to context processing, general intellectual functioning, and the genetic liability to schizophrenia.	2005	Neuropsychology	SOA	AX-CPT; Experiment 1 Only
MacDonald, Goghari, Hicks, et al.	A convergent-divergent approach to context processing, general intellectual functioning, and the genetic liability to schizophrenia.	2005	Neuropsychology	SOA	DPX; Experiment 1 Only
MacDonald, Goghari, Hicks, et al.	A convergent-divergent approach to context processing, general intellectual functioning, and the genetic liability to schizophrenia.	2005	Neuropsychology	SZ	DPX in Schizophrenia; Experiment 2 Only
Chung, Matthews, & Barch	The effect of context processing on different aspects of social cognition in schizophrenia.	2011	Schizophrenia Bulletin	SZ	Schizophrenia -- Medicated
Chung, Matthews, & Barch	The effect of context processing on different aspects of social cognition in schizophrenia.	2011	Schizophrenia Bulletin	SZ	Schizophrenia -- Medicated
Edwards, Barch, Braver	Improving prefrontal cortex function in schizophrenia through focused training of cognitive control	2010	Frontiers in Human Neuroscience	SZ	Schizophrenia -- Medicated
Henderson, Poppe, Barch, et al.	Optimization of a goal maintencance task for use in clinical applications	2012	Schizophrenia Bulletin	SZ	Schizophrenia
Henderson, Poppe, Barch, et al.	Optimization of a goal maintencance task for use in clinical applications	2012	Schizophrenia Bulletin	SZ	Schizophrenia
Lesh, Westphal, Niendam, et al.	Proactive and reactive cognitive control and dorsolateral prefrontal cortex dysfunction in first episode schizophrenia	2013	Neuroimage: Clinical	SZ	Schizophrenia
Lesh, Tanase, Geib, et al.	A Multimodal Analysis of Antipsychotic Effects on Brain Structure and Function in First-Episode Schizophrenia	2015	JAMA psychiatry	SZ	Schizophrenia -- Unmedicated
Lesh, Tanase, Geib, et al.	A Multimodal Analysis of Antipsychotic Effects on Brain Structure and Function in First-Episode Schizophrenia	2015	JAMA psychiatry	SZ	Schizophrenia -- Medicated
Richard, Carter, Cohen, & Cho	Persistence, Diagnostic Specificity and genetic liability for context-processing deficits in schizophrenia	2013	Schizophrenia Research	SZ	Schizophrenia; baseline only
Richard, Carter, Cohen, & Cho	Persistence, Diagnostic Specificity and genetic liability for context-processing deficits in schizophrenia	2013	Schizophrenia Research	SZ	Schizophrenia; baseline only
Maraver, Bajo, & Gomez-Ariza	Training on Working Memory and Inhibitory Control in Young Adults	2016	Frontiers in Human Neuroscience	D	distractors; pre-training collapsed across training groups
Morales, Gomez-Ariza, & Bajo	Dual mechanisms of cognitive control in bilinguals and monolinguals	2013	Journal of Cognitive Psychology	D	distractors; collapsed across bilinguals and monolinguals
Braver, Barch, & Cohen	Mechanisms of cognitive control: Active Memory, Inhibition, and the prefrontal cortex	1999	Pittsburgh (PA): Carnegie Mellon University.	D	distractors; Study 5 Only; SD converted from SEM
Braver, Barch, & Cohen	Mechanisms of cognitive control: Active Memory, Inhibition, and the prefrontal cortex	1999	Pittsburgh (PA): Carnegie Mellon University.	D	distractors; Study 5 Only; SD converted from SEM
Braver, Barch, Keys, et al.	Context processing in older adults: evidence for a theory relating cognitive control to neurobiology in healthy aging	2001	Journal of Experimental Psychology: General	D	distractors; YA only
Froeber & Dreisbach	How performance (non-)contingent reward modulates cognitive control	2016	Acta Psychologica	D	distractors; neutral control baseline phase only
Gomez-Ariza, Martin, & Morales	Tempering proactive cognitive control by transcranial direct current stimulation of the right (but not the left) lateral prefrontal cortex	2017	Frontiers in Neuroscience	D	distractors; sham group only, collapsed across blocks

