Assessment of Mechanisms Underlying Proactive Inhibition and Switching

by

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ABSTRACT

The ability to inhibit a planned but inappropriate response, and switch to executing a goal-relevant motor response, is critically important for the regulation of motor behaviors. Inhibition and switching could be mediated by various control mechanisms. Proactive control uses contextual information (cues) to plan the response for the target stimulus (probe) based on the expectation of a response inhibition or switching stimulus combination. Previous work has reported the involvement of several brain areas associated with proactive inhibition and switching, e.g., dorsolateral prefrontal cortex, anterior cingulate cortex, inferior frontal junction, and pre-supplementary motor area. However, how these areas interact and their functional role in different types of cognitive control is still debated. An AX-version of the continuous performance task (AX-CPT) was used to examine proactive inhibition and switching of motor actions. In a typical AX-CPT trial, a contextual cue stimulus is presented, followed by a probe stimulus after a specific inter-stimulus interval. As part of a trial sequence, if a target cue and target probe are presented, a target response is to be provided when the probe is observed. Otherwise, a non-target response is to be provided for all other stimuli. A behavioral switching AX-CPT experiment (48 subjects) was conducted to explore the parameters that induce a proactive shift in the motor response. Participants who performed the AX-CPT task with relatively shorter interstimulus interval predominantly and consistently exhibited proactive control behavior. A follow-up pilot study (3 subjects) of response inhibition versus response switching AX-CPT was performed using 256-channel high-density electroencephalography (HD-EEG). HD-EEG was used to identify the time course of cortical activation in brain areas associated with response inhibition. It was

observed that one out of three participants used a proactive strategy for response switching based on probe response error and probe response reaction time. Instantaneous amplitude spatial maps obtained from HD-EEG revealed cortical activity corresponding to conflict between proactively-prepared incorrect responses and reactively-corrected goal-relevant responses after the probe was presented.

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CHAPTER 1

INTRODUCTION

Humans interact with their environment by either executing, inhibiting a movement, or switching from a pre-planned or habitual goal irrelevant movement to a corrected goal-relevant response. These movements can be controlled either using contextual information (proactive) or as a corrective action after an interference event has occurred (reactive). There are two main competing theories attempting to explain the mechanism of proactive control. One of them speculates that there is a sustained goal and response maintenance until the target appears (Braver, 2012). Alternatively, it has been proposed that there could be transient goal activation when contextual cues are recognized, which would further guide the response to be provided for the target (Hikosaka & Isoda, 2010). Additionally, the functions of brain areas and their network associate with proactive and reactive inhibition are debated. The purpose of this study is to assess the neural correlates of proactive inhibition and response switching.

Control of movement: execution and inhibition

The ability to generate movements is critical for our interactions with the environment. However, this ability extends beyond movement *execution*: another equally important ability is movement *inhibition.* Execution involves performing an action, whereas inhibition consists of withholding a habitual or pre-planned response. *"Switching",* a subgroup of inhibition, is denoted by the suppression of a habitual or pre-planned response and its replacement with another appropriate movement. Such switching response could be based on movement execution error, sensory cues acquired

from the environment, task goals, rewards maximization, and/or risk or loss minimization.

Proactive versus retroactive response switching

Response switching could be facilitated by two mechanisms. When a particular action performed within a task results in an error and the individual learns from this error feedback, this leads the individual to further switching his/her action in the future. This behavior is defined as *retroactive switching* (Hikosaka & Isoda, 2010). For example: A grocery store employee may place a heavy item in a bag with limited space. If the bag loses its integrity while handing it over to the customer, the store employee will not place multiple heavy items in a bag in future instances. Conversely, if during the task and *before* an action is performed, the individual realizes his/her planned action is inappropriate based on contextual cues in their environment and therefore changes the action to be performed, this behavior is defined as *proactive* switching (Hikosaka & Isoda, 2010). For example: A grocery store employee could reach towards an item to place it in the bag. However, upon realizing the bag has lesser space and can fit only a small item, he/she might pick up another smaller item from the counter and place it in the bag. He/she may have done this to prevent overflowing of the bag or to prevent it from getting too heavy and losing its integrity when lifted off the counter.

According to Hikosaka and Isoda (2010), anterior cingulate cortex (ACC) monitors and detects conflict between the habitual or preplanned response and task goals, and reduced reward, to drive the error-based negative feedback for facilitating the change of action via the cortico-basal ganglia network (M. M. Botvinick, Carter, Braver, Barch, & Cohen, 2001). Additionally, ACC connections to the lateral prefrontal cortex (LPFC)

appear to mediate the executive role in the retroactive switching process (M. Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999). Functional Magnetic Resonance Imaging (fMRI) studies have revealed that proactive switching seems to be mediated by the pre-Supplementary Motor Area (pre-SMA) due to its role in strong inhibition of body movements and transient activity correlated with competing processes (Dove, Pollmann, Schubert, Wiggins, & Yves Von Cramon, 2000). Subsequent studies have used transcranial magnetic stimulation (TMS) to causally establish the relation between pre-SMA and response inhibition (Rushworth, Hadland, Paus, & Sipila, 2020). Stimulation of pre-SMA using TMS impaired the ability to inhibit responses. Along with pre-SMA, lateral prefrontal cortex (LPFC) has been shown to aid in selective inhibition of movements based on task-relevant goals and rules laid out for the task (Hikosaka & Isoda, 2010).

Proactive versus reactive response inhibition

According to the Dual Mechanism of Control (DMC), there are two main modes by which an action could be controlled, and that are slightly different from the switching mechanisms described above (Braver, 2012). Proactive control refers to a continuous process by which contextual cues are identified and task goals are maintained through the process of preparing for the action. If an individual notices the grocery items at home are beginning to deplete and goes to the grocery store to replenish the stock, this would be an example of *proactive control* of actions. *Reactive control* involves a late-corrective action being performed when a high-interference relevant event occurs which reactivates the task goals (Braver, 2012). If an individual goes to the grocery store only after the stock at home has depleted completely, then it is an example of reactive control.

The DMC framework predicts that proactive control, being a continuous process of task-goal maintenance, must be characterized by sustained anticipatory activity in the LPFC whereas transient activation of LPFC should correlate with reactive control along with activation of other regions of the brain such as ACC for conflict monitoring. Various experimental tasks, combined with neuroimaging techniques, have provided evidence for involvement of different brain areas and corresponding networks in proactive and reactive inhibition (Chiew & Braver, 2017). Specifically, fMRI studies have found strong cue-related activity in dorsolateral prefrontal cortex (dlPFC) in contextually-driven response tasks, e.g., the AX-version of the continuous performance task (AX-CPT)(Braver, Cohen, & Barch, 2009; Chiew & Braver, 2017). Another large fMRI study using the stop-signal task identified a superior parietal lobe (SPL) network exclusive to proactive inhibition, along with a DLPFC/ACC network and a ventrolateral prefrontal cortex (VLPFC), pre-SMA and inferior parietal lobe (IPL) network common to proactive and reactive inhibition (van Belle, Vink, Durston, & Zandbelt, 2014). During no-go and go versions of a stop-signal task, proactive inhibition was correlated with activity in the pre-SMA and right inferior frontal cortex (rIFC) (Aron, 2011). In a TMS stop-signal task study, pre-SMA and inferior frontal gyrus (IFG) were found to be strongly involved in inhibition though TMS administered to pre-SMA during switch signal trials did not significantly impair the responses (Obeso, Robles, Muñoz-Marrón, & Redolar-Ripoll, 2013). In Dias, Foxe, Javitt 2003, the researchers used a 64-channel EEG system while the participant performed various Go/No-go versions of AX-CPT. A P3 and contingent negative variation (CNV) activity was detected at FCz in 350-450 ms latency range after presentation of the no-go cue, which indicates proactive inhibition of the habitual

response in prefrontal cortex (Dias, Foxe, & Javitt, 2003). However, as they used only a 64-channel EEG system, they could not infer the extent to which pre-SMA and dlPFC contributed to the Event Related Potentials (ERPs).

The AX-Continuous Performance Task

The AX-Continuous Performance Task (AX-CPT) is a widely used contextually-driven response task used to study control mechanisms associated with response inhibition and switching. Participants are presented with contextual cue stimulus followed by a target probe stimulus after a brief inter-stimulus interval (ISI). The cue guides the response to be provided for the probe based on a set of contextual rules i.e. task goals. In behavioral and electroencephalography (EEG) studies of AX-CPT, ISIs are relatively short (~1000 ms; Ball & Brewer 2017; Dias et al., 2003), whereas they are relatively longer in fMRI studies (~2000 ms - 3500 ms; Lopez-Garcia et al., 2016). According to DMC framework, proactive control requires the task goals to be maintained until the appearance of the probe (Braver, 2012). Additionally, the response chosen or prioritized based on task goals, cue presented and probe expectancy, needs to be maintained until probe presentation. It has been shown that complex stimulus-response mapping rules combined with high attentional demand and response maintenance in working memory over a relatively longer period of time lead to neglect of the stimulus-response mapping rules, i.e., task goals in AX-CPT (Iveson, Tanida, & Saito, 2016). Hence, the duration of ISI is expected to be crucial in determining the extent to which proactive control can be used by participants. Therefore, it is hypothesized that shorter ISI will lead to participants consistently using proactive control.

Gaps of previous research

Although AX-CPT experiments have used different ISIs according to the task design (e.g., the neuroimaging technique used), there is no research studying the impact of ISI in AX-CPT on proactive control. Additionally, although multiple brain areas have been identified as contributing to different processes, how they communicate with each other, the specificity of their role in the control process, and how they perform these functions remain largely unknown. As noted by Dias et al. (2003), the processes that guide proactive inhibition and switching lie in a short latency range which cannot be captured by certain neuroimaging techniques such as fMRI due to its poor temporal resolution. To address these gaps, we first determined the effect of ISI on response inhibition strategies (proactive versus reactive). Next, we used the results of this behavioral study to design a study where a 256-channel HDEEG system was used to evaluate the proactive inhibition and proactive switching strategies, and corresponding neural correlates during response switching and no-go variations of an AX-CPT task. It is hypothesized that sustained frontal lobe activations will be observed between the presentation of the cue and probe stimulus indicating task goal maintenance (Braver, 2012). Additionally, conflict related activations between proactively prepared response or habitual response and probe stimulus interference will be observed after probe presentation in the AX-CPT task (Dias et al., 2003).

