Proactive and Reactive Cognitive Control Rely on Flexible Use of the Ventrolateral Prefrontal Cortex

Running title: Ventrolateral frontal cortex in cognitive control

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Abstract

The role of ventral versus dorsolateral prefrontal regions in instantiating proactive and reactive cognitive control (CC) remains actively debated, with few studies parsing cue versus probe-related activity. Rapid sampling (460 ms), long cue-probe delays and advanced analytic techniques (deconvolution) were therefore used to quantify the magnitude and variability of neural responses during the AX Continuous Performance Test (AX-CPT; N=46) in humans. Behavioral results indicated slower reaction times during reactive CC (AY trials) in conjunction with decreased accuracy and increased variability for proactive CC (BX trials). The anterior insula/ventrolateral prefrontal cortex (aI/VLPFC) were commonly activated across comparisons of both proactive and reactive CC. In contrast, activity within the dorsomedial and dorsolateral prefrontal cortex was limited to reactive CC. The instantiation of proactive CC during the probe period was also associated with sparse neural activation relative to baseline, potentially as a result of the high degree of neural and behavioral variability observed across individuals. Specifically, the variability of the hemodynamic response function (HRF) within motor circuitry increased after the presentation of B relative to A cues (i.e., late in HRF) and persisted throughout the B probe period. Finally, increased activation of right aI/VLPFC during the cue period was associated with decreased motor circuit activity during BX probes, suggesting a possible role for the aI/VLPFC in proactive suppression of neural responses. Considered collectively, current results highlight the flexible role of the VLPFC in implementing CC during the AX-CPT task but suggest large individual differences in proactive CC strategies.

Introduction

The Dual Mechanisms of Control (DMC) theory suggests that cognitive control (CC) is instantiated through either proactive or reactive processes (Braver et al., 2009; Braver, 2012). Proactive CC requires an individual to maintain goal-relevant information over sustained periods of time following an external or internal cue and is therefore metabolically expensive (Braver et al., 2009). In contrast, corrective actions to emergent and potentially competing sensory or motor representations (i.e., reactive CC) may require fewer neuronal resources due to the brief nature of the response (Morishima et al., 2010). It is well known that medial and lateral prefrontal cortex are critically involved in both mechanisms of CC (Niendam et al., 2012; Cavanagh and Frank, 2014; Shenhav et al., 2013; Badre, 2008; Brown and Braver, 2007). However, the exact role of these regions, their associated patterns of neuronal activity (i.e., transitory vs. sustained) and how they are affected by individual differences (i.e., variability in execution) remain actively debated (Irlbacher et al., 2014; Redick, 2014).

The dorsolateral (DLPFC) and ventrolateral (VLPFC) prefrontal cortex, the dorsal anterior cingulate/pre-supplementary motor cortex (dACC/preSMA) and the posterior parietal cortex have all been implicated in different aspects of working memory (Wager and Smith, 2003) and CC (Niendam et al., 2012). A ventral/dorsal split of the lateral prefrontal cortex has been suggested to respectively occur based on selection/judgment of stimuli versus manipulation/monitoring (Blumenfeld and Ranganath, 2007; Petrides, 2005), stimulus properties pertaining to “What” versus “How” (O'Reilly, 2010), as well as for reactive CC versus proactive CC/working memory (Braver et al., 2009). Specifically, preparatory (e.g., cue or context-driven) task demands have primarily been associated with sustained DLPFC activity (Braver et al., 2009; Lesh et al., 2013). Behavioral measures of proactive CC are also correlated with working

memory capacity and fluid intelligence (Kane and Engle, 2002; Redick and Engle, 2011; Redick, 2014), suggesting that they are more variably employed across both healthy individuals and neuropsychiatric patient groups as a function of individual differences (Barch and Ceaser, 2012; Richmond et al., 2015).

In contrast, reactive CC has traditionally been associated with engagement of the VLPFC and dACC/preSMA, as well as with more transient DLPFC activation (Braver et al., 2009; Irlbacher et al., 2014). VLPFC activation during reactive CC tasks occurs during the inhibition of prepotent motor responses (Swick et al., 2011; Aron et al., 2014), the unexpected appearance of salient stimuli (Levy and Wagner, 2011) and the resolution of conflict between competing stimuli (D'Esposito et al., 1999). Similarly, the dACC/preSMA has been typically associated with detecting increases in error likelihood, sensory and/or response conflict (Botvinick et al., 2004; Carter and van Veen, 2007), or a combination of these factors (Shenhav et al., 2013). Although many tasks have been used to examine CC, the AX-CPT task (Cohen et al., 1999) has classically been used to measure both reactive ('AY' trials) and proactive (cues and 'BX' trials) processes in the same experimental framework.