Authors	Study Title	Study Year	Journal	Inclusion	Notes
Paxton, Barch, Racine, & Braver	Cognitive Control, goal maintenance, and prefrontal function in healthy aging	2008	Cerebral Cortex	Post-hoc OA	Exp 1 older adults; "Word AX-CPT"
Paxton, Barch, Racine, & Braver	Cognitive Control, goal maintenance, and prefrontal function in healthy aging	2008	Cerebral Cortex	Post-hoc OA	Exp 1 older adults; "Word AX-CPT"
Braver, Satpute, Rush, et al.	Context processing and context maintenance in healthy aging and early stage dementia of the Alzheimer's type	2005	Psychology and aging	Post-hoc OA	older adults; "young-old" only; SD converted from SEM
Braver, Satpute, Rush, et al.	Context processing and context maintenance in healthy aging and early stage dementia of the Alzheimer's type	2005	Psychology and aging	Post-hoc OA	older adults; "young-old" only; SD converted from SEM
Paxton, Barch, Racine, & Braver	Cognitive Control, goal maintenance, and prefrontal function in healthy aging	2008	Cerebral Cortex	Post-hoc OA	Exp 2 older adults; 2 particpants also particpated in Paxton 2008 Experiment 1
Braver, Barch, Keys, et al.	Context processing in older adults: evidence for a theory relating cognitive control to neurobiology in healthy aging	2001	Journal of Experimental Psychology: General	Post-hoc OA	older adults; baseline only; SD converted from SEM

APPENDIX 2

Chapter 2 Supplement

Supplemental Methods:

2.2.3
Trial Counts by Delay/Cue Condition

	Mean	SD	Min	Max
Known Short A	125.333	10.712	104	153
Known Short B	23.972	4.372	16	33
Known Long A	131.639	10.145	104	149
Known Long B	24.194	4.111	14	33
Unknown A	129.306	10.000	112	153
Unknown B	21.417	3.974	12	29

2.3.1
Behavioral Shift Index (BSI)

The following formula generates a single proactive/reactive BSI value:

$(aY - bX) / (aY + bX)$

Higher BSI scores are associated with a greater use of proactive control, whereas lower BSI scores are associated with a greater use of reactive control. If context activation/updating abilities are intact, proactive control should bias responses based on context (Braver, Barch, & Cohen, 1999) and manifest in impaired performance on AY trials (Braver, Satpute, Rush, Racine, & Barch, 2005), during which a robust pre-potent response must be inhibited. By considering the relationship between BSI and cue-locked neural activity, we can resolve whether different neural responses to cued task demands bias behavior toward proactive or reactive control. It is important to note that BSI operationalizes proactive control as a unitary construct, and may not account for differences in the types of preparation used during the cue-probe delay.

2.3.3
Principal Component Analysis

To ensure that our PCA components were not driven by the unknown delay condition, we resolved the principal components for all cue (A, B) and known delay (known short, known long) cued delay types. The first component (158 ms post-cue) explained 29.210% of variance between conditions, and was maximal at PO3 and PO4 (and FCz). This component highlighted a main effect of cue type (B>A). PC2 explained 18.004% of the variance, and was maximal at 468 ms post-cue, at AFz/F1, F8, FT7, and Oz. The spatial and temporal features selected by PCA, as well as their weightings, were nearly identical for all conditions vs. only known delays.

2.3.4
Time-frequency ROIs

For AFz, power was maximal between 300-700 ms at 2-6 Hz. Inter-trial phase consistency (ITPC) at AFz was maximal at two peaks: 1-3 Hz, between 300-700 ms, and 4-8 Hz, between 150-350 ms. At F8, power was maximal between 200-700 ms from 3-7

Hz. ITPC at F8 showed 2 maximal ROIs, 1-4 Hz from 200-600 ms (dashed rectangle), and 5 Hz-7 Hz from 200-300 ms (solid rectangle).
For FT7, power was maximal between 200-800 ms from 3-7 Hz. FT7 ITPC showed two peaks, 4-8 Hz from 100-300 ms, and 1-3 Hz from 200-800 ms.

Phase synchrony between mid-frontal (FCz) and left prefrontal FT7 was maximal between 200-600 ms, from 3-7 Hz. Phase synchrony from mid-frontal FCz and right prefrontal F8 was maximal between 200 and 800 ms, from 3-7 Hz. Because the phase-synchrony ROIs were very long (400-600 ms in duration), we computed phase synchrony at early (first half) and late (second half) windows of the maximal phase synchrony ROI across conditions. Thus, FT7 was analyzed at early 200-400 ms and late 400-600 ms windows. F8 was analyzed at early 200-500 and late 500-800 ms windows.

2.3.5

A 2 (Cue: A vs. B) x 3 (Delay: unknown vs. known short vs. known long) ANOVA structure would have confounded delay length and delay knowledge differences. A lack of cue x delay interaction in a 2x3 ANOVA may fail to identify important differences elicited by different known delay lengths, or between unknown delay and a single known delay condition.

Supplemental Results:

3.1.1
DPX Accuracy and Reaction Time

Collapsing across delay conditions, overall accuracy for each cue-probe combination is as follows: AX=96.9% +/- 2.0%; AY=81.2% +/- 9.4%; BX=92.9% +/- 7.0%; BY=97.6% +/- 3.3%.