CHAPTER 2

METHODS

Behavioral AX-CPT – Participants

Fifty-eight right-handed (self-reported) native English speakers who were freshmen students at Arizona State University (ASU) participated in the study. The participants (26 males) had no known history of neurological disorders and all had normal to corrected-to-normal vision. All participants were naïve to the purpose of the study and provided their written consent prior to performing the experiment. The participants were compensated with partial credit as part of a course for completing the experiment. Four of the fifty-eight participants could not complete the experiment and the response accuracy for six other participants was less than 75%. Therefore, ten of the fifty-eight subjects were excluded from analysis. The study protocols were approved by the Office of Research Integrity and Assurance at ASU.

Behavioral AX-CPT – Task design

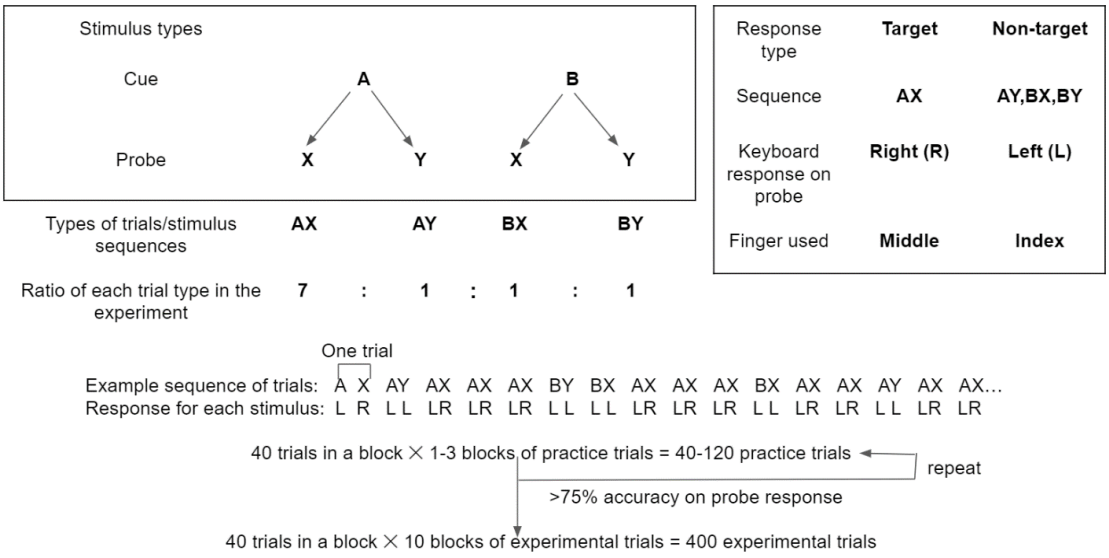
Control mechanisms are critically important for regulation of motor behavior. The participants performed AX-CPT, a contextually-driven response task, which is used to investigate the two types of cognitive control mechanisms: proactive and reactive (Braver, 2012). The task setup involves a computer screen where visual stimuli are displayed, a keyboard for the participant to record their keypress response, and headphones to present audio feedback during the experiment. The experiment was designed using OpenSesame (Mathôt, Schreij, & Theeuwes, 2012). The participant was comfortably seated throughout the experiment.

The task design is shown in Figure 2.1. As part of the AX-CPT task, a sequence of letters appeared on the screen individually and the participant was instructed to respond to each letter by pressing a key on the keyboard as fast as they could. Once the participant responded to a letter, an asterisk (*) replaced the letter until the next visual stimulus appeared. Letters A and B were designated as *cues* that provided the contextual information to guide the response for the subsequent *target* letters X and Y. In each sequence, cues occurred prior to a probe resulting in 4 possible sequences, i.e. AX, AY, BX and BY that could each constitute a trial. These sequences were presented randomly throughout the experiment. If an X is preceded by an A, the participant was instructed to respond by pressing the right arrow button on the keyboard with the middle finger of their right hand (Figure 2.1). This response is denoted as a *target response*. For all other letters presented including the cue, the participant must respond by pressing the left arrow button on the keyboard with the index finger of their right hand. This response is denoted as a *non-target response* (Figure 2.1). Throughout the experiment, a sound was presented as feedback to indicate incorrect response for a letter. Trial type AX (target response sequence) constituted 70% of the experimental trials, whereas AY, BX and BY (non-target response sequences) contributing 10% each, leading to a total number of 400 experimental trials per subject. These experimental trials were equally distributed across 10 blocks of 40 trials each. Each participant was given as much time as he/she wished as a break at the end of each block before starting a new block of trials. Before performing the experimental trials, participants had to complete a minimum of one block of 40 practice trials and attain a minimum accuracy of 75% on the probe letter responses for each trial type. During the practice trials, along with audio feedback for incorrect

responses, visual feedback about their performance was presented by a plus (+) for a correct response and minus (-) for an incorrect response after every letter to facilitate learning of the task.

Figure 2.1

Behavioral AX-CPT task design

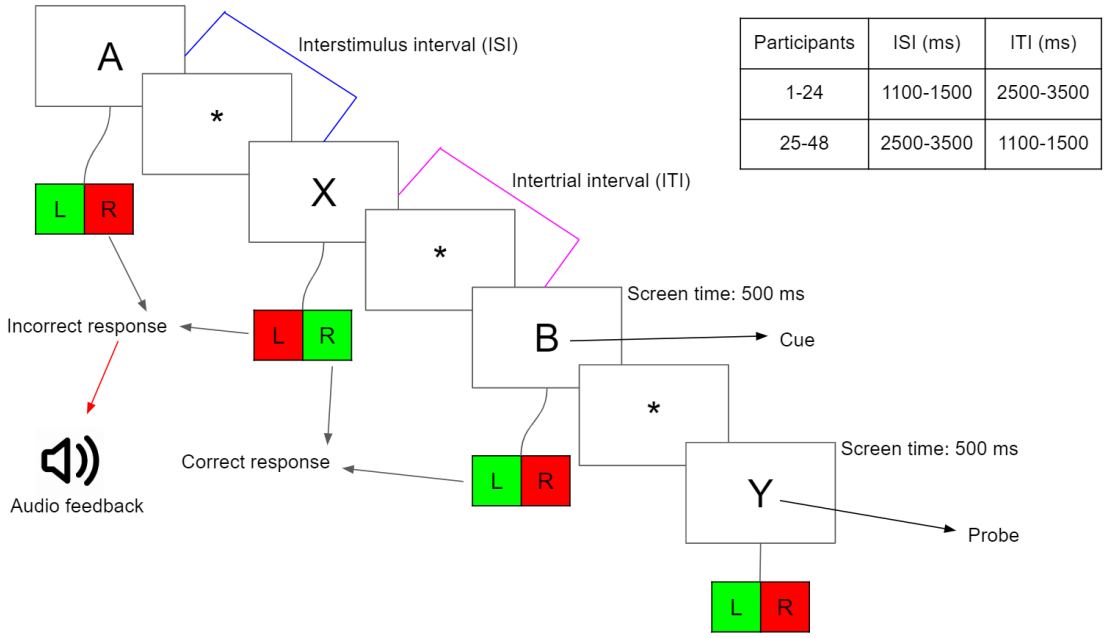


The duration of the epoch between the presentation of a cue and probe is called the *inter-stimulus interval* (ISI), whereas the *inter-trial interval* (ITI) is defined as the epoch between the end of a trial and presentation of the cue on the next trial. To quantify the effects of ISI and ITI on participants' performance, for the first 24 participants we used ISI and ITI that ranged between 1100-1500 ms and 2500-3500 ms, respectively, whereas for the next 24 participants we used opposite ranges of ISI and ITI, i.e., ISI = 2500-3500 ms and ITI = 1100-1500 ms. We used five values at 100-ms increments (1100, 1200, 1300, 1400, and 1500) and presented them an equal number of times in random order during a block of trials to jitter ISI or ITI (first and second group of participants, respectively). A similar design was used for ISI and ITI (second and first

group of participants, respectively) where we used 250-ms intervals (2500, 2750, 3000, 3250 and 3500) that were presented an equal number of times and randomized within a block.

Figure 2.2

Behavioral AX-CPT trial structure



Participants	ISI (ms)	ITI (ms)
1-24	1100-1500	2500-3500
25-48	2500-3500	1100-1500

In the classic AX-CPT task (Locke & Braver, 2008), A and X are consistently designated as the cue and probe, respectively, and constitute the target sequence while letters that are considered the non-target cue and probe, i.e. B and Y could vary between experiments which may confound the effects seen during the AX-CPT task due to biasing subjects' responses towards the letters A and X (Hillyard, Hink, Schwent & Picton, 1973). Hence, during the experiment each participant was presented with a different letter designated as the cue and probe constituting the target and non-target sequences (Table 2.1)

Table 2.1

Probes and cues designated for participants in experiment 1

Sub ID	Cue 1 (A)	Cue 2 (B)	Probe 1 (X)	Probe 2 (Y)
01 & 25	Y	X	B	A
02 & 26	Y	X	A	B
03 & 27	Y	B	X	A
04 & 28	Y	B	A	X
05 & 29	Y	A	X	B
06 & 30	Y	A	B	X
07 & 31	X	Y	B	A
08 & 32	X	Y	A	B
09 & 33	X	B	Y	A
10 & 34	X	B	A	Y
11 & 35	X	A	Y	B
12 & 36	X	A	B	Y
13 & 37	B	Y	X	A
14 & 38	B	Y	A	X
15 & 39	B	X	Y	A
16 & 40	B	X	A	Y
17 & 41	B	A	Y	X
18 & 42	B	A	X	Y
19 & 43	A	Y	X	B
20 & 44	A	Y	B	X
21 & 45	A	X	Y	B
22 & 46	A	X	B	Y
23 & 47	A	B	Y	X
24 & 48	A	B	X	Y

Behavioral AX-CPT – Data analysis

The analysis focused on *(a)* accuracy, *(b)* percentage error, and *(c)* reaction time (RT) of probe response:

(a) **Accuracy**: Response accuracy was defined as the percentage of correct response trials for a given condition, i.e. AX, AY, BX and BY.

(b) **Percentage error**: A trial could be classified as incorrect due to an incorrect probe response, incorrect cue response, early response for the cue, or early response for the probe. We analyzed the contribution of these four types of errors to the overall error rate for each condition across the entire experiment for each participant. It should be noted that the error due to incorrect probe response contributed the most (~80%) to overall error rate. Hence, the rest of the error analysis was performed for trials with incorrect probe response, probe and cue RTs > 200 ms, and correct cue response.

(c) **Probe response reaction time:** The probe response reaction time is the most important parameter because it reveals the strategy, i.e. proactive or reactive, exhibited by participants to complete the task successfully with minimum errors. Shorter probe RTs typically reveal habitual or proactive strategy due to the response prepared in advance based on contextual cue recognition and probe expectancy while longer RTs indicate a late corrective reactively prepared response. Probe reaction time is defined as the amount of time required for the participant to execute the response after they have provided with the cue.

Responses with RTs less than 200 ms were considered anticipatory responses as it is quite likely that the participant executed a prepared response without even observing the

stimulus presented. Hence, trials with RTs less than 200 ms to the cue, probe or both were omitted from the analysis. Furthermore, we excluded trials with incorrect cue responses from analysis as these denote participants' failure to perceive or interpret the cue. In these cases, even if participants had responded to the probe correctly as it might have been just a matter of chance. Hence, a correct trial was defined as a trial with a correct cue *and* probe response with a response time for each longer than 200 ms. The trial responses and RTs were extracted for AX, AY, BX and BY conditions to be analyzed separately.

Data analysis was performed using MATLAB. All the parameters described above were calculated and averaged for each condition for each participant and across participants. To observe change in strategy (proactive or reactive) utilized across the experiment the parameters were averaged considering successive blocks one at a time (running average) i.e. blocks 1 and 2; blocks 1, 2 and 3; blocks 1, 2, 3 and 4, and so on. The probe response error of participants from group 1 with shorter ISI, i.e. first 24 participants and the participants from group 2 with longer ISI i.e. 25-48 participants, were averaged to obtain two population average probe response error to assess the effects of ISI.

Before quantifying the strategy utilized by participants in the AX-CPT task, the error rate was corrected by adding 0.5 to the total number of errors, adding 1 to the total number of usable trials, and dividing them to obtain the corrected error rate for each trial type of a participant. The proactive behavioral index (PBI) was computed using error rates and probe RTs as (AY-BX)/(AY+BX) for each parameter. The composite PBI was obtained by averaging the error and RT based PBI for individual subjects. A positive PBI

indicates that the participant predominantly used proactive control throughout the task while a negative PBI reveals reactive control strategy used to perform the AX-CPT task. Furthermore, z-scores of the AX hits, BX false alarms, and AY false alarms were calculated (Gonthier, Macnamara, Chow, Conway, & Braver, 2016). The d'-context is Z[H(AX)]-Z[F(BX)] while A-cue bias is calculated as 0.5*(Z[H(AX)]+Z[F(AY)]) where Z[] is the z-score of the quantity, H() denotes the hits for the condition, and F() is the false alarm for the condition. A-cue bias, d'-context and PBI were averaged across participants within a group to quantify the strategy predominantly exhibited by each group.

One-tailed t-test was performed on group averaged A-cue bias, d'-context and PBI for determining the significance of the group results. Additionally, two-tailed t-test was performed on the AX-CPT statistical quantities to explore the difference between the predominant strategy used by the two groups.

Behavioral AX-CPT – Predictions

As the percentage of AX trials is very high (70%), the participants should develop a habitual tendency towards the target response which they need to override 10% of the time each for the AY, BX and BY trials. This could be executed either based on the cues displayed (proactive) or after the probe is displayed based on the combination of the cue and probe sequence in the trial (reactive). Due to this habitual response, we would expect few probe and cue errors *and* fast probe response RTs on the AX trials. We would see a similar effect on the BY trials as no matter which strategy the participant adopted, he/she will typically perform well on these trials as they consist of the non-target probe *and* non-target cue. Hence, BY is considered the *control condition* throughout the experiment. If a

participant is adopting a proactive strategy as a 'default' during the experiment and prepare their response based on the cue, the error rates, and the probe response RT for BX trials, should be lower than that for AY trials. However, error rates and probe response RT should be greater for BX trials than BY and AX trials, as they involve a change of response relative to what would be typically expected while withholding a habitual response associated with probe X conditioned by the cue A. Also, RTs and error rates for the AY trials must be greater than all conditions when the participant is provided with the "A" cue because he/she is conditioned to prepare an incorrect target response for the probe Y. When a participant follows a reactive strategy, the response for the AX and BY trials are expected to be similar to those as exhibited while using proactive control i.e. less errors and short RTs. However, as subjects focus on the probe more than the cue, they are bound to make more errors on the BX trials and respond slower to those trials than in AY trials.

High-density EEG studies of AX-CPT – Background

Humans control movements to perform tasks in their daily life by either inhibiting a planned action or executing it. In addition, actions can be performed by simultaneously inhibiting a predetermined or habitual response while executing another movement, this phenomenon being referred to as *switching response* (Kenner et al., 2010). This is observed during the AX-CPT task when the AX-driven habitual response is overridden to perform a non-target response during the other conditions, i.e. AY, BX and BY. Therefore, there is a possibility that the brain signals associated with response switching could consist of components associated with response inhibition and execution. During the AX-CPT task designed for response inhibition, it is challenging to determine whether

subjects adopt a proactive or reactive strategy due to lack of RTs and unreliable error rates associated with inhibition. Hence, we used high-density electroencephalography (HD-EEG; 256 electrodes) to compare brain signals associated with response inhibition and response switching during performance of the AX-CPT. The rationale for using HD-EEG is that it allows for better source localization of brain signals than lower-density electrode arrays (i.e., 64 or 128).

High-density EEG studies of AX-CPT – Participants

Three right-handed (self-reported) native English speakers who were students at Arizona State University (ASU) participated in the pilot phase of this experiment. The participants had no known history of neurological disorders and all had normal to corrected-to-normal vision. All participants were naïve to the purpose of the study and provided their written consent prior to performing the experiment. The participants were compensated with a monetary amount for completing the experiment. Due to line noise in the EEG data and system limitations, only one participants data was analyzed and is presented in the results for this experiment. The study protocols were approved by the Office of Research Integrity and Assurance at ASU.

High-density EEG studies of AX-CPT – Electrode positioning

Prior to the experiment, T1 structural MRI volumes of the participants were obtained using a 3D MPRAGE sequence (TR = 2300 ms, TE = 4.5 ms, 1 x 1 x 1.1 mm^3 voxels, field of view 240 x 256 mm^2, 180 sagittal slices) in a Philips Ingenia 3T scanner with a 32-channel head coil to co-register electrode placement for source localization analysis. These scans were obtained from another study the participants were previously part of about 2 years ago. The MRI scans were processed using Brainsuite and consisted

of a cortical extraction sequence and surface-volume registration process for labeling different brain regions. The resulting volume was further processed using the BrainSight neuronavigation system (Rogue industries) to mark fiducials in the virtual space which included the nasion, tip of the nose, philtrum, right and left tragus and periauricular notch. During the experiment, registering these anatomical points relative to the MRI scans aided electrode position co-registration. Electrode positions in MNI space were obtained by placing the HD-EEG cap on one of the participants randomly chosen, registering their head to the MRI scan, and manually recording the electrode positions using BrainSight. The resulting electrode positions were used as a template for obtaining electrode positions of other participants by registering their MRIs in MNI space. They were optimized for each participant by registering their head relative to the MRI scans using BrainSight before the experiment using the fiducial landmarks as reference mentioned before.

High-density EEG studies of AX-CPT – Task design

The task setup is similar to experiment 1 (behavioral AX-CPT) experiment described previously (Figure 2.1). An MRI compatible 256-channel EGI EEG system was used to record EEG data at a sampling rate of 1 kHz. During the entire experiment, the impedances were kept below 50 kΩ. Cz was used as reference while recording EEG data. E-Prime (Psychology Software Tools, Pittsburgh, PA) was used to present the stimuli throughout the experiment.

Experiment 2 (HD-EEG AX-CPT experiment) consisted of one session each of no-go AX-CPT and go AX-CPT counterbalanced across participants (Figure 2.5). The HDEEG AX-CPT task design was as described for experiment 1 wherein each trial

sequence consisted of a cue followed by a probe. To prevent stimulus confounds (Hillyard, Hink, Schwent & Picton, 1973), the target sequence cue and probe corresponding to AX in experiment 1 were randomly chosen among the following letters: A, E, G, P, X, F, J and M. Among the six other letters, 3 were randomly chosen as the non-target cues while those remaining were designated as non-target probes resulting in 16 possible trial sequences. For example, if A is the target cue, X is the target probe, E, G and P are non-target cues and F, J and M are non-target probes, then the resulting conditions are as shown in Table 2.2. This creates a stronger bias to conditioning a habitual response towards the target sequence. Irrespective of the stimuli sequence used for a participant, the corresponding trial conditions are denoted as shown in Table 2.2.