We evaluated the effects of delay knowledge and length on accuracy for AY, and found no significant effect of delay knowledge ($F(1,35)=.203$, $p=.655$), delay length ($F(1,35)=.496$), or the interaction of delay knowledge x delay length ($F(1,35)=.182$), $p=.673$). BX accuracy was not altered by delay knowledge ($F(1,35)=1.941$, $p=.172$). There was no interaction between delay knowledge and delay length for BX accuracy ($F(1,35)=.015$, $p=.903$). BSI Accuracy did not show significant effects of delay knowledge ($F(1,35)=.211$, $p=.649$), delay length ($F(1,35)=.448$, $p=.510$), nor knowledge x length interaction ($F(1,35)=.229$, $p=.635$).

There were no significant effects of delay knowledge ($F(1,35)=.422$, $p=.520$), delay length ($F(1,35)=1.195$, p=..282), or a knowledge x length interaction ($F(1,35)=1.729$, $p=.197$) for AY reaction time. There were no significant effects of delay knowledge ($F(1,35)=.430$, $p=.516$) on BX reaction time. There was a marginally significant effect of delay length on BX reaction time ($F(1,35)=2.966$, $p=.094$), such that BX reaction time was increased on long delay trials (mean=341.7 ms; sd=114.3 ms)

relative to short delay trials (mean=320.1 ms; sd=82.5 ms). There was no significant interaction of delay knowledge and delay length on BX reaction time ($F(1,35)=.173$, $p=.680$). BSI Accuracy did not show significant effects of delay knowledge ($F(1,35=.858$, $p=.361$), delay length ($F(1,35)=.321$, $p=.575$), nor knowledge x length interaction ($F(1,35)=1.378$, $p=.248$). In summary, our delay knowledge and length manipulations resulted only in a marginal increase in BX reaction time for long relative to short delay trials.

3.2.1

ERP Fixed Effects of Delay and Control Demands

AFz

A 2 (Cue) x 3 (Delay) repeated measures ANOVA for amplitude (400-600 ms) showed main effects of cue type ($F(1,35)=9.056$, $p=.005$) and delay ($F(2,34)=10.112$, $p<.001$). In a 2x2 repeated measures ANOVA for known long versus unknown delay, mean amplitude (400-600 ms) showed a delay knowledge x cue interaction ($F(1,35)=5.280$, $p=.028$) that did not survive Bonferroni correction. AFz mean amplitude did not differ by unknown versus short known timing demands ($F(1,35)=2.367$, $p=.133$). AFz slope also showed no differences by delay knowledge.

In a 2 (Cue: A vs. B) x 3 (Delay: known short vs. known long vs. unknown) repeated measures ANOVA, AFz slope (400-600 ms) showed a significant main effect of cue ($F(1,35)=21.771$, $p<.001$), with a positive slope for A cues and a negative slope for B cues.

In post-hoc tests, we examined fixed effects of delay length and cue type at immediately posterior electrodes Fz and FCz. At Fz, a 2 (Cue) x 2 (Delay: known short vs. known long) ANOVA for amplitude showed that there were no main effects of delay ($F(1,35)=2.847$, $p=.106$) or cue ($F(1,35)=4.870$, $p=.034$), and no delay x cue interaction ($F(1,35)=1.135$, $p=.294$). Similarly at FCz, a 2 (Cue) x 2 (Delay: known short vs. known long) ANOVA for amplitude showed that there were no main effects of delay ($F(1,35)=.515$, $p=.478$) or cue ($F(1,35)=.060$, $p=.809$), and no delay x cue interaction ($F(1,35)=.742$, $p=.395$).

F8

At F8, a 2x2 repeated measures ANOVA on known short versus known long mean amplitude from 400-600 ms shows a main effect of known delay length ($F(1,35)=5.927$, $p=.020$), such that known long delay activity was sustained at a higher amplitude vs. known short delay activity. There was a main effect of cue on slope ($F(1,35)=5.375$, $p=.026$) (A>B). At F8, tests for main effect of cue type and cue x delay interactions on amplitude (400-600 ms) were non-significant (cue $F(1,35)=.216$, $p=.645$; cue x delay $F(1,35)=.428$, $p=.517$).

F8 amplitude did not differ by unknown vs known short ($F(1,35)=.595$, $p=.446$) nor unknown versus known long ($F(1,35)=2.420$, $p=.129$). F8 slope did not differ by unknown versus short known ($F(1,35)=0.347$, $p=.560$) nor unknown versus known long ($F(1,35)=.015$, $p=.902$).

FT7

A 2x2 repeated measures ANOVA on slope from 400-600 ms revealed a main effect of cue ($F(1,35)=6.360$, $p=.016$) (A>B). At FT7, we observed no main effect of delay ($F(1,35)=1.212$, $p=.278$), no main effect of cue type ($F(1,35)=.001$, $p=.974$), and no delay x cue interaction ($F(1,35)=.256$, $p=.616$) on amplitude (400-600 ms). There was no effect of delay or cue x delay interaction on slope (400-600 ms) (delay $F(1,35)=.001$, $p=.975$); cue x delay $F(1,35)=.553$, $p=.462$). FT7 amplitude did not differ between unknown and known short or known long delay, nor did FT7 slope.

3.2.2

ERP Mixed Effects of Impulsivity x Delay and Control Demands

At right pre-frontal F8 (Figure 5B), a 3-way ANOVA on mean amplitude (400-600 ms) shows that impulsivity (bottom vs. top third) conferred a significant cue x delay x impulsivity group interaction ($F(1,24)=4.328$, $p=.048$). For Low (but not High) impulsivity participants, we observe increased sustained activity selective to Long B cues (t-test $p=.029$). However, the 3-way ANOVA did not survive Bonferroni correction.

At left frontal FT7, a 2 (impulsivity: high vs. low) x 3 (delay: unknown vs. known short vs. known long) x 2 (cue: A vs. B) ANOVA revealed a significant impulsivity x delay interaction on slope ($F(2,23)=7.845$, $p=.003$).

3.2.3

Time Frequency

Power

At AFz, a 2 (cue) x 2 (known delay) repeated measures ANOVA of delta/theta power 300-700 ms post-cue revealed a main effect of cue type ($F(1,35)=28.662$, $p<.001$), but no effect of delay or cue x delay interaction. For F8, activity was maximal between 200-700 ms from 3-7 Hz. A 2(cue) x 2 (delay) repeated measures ANOVA revealed a main effect of cue type, but no effect of delay or cue x delay interaction.

At FT7, delta/theta power was significantly different between known short vs. known long delay ($F(1,35)=4.786$, $p=.036$), with greater sustained power for short known vs. long known delay. There was no effect of impulsivity group on delta/theta power.

ITPC

ITPC at medial prefrontal AFz showed a main effect of cue (B>A) ($F(1,35)=13.538$, $p<.001$). At right pre-frontal F8 (Supplemental Figure 4), delta ITPC showed a main effect of cue type (B>A) ($F(1,35)=9.090$, $p=.005$). Also at F8, theta ITPC showed a significant main effect of delay ($F(1,35)=5.695$, $p=.023$), with short delay cues showing greater ITPC relative to long delay cues. At left frontal FT7 (Supplemental Figure 5), delta ITPC showed a main effect of delay length ($F(1,35) = 4.365$, $p=.044$), such that short delay cues showed greater ITPC relative to long delay cues.

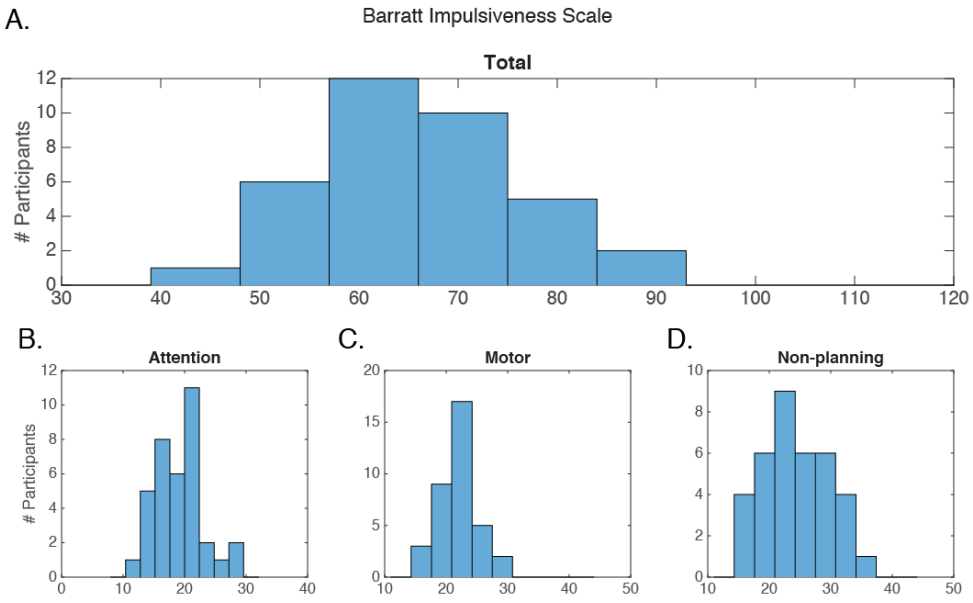
ICPC

ICPC from mid-frontal FCz to left prefrontal FT7 from 400-600 ms, showed a significant main effect of cue ($F(1,35)=4.260$, $p=.047$), and a significant delay x cue