Table 2.2

Example stimulus trial sequences

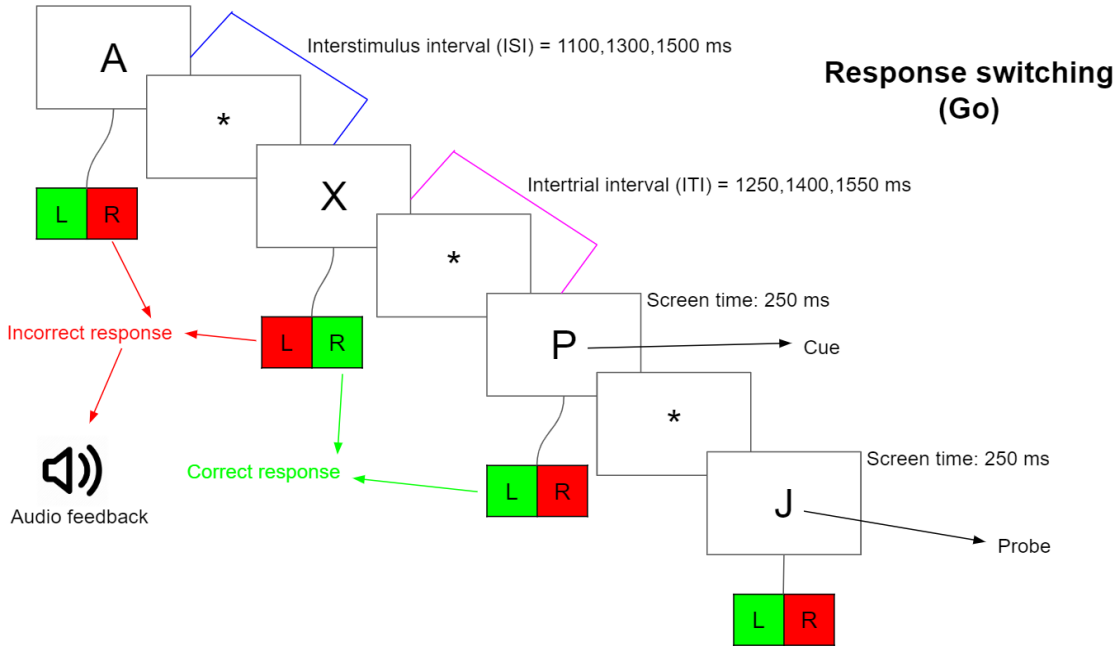
Behavioral AX-CPT		HD-EEG AX-CPT	
Conditions	% trials each	Stimulus sequence	% trials each
Target: AX	70	AX	70
Non-target: AY	10	AF, AJ, AM	3.33
Non-target: BX	10	EX, GX, PX	3.33
Non-target: BY	10	EF, EJ, EM, GF, GJ, GM, PF, PJ, PM	1.11

Unlike experiment 1, during the response switching/go-AX-CPT, responses involve both hands. The task was designed to explore possible lateralized readiness potential (de Jong, Gladwin, & ’t Hart, 2006; Van Vugt, Simen, Nystrom, Holmes, &

Cohen, 2014) which could help quantify control mechanisms in terms of EEG. When a cue or non-target probe is presented during *go-AX-CPT*, the participant is instructed to respond by pressing the non-target key with the index finger of their left hand. A target key was to be pressed with the index finger of their right hand if a target probe was displayed on the screen as shown in Figure 2.3.

Figure 2.3

Response switching (go-AX-CPT) trial structure



In the response inhibition/no-go-AX-CPT session, to maintain uniformity and allow comparison across sessions, the target probe response is same as used in the go-AX-CPT. Inhibition was introduced in the *no-go-AX-CPT* by instructing participants to provide no response when they observed the non-target probe or cue as illustrated in Figure 2.4. For clarity, the information described above is presented in Table 2.3. Audio feedback for incorrect response was provided through the entire experiment.

Additionally, plus (+) and minus (-) visual feedback was presented during practice trials of both sessions for correct and incorrect responses, respectively, to facilitate task learning.

Figure 2.4

Response inhibition (no-go AX-CPT) trial structure

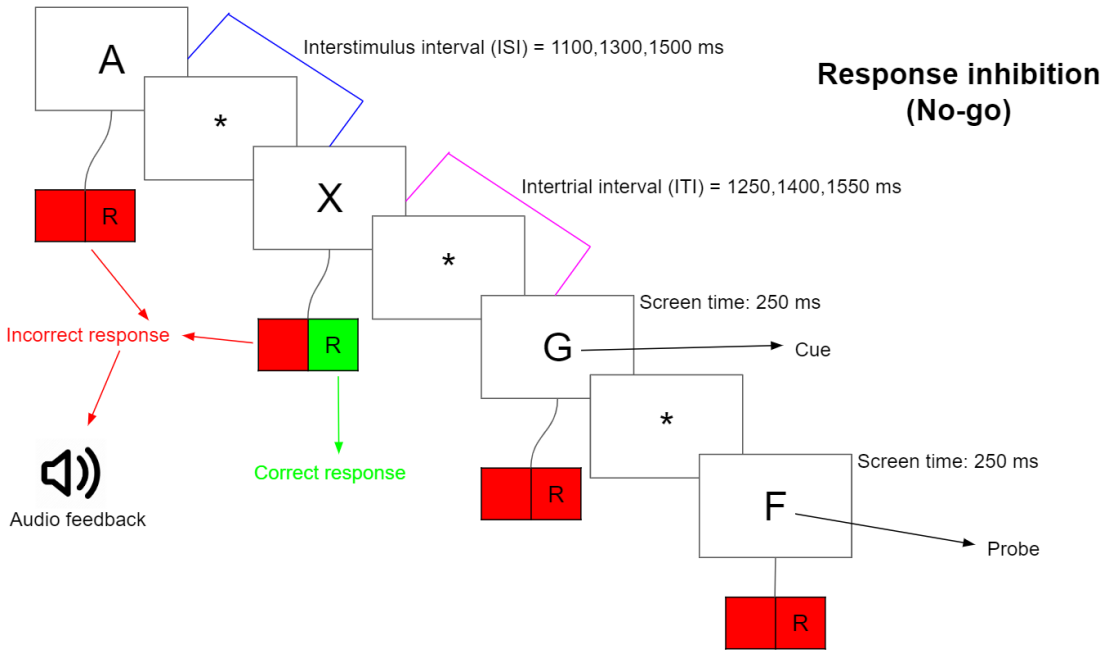


Table 2.3

Responses for stimuli in experiment 2

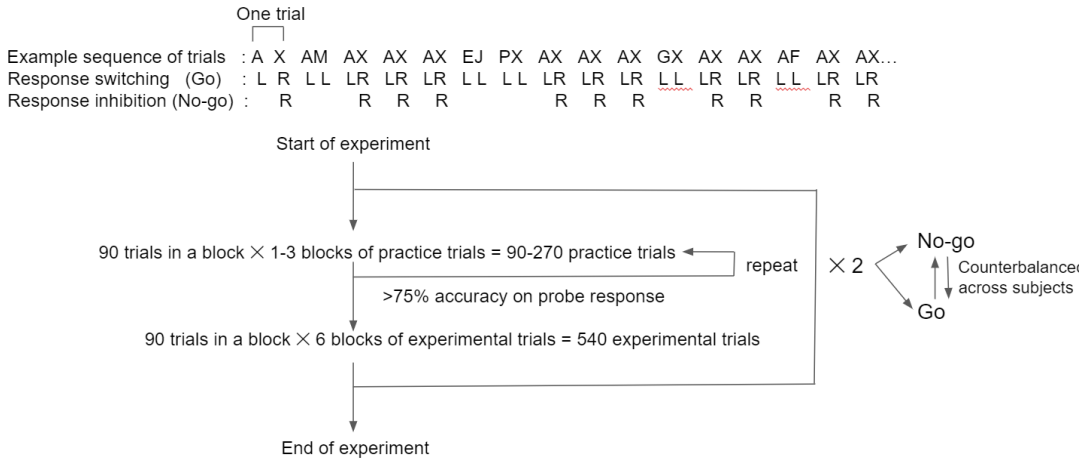
Session Type	Response Inhibition				Response Switching			
Stimulus Type	Target		Non-target		Target		Non-target	
Stimuli	Cue	Probe	Cue	Probe	Cue	Probe	Cue	Probe
Keyboard Response	NR[a]	R[b]	NR	NR	L[c]	R	L	L

[a]No Response. [b]Pressing target key with index finger of right hand. [c]Pressing non-target key with index finger of left hand

During a trial, the cue and probe were presented for 250 ms each. Based on the results of experiment 1 (behavioral response switching AX-CPT), we determined that group 1 exhibited increased and consistent proactive control. Hence, we used the same ISIs used for Experiment 1 with random jitter (1100, 1300 and 1500 ms) uniformly distributed within a block. Similarly, ITI was uniformly distributed within a block (1250, 1400 and 1550 ms; Figures 2.3 and 2.4). Each block of a session consisted of 90 trials. Six blocks of experimental trials were administered in one session. The participant had to complete at least one block of 90 practice trials, achieve a probe accuracy of minimum 75% to continue through the experimental trials, or else they would have to repeat the practice trials block. Non-time bound breaks were provided between sessions though there was a mandatory break of one minute after alternating experimental blocks.