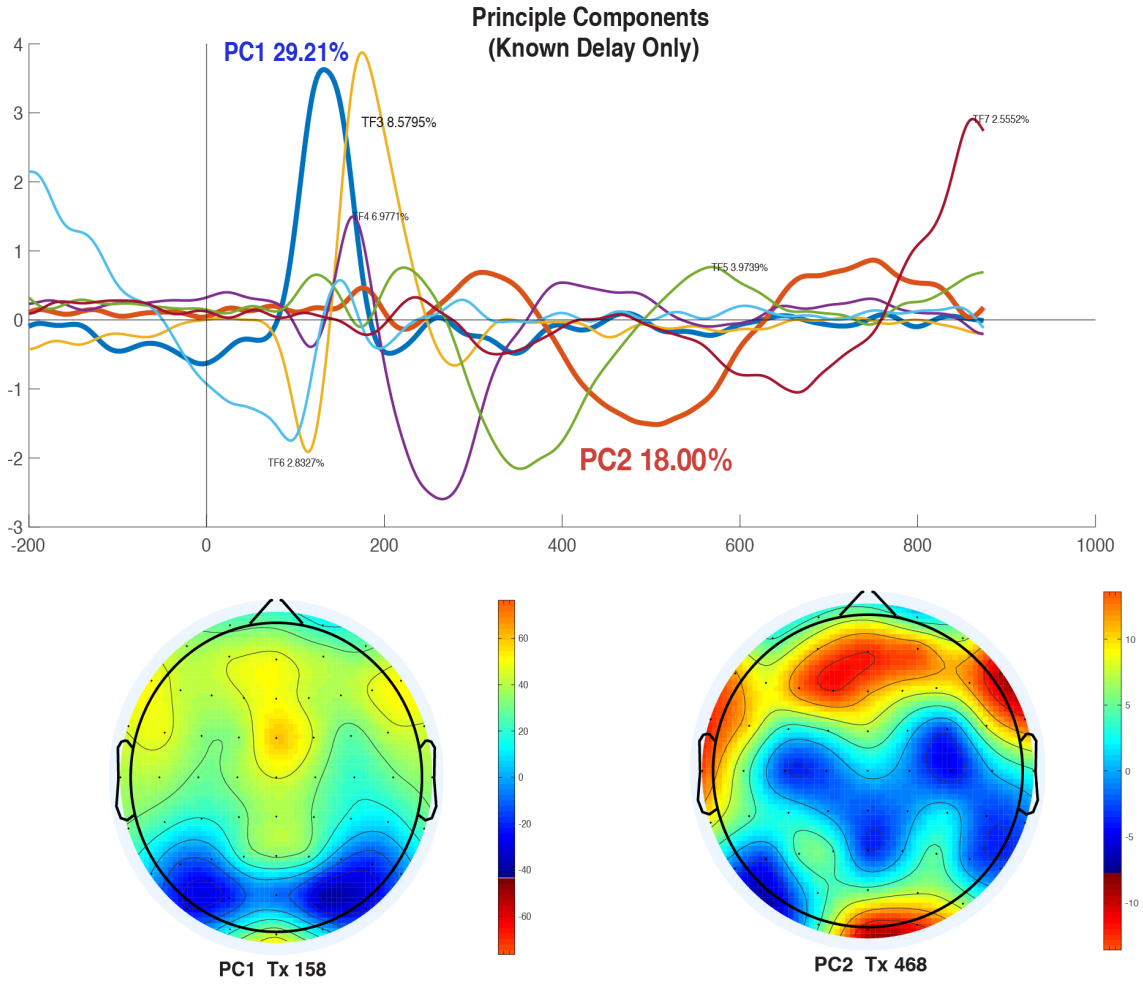
interaction ($F(1,35)=5.595$, $p=.024$). There was also a main effect of cue on FCz:F8 synchrony from 500-800 ms ($F(1,35)=4.895$, $p=.034$).

Supplemental Figures:

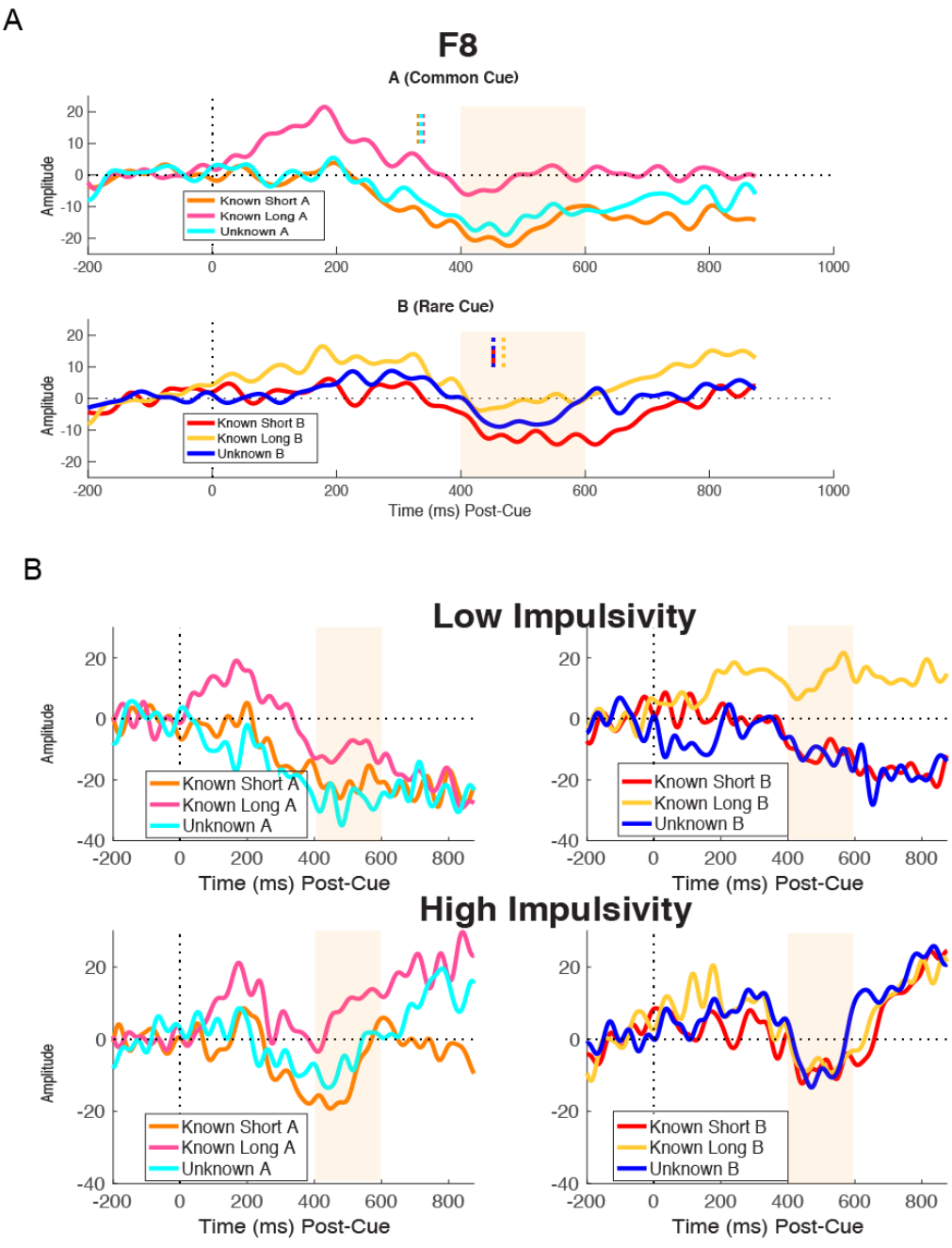
Supplemental Figure 1: Histograms of Barratt Impulsiveness Scores. X-axis scales correspond to the full possible range of scores on that measure. 2A. Total score. 2B. Attention sub-scale. 2C. Motor sub-score. 2D. Non-planning sub-score.