Figure 2.5

Experiment 2 flow



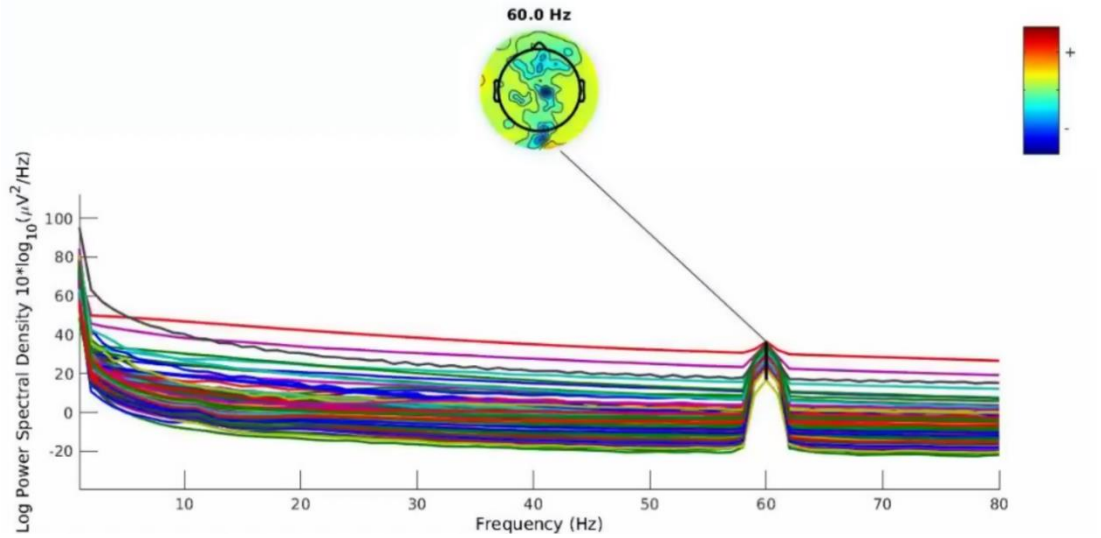
High-density EEG studies of AX-CPT – Data analysis

The behavioral data analysis was performed using MATLAB and focused on accuracy, percentage error, RT of the cue and probe response as described for the experiment 1. As no response is instructed for certain stimuli in the no-go-AX-CPT, RT analysis was not performed for the data obtained for the corresponding experimental trials although the accuracy and probe percentage error were computed as described in section 3.1 (Behavioral AX-CPT – Data analysis).

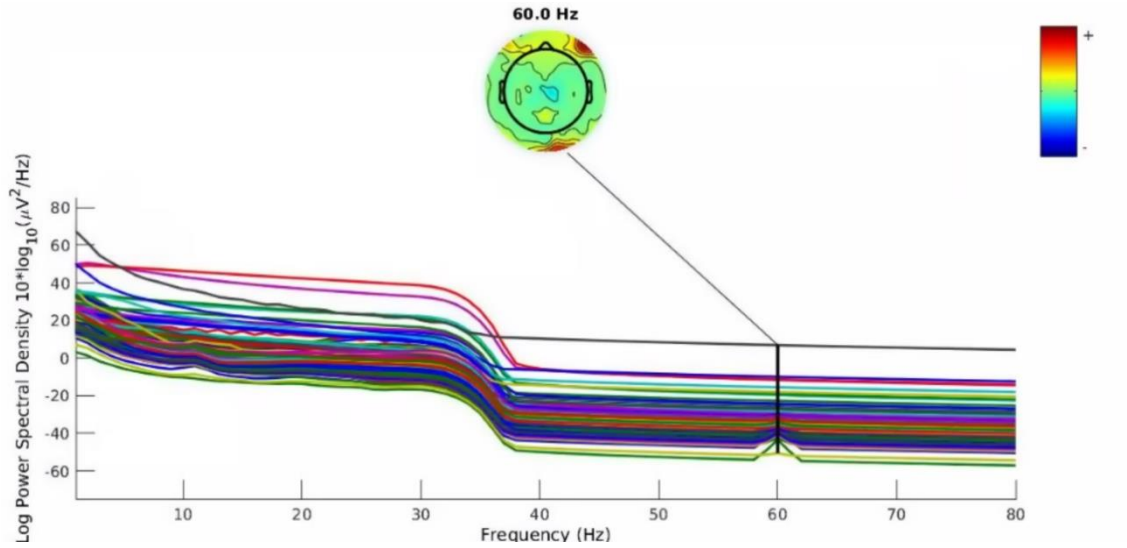
EEG data was processed using EEGLAB and ERPLAB in MATLAB. First, the data was downsampled to 250 Hz and then it was high-pass filtered at 0.5 Hz. 60 Hz line noise was then removed from the data. Furthermore, bad channels were rejected form the data and independent component analysis (ICA) was performed to identify blinks components and other artifacts. Blinks were removed based on the ICA component identified. Bins were assigned to the data to identify and group the correct trials of the no-go and go- AX-CPT and their respective conditions. Epochs were extracted based on the bins assigned and the data was baseline corrected 200 ms before cue stimulus. The epochs were then referenced based on the probe stimulus. The resulting data was then low pass filtered at 30 Hz. Moving-window peak to peak based artifact rejection was performed and the bad electrodes were interpolated. Average referencing was then performed. Eventually, the ERP signals and scalp maps were obtained by averaging across trials within the same bin. Figure 2.6 displays the spectral maps and frequency component of subject 3 data before and after processing.

Figure 2.6

Power spectral density of the EEG data of subject 3



Raw data of participant



Data post processing using EEGLAB

CHAPTER 3

RESULTS

Behavioral AX-CPT results

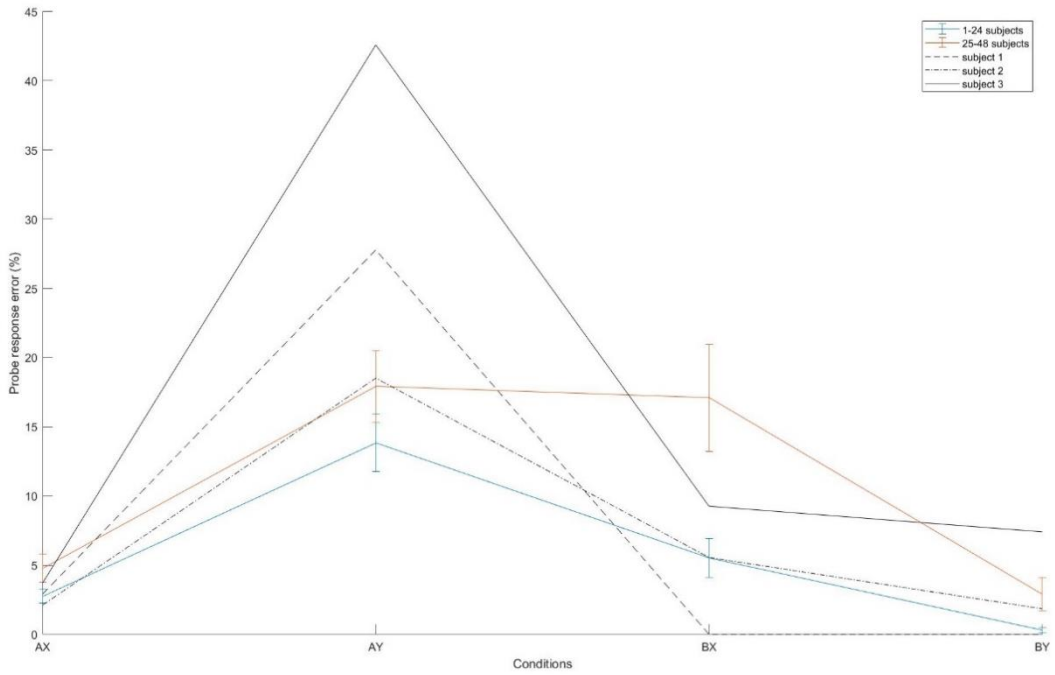
Ten subjects were excluded for the data analysis as either they could not complete the experiment or had high probe response error rates (> 70%) for individual conditions of the AX-CPT task. This could suggest their failure to understand or comply with the instructions provided prior to the experiment. Therefore, the final sample used for data analysis consisted of 48 participants.

If the participant predominantly used proactive control strategy, it would be expected that the error rate associated with the AX trials would be relatively lower than AY and BX trials. At the same time, as there is a small expectancy-based error associated with the probability of an A followed by a Y (10%), AX trials would have an error rate greater than BY trials. Proactive control enables the participant to prepare an anticipatory response based on the cue. This makes it extremely difficult to override the habitual target response induced by high percentage of AX trials and enable a non-target response for the AY trials. This is expected to result in high probe response error rates on AY trials. Meanwhile, the probe response error rate for the BX trials is expected to be lower than for AY trials. Specifically, and irrespective of the strategy participants use, i.e., proactive (cue-dependence) or reactive (probe-dependency), the probe response error is expected to be lowest for BY trials because both cue and probe guide a non-target response irrespective of the condition. Note that the probe error rates will be reversed in reactive control relative to proactive control due to probe-dependence response.

All of these expectations for proactive control were met more consistently by group 1 relative to group 2 (figure 3.1).

Figure 3.1

Average probe response error rate of subjects from experiment 1



Note: Subject probe response error of 3 representative subjects (black lines) from pilot experiment 2 for comparison.

It can be observed from figure 3.2 that the probe response RTs associated with AX and BY trials are similar irrespective of the strategy used by the participant as AX is a habitual response while in BY trials, the cue and probe guide non-target response irrespective of the condition. As high probability of AX trials leads to forming a habitual response, relative slowing down (higher RT) in AY trials is indicative of proactive control. For the same reason, the BX trials are relatively faster. If the participant had used

reactive control, the relative difference between probe response RTs for AY and BX trials would be expected to be reversed.

Figure 3.2

Average probe response RT of subjects from experiment 1

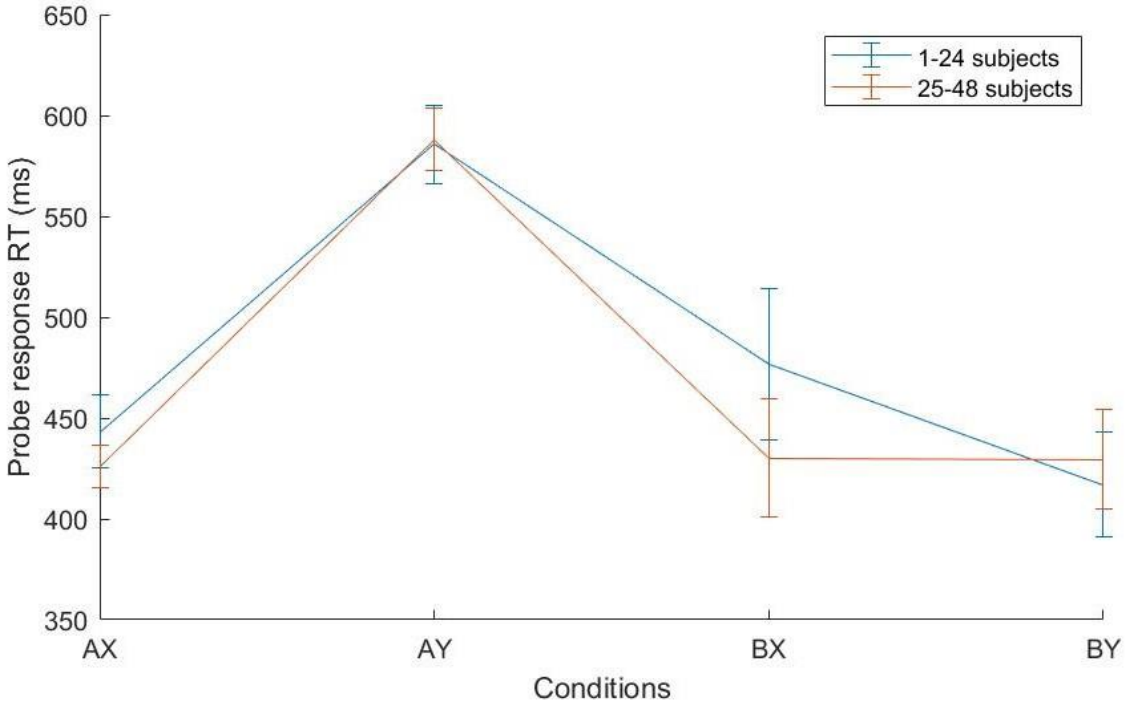


Table 3.1

AX-CPT statistical quantities

Computed across/Quantity	A-cue Bias	d'- context	PBI error	PBI probe RT	Composite PBI
1 to 24 subjects	**.893(.140)**	.535(.291)	**.299(.098)**	**.112(.029)**	**.206(.059)**
25 to 48 subjects	**.988(.140)**	**.714(.268)**	.105(.112)	**.134(.026)**	.119(.065)
p-value	.632	.653	.197	.582	.331

Note: A-cue bias, d'-context, probe error based proactive behavioral index (PBI), probe RT based PBI and composite PBI averaged across group 1: shorter ISI (1^{st}-24^{th} subjects) and group 2: longer ISI (25^{th}-48^{th} subjects) with standard error in parentheses (Row 1 and Row 2). P-value of between the groups t-test for each of the statistically quantities mentioned (Row 3). Values in bold denote statistically significant values (see text for details).

A-cue bias indicates the tendency of participants to make a target response following the probe in an A-cue based trial (AX or AY) irrespective of the probe displayed (Richmond et. al 2015). This reflects the extent of response habituation created by the high probability of AX trials. It is calculated as 0.5*(Z[H(AX)]+Z[F(AY)]) where H() denotes the hits for the condition, F() is the false alarm for the condition and Z[] is the z-score as presented in figure 3.3. and figure 3.4 for probe error and accuracy, respectively. The $p < 0.001$ for individual groups indicating the habituation created by AX trials is highly significant for both groups. The ability to use contextual information provided by the cues (A or B) to prepare a response for the probe is captured by d'-context (Barch et al., 2001). It is calculated as Z[H(AX)]-Z[F(BX)] based on AX hits and

BX false alarms derived from the z-scores of the probe error and accuracy presented in figure 3.3 and figure 3.4. The d'-context for the group 1 with shorter ISI is not significant ($p > 0.05$), whereas it is significant for group 2 with longer ISI ($p < 0.05$). Proactive behavioral index (PBI) captures the relative difference of probe error rate and RTs between AY and BX trials (Braver, Paxton, Locke, & Barch, 2009). It is computed at (AY-BX)/(AY+BX) for error rates and probe RTs and then the resulting values are averaged to obtain composite PBI. The PBI values of individual subjects of group 1 and group 2 are presented in table 3.2 and table 3.3, respectively. RT based PBI for both groups is high significant as $p < 0.001$. Error-based PBI and composite PBI for group 1 with shorter ISI is significant as $p < 0.05$ while it is not significant for group 2 with longer ISI. Hence, shorter ISI (1-1.5 s) were chosen for the design of the experiment 2. We found no between-group significant difference for the above-described measures.

Table 3.2:

Proactive Behavioral Index (PBI) of subjects of group 1(shorter ISI) from experiment 1

Subject ID	Probe error based PBI	Probe RT based PBI	Composite PBI
1	-0.5	-0.029	-0.264
2	-0.179	-0.096	-0.137
3	0.154	0.073	0.114
4	0.721	0.043	0.382
5	0.8	-0.01	0.395
6	-0.319	0.03	-0.145
7	0.909	0.247	0.578
8	0.222	0.341	0.282
9	0.291	-0.072	0.11
10	0	0.071	0.035
11	-0.562	-0.117	-0.34
12	-0.297	-0.06	-0.179
13	0.417	0.186	0.301
14	-0.167	0.084	-0.042
15	0.889	0.089	0.489
16	-0.012	-0.046	-0.029
17	0.919	0.203	0.561
18	0.4	0.169	0.284
19	0.928	0.199	0.564
20	0.566	0.28	0.424
21	0.542	0.215	0.378
22	0	0.258	0.129
23	0.678	0.25	0.464
24	0.786	0.372	0.579

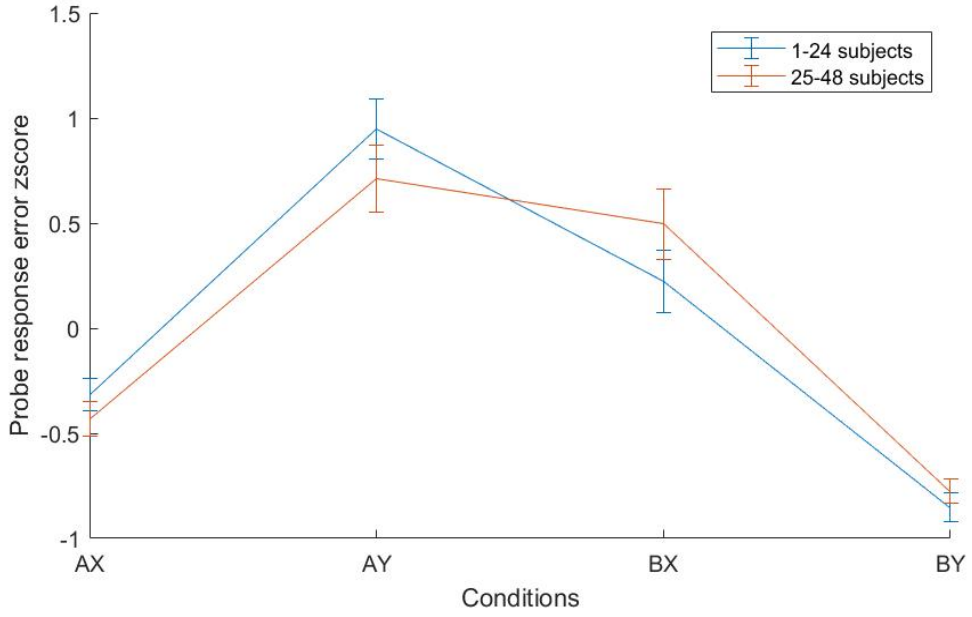
Table 3.3:

Proactive Behavioral Index (PBI) of subjects of group 2 (longer ISI) from experiment 1

Subject ID	Probe error based PBI	Probe RT based PBI	Composite PBI
25	0.693	0.198	0.446
26	-0.234	0.042	-0.096
27	-0.364	0.066	-0.149
28	0.125	0.125	0.125
29	0.796	0.179	0.487
30	-0.5	-0.068	-0.284
31	0.857	0.112	0.485
32	0.75	0.295	0.523
33	0.348	0.166	0.257
34	0.928	0.15	0.539
35	0.201	0.378	0.29
36	0.16	0.082	0.121
37	-0.271	0.04	-0.115
38	-0.954	-0.013	-0.484
39	-0.118	0.074	-0.022
40	-0.625	-0.019	-0.322
41	0.272	0.276	0.274
42	-0.364	0.221	-0.071
43	-0.238	0.005	-0.116
44	0.075	0.196	0.135
45	-0.154	-0.054	-0.104
46	0.66	0.367	0.513
47	-0.465	0.082	-0.191
48	0.94	0.304	0.622

Figure 3.3:

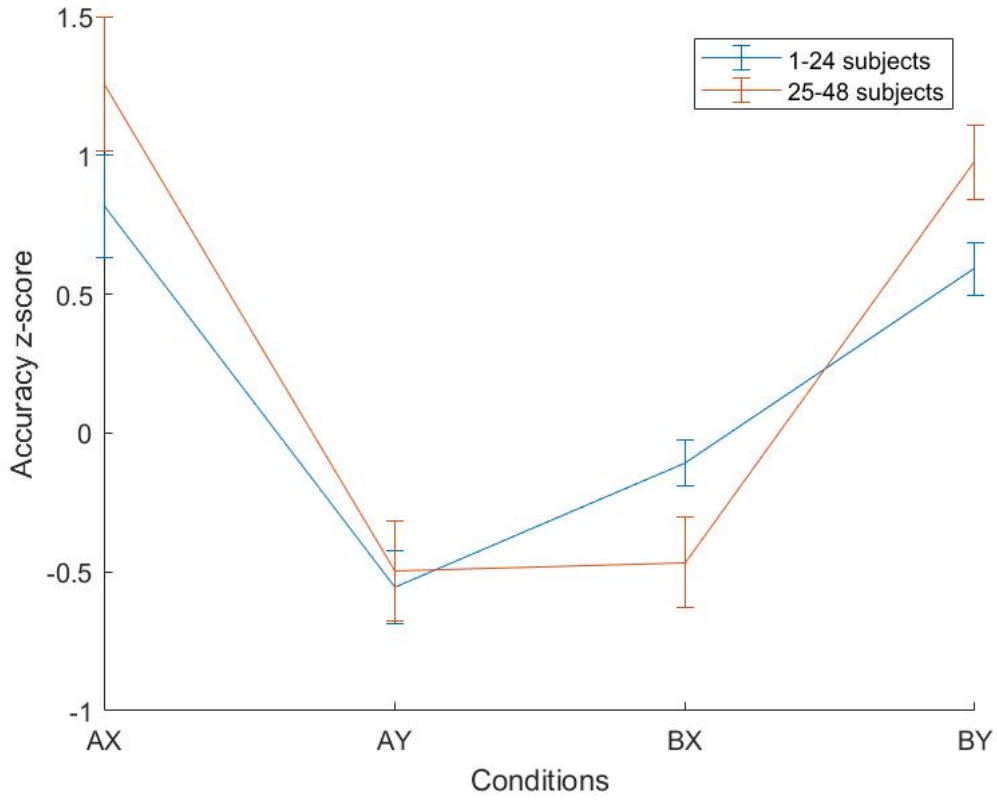
Average probe response error z-score of subjects from experiment 1



Recognition of the contextual cues triggers task goals which are required to be maintained till the appearance of the probe (Braver, 2012). Based on the significant values obtained for proactive control exhibited by group 1, it appears that ISI is crucial in eliciting a proactive control strategy. To address the neural mechanisms underlying proactive control, we used the same ISIs used for group 1 for the experiment 2 (HD-EEG AX-CPT experiment), i.e., 1100 ms -1500 ms.