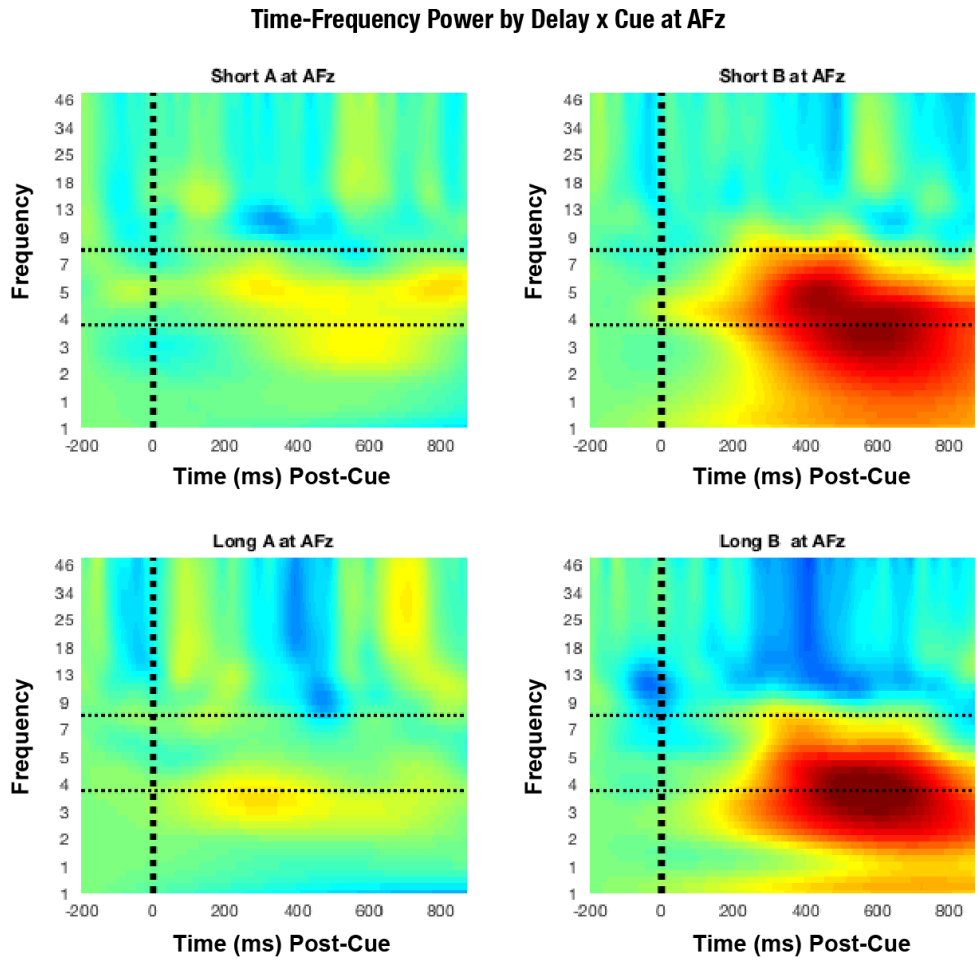
Supplemental Figure 2: Principal Component Analysis of Early Cue-Probe Delay (0-874 ms post-cue) from Known Short and Known Long conditions only. 1A. The top 7 temporal principle components are plotted, along with the percent of variance attributed to that component. Topoplots (inset) depict the maximal regions of activation for that particular component at its peak.



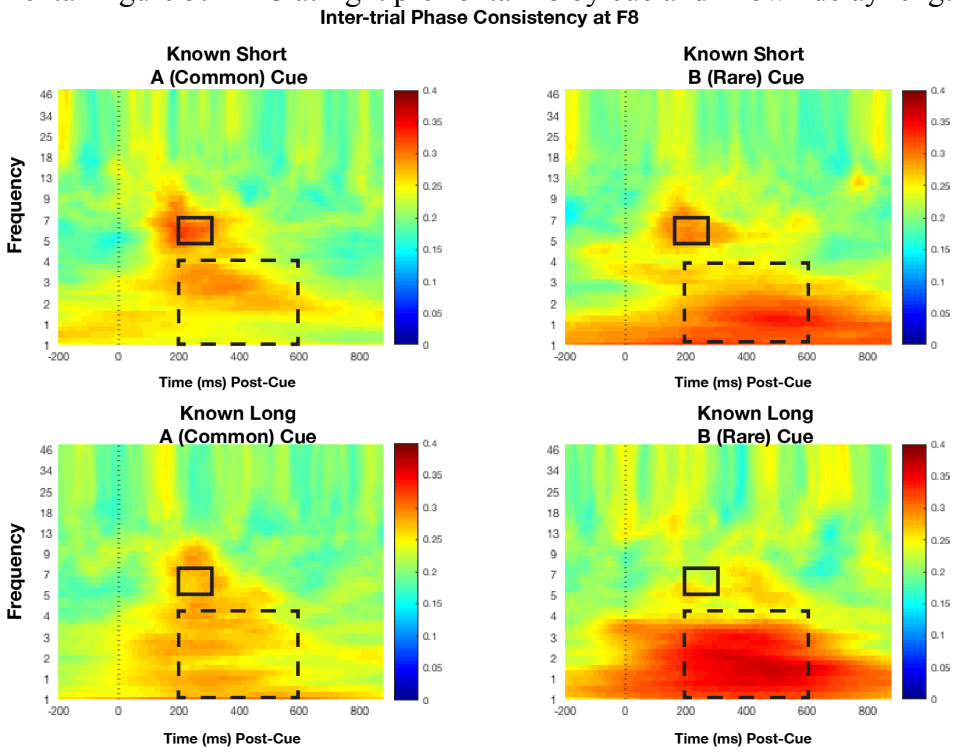
Supplemental Figure 3: Cue-locked Laplacian ERPs at right prefrontal F8.
S3A. ERPs to A cue (upper plot) and B cue (lower plot) by delay condition. S3B. ERPs to A cue (left plots) and B cue (right plots) by trait impulsivity. Groups derived from bottom third and top third of impulsivity scores (BIS-11 Total).