Figure 3.4

Average accuracy z-scores of subjects from experiment 1



High-density EEG studies of AX-CPT results

The probe response error of individual participants of the pilot experiment 2 is displayed in figure 3.1. As described in the previous section, the pattern of probe response error rate reflects the extent to which participants use a proactive control strategy. However, only one out of three subjects (#3) exhibited proactive control strategy (figure 3.5). This is in contrast to the findings of experiment 1, where it was found that ~75% of participants in group 1 exhibited proactive control. For subject 1, the median probe response time for AY, BX and BY trials were lower than AX trials. For subject 2, the median probe response time for AY and BX trials were the same while that for the

BY trials was slightly higher. Hence, EEG data was analyzed only for subject 3 and the results are presented in figure 3.7.

Figure 3.5

Subject probe response RTs for motor-response switching from experiment 2

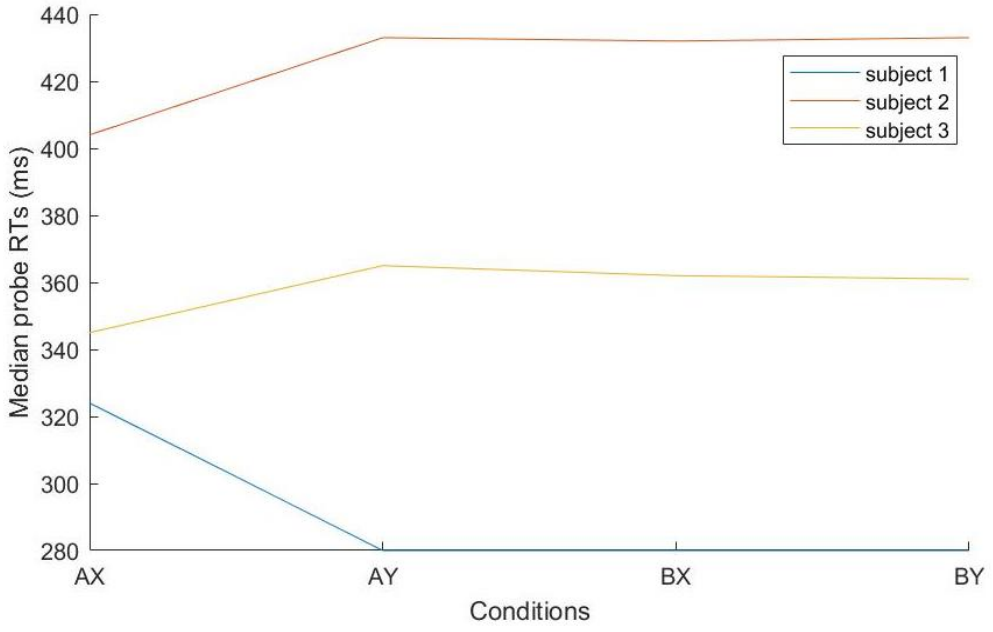
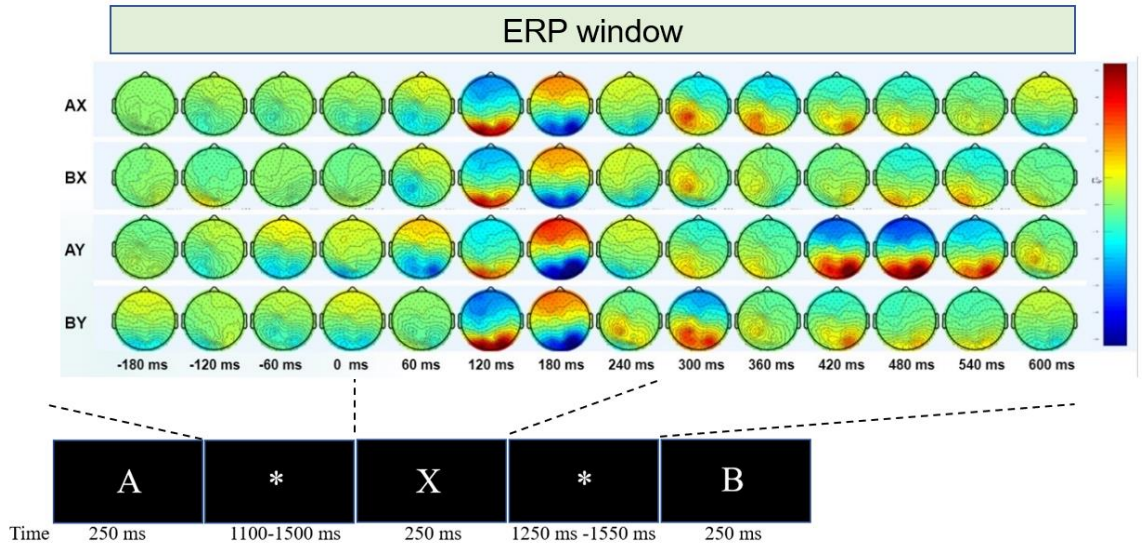


Figure 3.6

Instantaneous amplitude EEG scalp maps of subject 3 for motor switching from experiment 2



As it can be observed from figure 3.6, after presentation of the probe there is a characteristic posterior activation associated with observation of the probe at 120 ms followed by a strong frontal lobe activation at 180 ms which indicates processes associated with controlling actions and deciding the response for the probe. It is observed that for the AY trials, there is relatively more frontal lobe activity than the other conditions indicative of strong conflict recognition. A strong activation around 420 ms after probe presentation observed in the posterior region for AY trials but after the probe response has been provided. The BY trials display a similarly shaped activation around 300 ms after probe presentation but before the probe response is provided. AX and BX trials display similarly shaped activations in the posterior region around 300 ms after probe presentation but before the probe response is provided. It is speculated that these activations observed are related to the probe interference with the proactively planned

response in the AX, BX and BY conditions. While in the AY trials, it is related to probe interference with the reactively planned response. This is speculated because the nature of activations in the similar probe interference trials i.e. AY and BY (Y-probe interference) and AX and BX (X-probe interference) have similar shapes. Additionally, the timing associated with these interferences are similar for proactively controlled probe responses i.e. AX, BX and BY but they occur at a different time for the reactively controlled response i.e. AY. To confirm these speculations, these experiments need to be repeated with a bigger sample of subjects.

CHAPTER 4

DISCUSSION AND CONCLUSION

Proactive control mechanisms

During proactive control, task goals are activated when contextual cues are observed. Based on probe stimulus expectancy and task goals, response(s) is prioritized and prepared in advance. Response(s) and task goals are required to be maintained during the ISI between the cue and the probe. Hence, it was hypothesized that duration of the inter-stimulus interval is crucial to exhibiting the proactive control strategy. EEG and fMRI-based AX-CPT experiment typically use shorter or longer ISI, respectively due to the requirements of neuroimaging studies. However, no research to date has explored how ISI influences proactive control. Additionally, ERP and EEG studies require a high number of trials with consistent performance to be able to observe significant effects. These considerations motivated experiment 1, which was used to explore different versions of the motor response switching AX-CPT.

In the results of the first experiment, no significant differences were observed between groups, but some individual indices of the group were significant as shown in table 3.1. Specifically, error rate of both groups for AY trial were ~15%. This indicates that for a considerable number of AY trials, for which a target response was prepared in advance based on expectation of an X-probe following an A-cue, a corrective reactive mechanism was utilized to respond with a non-target response for the AY trial. Additionally, frontal lobe activity is perceived about ~60 ms (figure 3.6) before the probe occurrence in the AY and BY trials which could be related to task goal maintenance. Also, probe-interference of proactively controlled trials i.e. AX, BX and BY occur

around ~300 ms after probe presentation but before the probe response is performed (figure 3.6). But for the reactively controlled trial i.e. AY, probe-interference occurs after the probe response is executed i.e. ~ 420 ms. These results suggest that the task-goals are possibly maintained over time even after the probe response is executed based on the control mechanism utilized by the participant.

When the participants were observed by the researcher, in multiple AY trials even though the participant had executed an incorrect target response, almost immediately the participant would provide the corrected non-target response. Unfortunately, due to experiment coding software (OpenSesame) limitations, this late-corrected response could not be recorded. Hence, E-Prime (Psychology Software Tools, Pittsburgh, PA) is used in the experiment 2 (HD-EEG AX-CPT experiment).