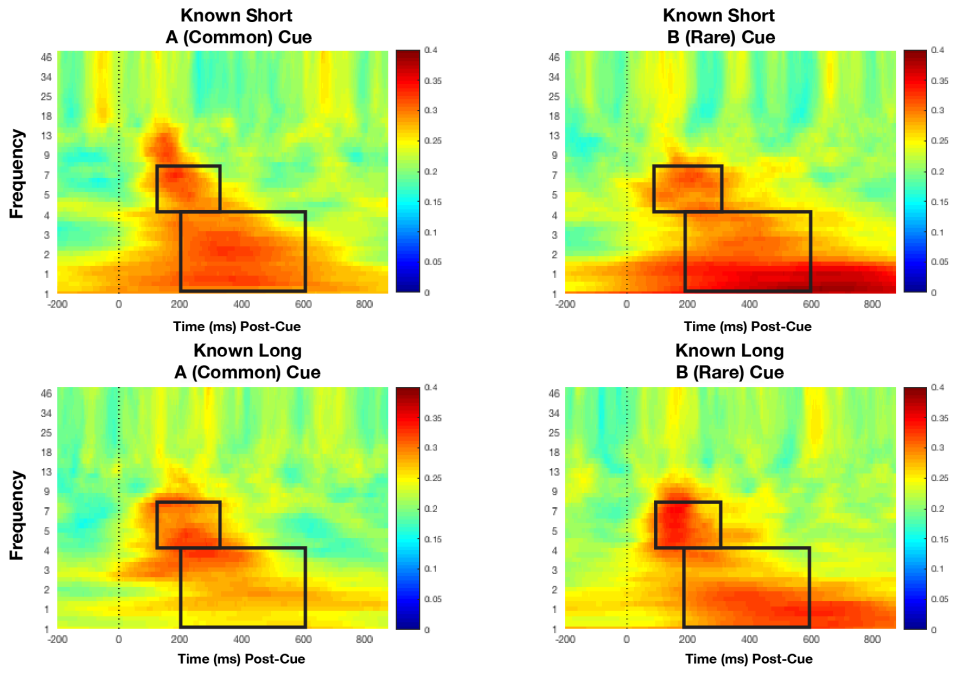
Supplemental Figure 4: Time-frequency power at medial pre-frontal AFz by cue and known delay length.



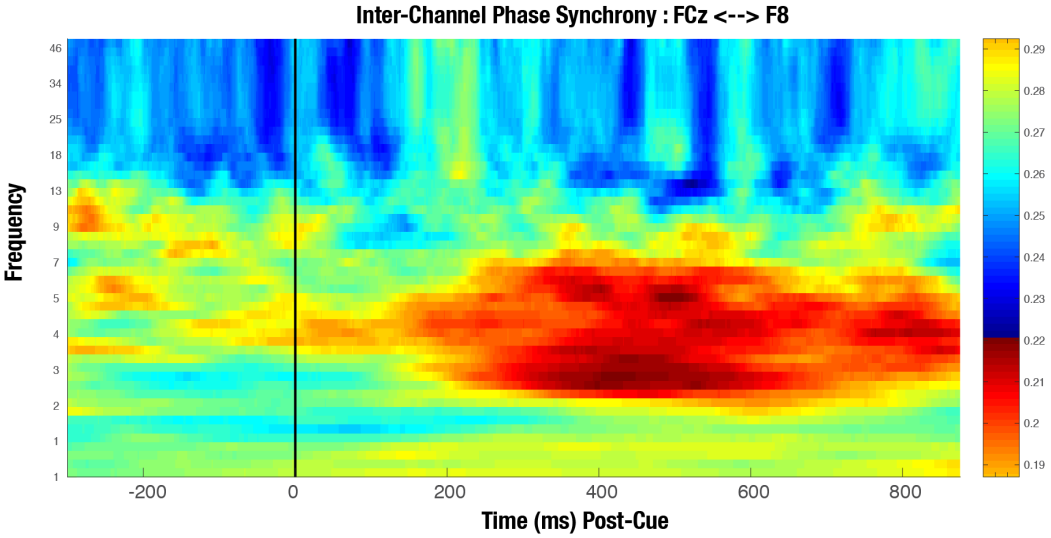
Supplemental Figure 5: ITPC at right prefrontal F8 by cue and known delay length.



Supplemental Figure 6: ITPC at left frontal FT7 by cue and known delay length.



Supplemental Figure 7: FCz:F8 ICPC all-condition average



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