Longer ISIs led to greater errors in AY trials (figure 3.1). This could indicate that either the late corrective response could not be maintained or there was an increasing difficulty to maintain the late corrective response with longer ISIs. It could also mean that even if the late corrective response were maintained, it could not be executed in a timely manner as the maintenance of task goals could not activate the reactive control to correct the pre-planned response. This suggests that proactive and reactive control are complementary and not exclusive mechanisms. This also suggests a need to investigate EEG-based brain signals in response-corrected AY trials to arrive at meaningful conclusions.

Change in proactive and reactive control strategy was observed between blocks of some participants in both groups. Based on probe-error based PBI, probe RT-based [BI and composite PBI displayed in table 3.2, ~17 participants from group 1 exhibited

proactive control consistently throughout the experiment. On the other hand, ~13 participants from group 2 exhibited proactive control (table 3.3). Additionally, among the data collected from 58 participants, ~8 participants data was rejected due to high error rates. Most of the data that was rejected from the analysis due to high error rates involved the experimental design with longer ISI (~6 participants). Only 2 participants were rejected from group 1. This indicates that performing AX-CPT with longer ISI proactively was relatively more difficult than with shorter ISI. Error-based PBI and composite PBI were significant for group 1 with shorter ISI but it was not for group 2 with longer ISI (table 3.1) which indicates a need to resort to reactive control for increasing efficiency on the task. This implies shorter ISI leads to marginally consistent proactive behavior.

Increasing attentional demands, complex stimulus-response task goals and maintenance of response during ISI influences participants to neglect the task goals and resort to reactive control (Iveson et al., 2016). Additionally, in the experiment 1 manipulation of relatively shorter ITI in group 2 (longer ISI) for maintaining consistent duration of a trial across experiment 1 led to lesser time available for executing probe response. This additional pressure along with other task demands may have further influenced the participant to resort to reactive control. Hence, the decreased use of proactive control by participants of group 2 may not solely be dependent on longer ISI but also shorter ITI.

Eventually, the results of experiment 1 were used to optimize the experimental design that would influence participants to use proactive control to successfully perform the task in most trials. It was observed that having relatively shorter ISI (1-1.5 s)

marginally but significantly influenced more participants to consistently use proactive control while performing the AX-CPT task. Even though shorter ISI did not influence the probe RTs, there was significant change in the error rates which is one of the key measures of proactive control. Hence, shorter ISIs were used in the follow-up HD EEG AX-CPT experiments.

Cortical activity involved with inhibition

During the pilot HD-EEG AX-CPT experiments, strong conflict-based activations were observed in the AY trials in the frontal cortex at ~ 180 ms compared to the other AX-CPT conditions. This possibly indicates a need to inhibit the previously prepared target response based on habitual tendency induced by AX trials. Additionally, after providing the response to the probe at ~ 420 ms there is a strong activation in the posterior region. This possibly indicates the Y-probe interference with the late corrective reactively prepared response. Similarly probe interference is observed in the AX, BX and BY trials before response is executed as the responses were proactively prepared in advance and maintained until they were required to be executed. These results as displayed in figure 3.6 are consistent with the mechanism of proactive control as observed in the literature (Janowich & Cavanagh, 2019).

Future work

Further work is needed to address limitations of the present study. Specifically, a larger sample size (~15 participants) is needed to study the response switching and response inhibition AX-CPT task with 256-channel HD-EEG. This is imperative for obtaining interpretable results using the EEG signals associated with proactive inhibition and response switching.

Multiple areas of the brain that lie close to each other are speculated to be involved in proactive inhibition, such as dlPFC and pre-SMA. Usually 64 channel EEG systems are used for studying proactive inhibition and response switching (Dias et al., 2003). However, due to EEG poor spatial resolution, such electrode layout is not suitable for isolating the source of the brain signals. To address this issue, we recorded EEG activity using a high-density (256) electrode array.

Based on previous ERP studies and our observations of the activation map (fig. 3.6), it is inferred that the signals associated with control mechanisms are of the order of few 100 ms. Therefore, fMRI studies – although helpful in isolating the brain networks associated with inhibition control mechanisms – cannot identify the temporal dynamic of brain area interactions and mechanisms underlying proactive control due their poor temporal resolution (Bickel, Dias, Epstein, & Javitt, 2012). Hence, as part of the next steps of this project, source localization will be performed on the EEG signals obtained which will provide insight into the brain areas and networks associated with proactive inhibition. Eventually, neuromodulation methods such as transcranial focused ultrasound and/or TMS will be used to establish causative role of the different network of brain areas involved in proactive inhibition.

Additionally, lateralized readiness potentials (LRPs) will be used to explore the activation of M1 during the task. This will provide insight in defining the proactive control better in terms of EEG signals associated with it. In general, response inhibition could be either performed be inhibiting all the impending movements or selectively inhibiting undesirable movements while allowing certain others to be performed (Coxon, Stinear, & Byblow, 2007). In theory, response switching could be performed either be

first inhibiting all undesirable impending actions and then planning and executing the required action or by selectively inhibiting the undesirable movement and simultaneously executing a desirable action. At a higher level of control, inhibition and switching could be performed either proactively or reactively. It is speculated that if contextual cues are recognized a prior during the B-cued trials we would expect to see minimal activity in the M1 due to proactive inhibition while in the A-cued trial we would see significant activation of the M1 prior to probe presentation during inhibition. Though based on the primary mechanism associated with response switching, it is expected that there could be transient or sustained activation of M1.

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APPENDIX A

ASU IRB APPROVAL FOR EXPERIMENT 1

APPROVAL: EXPEDITED REVIEW

Christopher Blais

CLAS-NS: Psychology

480/965-759

chris.blais@asu

.edu

Dear Christopher Blais:

On 9/21/2019 the ASU IRB reviewed the following protocol:

Type of Review:	Initial Study
Title:	The neural mechanisms of cognitive control
Investigator:	Christopher Blais
IRB ID:	STUDY00010660
Category of review:	(4) Noninvasive procedures, (7)(a) Behavioral research
Funding:	None
Grant Title:	None
Grant ID:	None
Documents Reviewed:	• Behavioral SONA Consent, Category: Consent Form; • EEG SONA consent, Category: Consent Form; • Sample recruitment, Category: Recruitment Materials; • HRP-503a-TEMPLATE_PROTOCOL_ControlProcessesV02-10-15.docx, Category: IRB Protocol;

The IRB approved the protocol from 9/21/2019 to 9/20/2024 inclusive. Three weeks before 9/20/2024 you are to submit a completed Continuing Review application and required attachments to request continuing approval or closure.

If continuing review approval is not granted before the expiration date of 9/20/2024 approval of this protocol expires on that date. When consent is appropriate, you must use final, watermarked versions available under the "Documents" tab in ERA-IRB.

In conducting this protocol, you are required to follow the requirements listed in the INVESTIGATOR MANUAL (HRP – 103).

Sincerely,

IRB Administrator

cc:

Christopher Blais

Jacob Schuler

Hansol Rheem

APPENDIX B

ASU IRB APPROVAL FOR EXPERIMENT 2 (2019-2020)

APPROVAL: CONTINUATION

Marco Santello

School of Biological and Health Systems Engineering (SBHSE)

480/965-8279

Marco.Santello@asu.edu

Dear Marco Santello:

On 4/4/2019 the ASU IRB reviewed the following protocol:

Type of Review:	Continuing Review
Title:	Neural and behavioral basis of sensorimotor control and learning
Investigator:	Marco Santello
IRB ID:	STUDY00006050
Category of review:	(4) Noninvasive procedures
Funding:	Name: NSF: Directorate for Social, Behavioral & Economic Science (SBE), Grant Office ID: 00014638, Funding Source ID: 1827752
Grant Title:	None
Grant ID:	None
Documents Reviewed:	• Consent Form_Updated.pdf, Category: Consent Form; • Study Recruitment Form.pdf, Category: Recruitment Materials;

The IRB approved the protocol from 4/4/2019 to 3/27/2020 inclusive. Three weeks before 3/27/2020 you are to submit a completed Continuing Review application and required attachments to request continuing approval or closure.

If continuing review approval is not granted before the expiration date of 3/27/2020 approval of this protocol expires on that date. When consent is appropriate, you must use final, watermarked versions available under the "Documents" tab in ERA-IRB.

In conducting this protocol you are required to follow the requirements listed in the INVESTIGATOR MANUAL (HRP-103).

Sincerely,

IRB Administrator

cc: Justin Fine
Scott Boege
Simone TOMA
Marco Santello
Maria Fini
Justin Fine

APPENDIX C

ASU IRB APPROVAL FOR EXPERIMENT 2 (2020-2021)

APPROVAL: CONTINUATION

Marco Santello

School of Biological and Health Systems Engineering (SBHSE)

480/965-8279

Marco.Santello@asu.edu

Dear Marco Santello:

On 3/27/2020 the ASU IRB reviewed the following protocol:

Type of Review:	Continuing Review
Title:	Neural and behavioral basis of sensorimotor control and learning
Investigator:	Marco Santello
IRB ID:	STUDY00006050
Category of review:	
Funding:	Name: NSF: Directorate for Social, Behavioral & Economic Science (SBE), Grant Office ID: 00014638, Funding Source ID: 1827752
Grant Title:	None
Grant ID:	None
Documents Reviewed:	• Consent Form_updated_new.pdf, Category: Consent Form; • Study Recruitment Form_updated_new.pdf, Category: Recruitment Materials;

The IRB approved the protocol from 3/27/2020 to 3/26/2021 inclusive.

Three weeks before 3/26/2021 you are to submit a completed Continuing Review application and required attachments to request continuing approval or closure.

If continuing review approval is not granted before the expiration date of 3/26/2021 approval of this protocol expires on that date. When consent is appropriate, you must use final, watermarked versions available under the "Documents" tab in ERA-IRB.

In conducting this protocol, you are required to follow the requirements listed in the INVESTIGATOR MANUAL (HRP-103).

Sincerely,

IRB Administrator

cc: Archana Shashidhar Mysore

Simone Toma

Marco Santello

Maria Fini

Justin Fine

Jacob Schuler

Yen-Hsun Wu

Jacob Perrine

Catherine Nunez

Michael Ruta