The current study therefore used rapid data acquisition techniques, long cue-probe delays within the AX-CPT task (Paxton et al., 2008; Paxton et al., 2006) and deconvolution to *decouple* the neural responses that occur during cue and probe phases of reactive and proactive CC. Based on previous literature (Paxton et al., 2006; Paxton et al., 2008; Braver et al., 2009), we hypothesized increased and sustained DLPFC activity for cues that predicted upcoming probe status with 100% accuracy (i.e., 'B' > 'A' cues), with DLPFC activity subsequently persisting into probe periods with higher proactive demands (i.e., 'BX' trials). We also hypothesized that proactive CC would result in more variable behavioral and neural responses as a result of

individual differences in implementation (Carter and van Veen, 2007; Lopez-Garcia et al., 2016; Richmond et al., 2015). In contrast, we predicted that probes with high reactive CC demands (i.e., 'AY' probes) would be associated with increased activation within the dACC/preSMA and VLPFC, and would exhibit a more homogeneous pattern of behavioral and neural responses across individuals.

Materials and Methods

Participants

Fifty-two adult volunteers between the ages of 18-50 participated in the experiment. Two participants were excluded due to an inability to learn the task. No participants were identified as a motion outlier (more than 3 times the interquartile range on 2 of 6 framewise displacement parameters; Mayer et al., 2007). Four participants were removed for poor behavioral performance during the task (accuracy below 68% on any single trial type, defined as chance based on a binomial distribution). There were no outliers on response time (RT) data on any measure. The final cohort therefore included 46 participants (28 males; mean age = 31.8±7.4 years; mean education = 15.2±1.9 years).

Exclusion criteria consisted of 1) a history of severe neurological incidents or diagnoses (including head injury with greater than 30 minutes of loss of consciousness), 2) a developmental disorder (autism spectrum disorder or intellectual disability), 3) contraindications for MRI, 4) current pregnancy, 5) history of substance abuse/dependence or current use (confirmed with negative urine drug screen), 6) presence of any psychiatric disorder, 7) a first-degree relative with a psychotic spectrum disorder, or 8) a score of greater than 29 on the Beck Depression Inventory (BDI; Beck et al., 1996). All participants provided informed consent according to institutional guidelines at the University of New Mexico Health Sciences Center.

Clinical and Neuropsychological Assessments

The Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Battery (MCCB; Kern et al., 2008; Nuechterlein et al., 2008) was used as an independent and validated measure of neuropsychological functioning. A vigilance factor was derived from a continuous performance test whereas a planning factor was derived from the Mazes subtest. Finally, a working memory factor was collectively derived from the Wechsler Memory Scale III Spatial Span and Letter Number Span. Domain t-scores were obtained based on normative data for all factors (Kern et al., 2008; Nuechterlein et al., 2008).

Task Description

All participants completed an AX-CPT task (Figure 1A and 1B) in which they monitored a continuous series of visual cues (the letters A, R, V, P, S and E; duration = 500 ms) and auditory probes (the letters X, Q, F, I, M and U; duration = 500 ms). A visual cue was used with an auditory probe as previous studies indicate this combination results in maximum crossmodal cueing effects (Yang and Mayer, 2014). Non-'A' (hereafter referred to as B cues) and non-'X' (hereafter referred to as Y probes) letters were selected to be visually or aurally distinct from their respective counterparts. Participants pressed a button with either their right index ("yes" response) or middle ("no" response) finger following the presentation of each cue and each probe. Button presses were logged between 100 ms - 2000 ms following stimuli to exclude anticipatory or late responses, respectively. The inter-stimulus interval (2760 to 3680 ms) and inter-block interval (4060 to 4980 ms) were jittered with a minimum delay of approximately 2.7 s to minimize non-linear summing of the hemodynamic response function (HRF) between the cue and probe phases and to decrease temporal expectations (Glover, 1999). The resulting design

matrix was mathematically well-conditioned and invertible with only moderate collinearity among the various behavioral regressors.

The cue letter A occurred on 80% of total trials. The target sequence consisted of an A cue followed by an X probe, and this AX cue/probe sequence occurred on 70% of the total trials. Participants indicated the appearance of the target sequence with a "yes" response following the probe. Participants responded to all cues (the letters A, R, V, P, S and E) and all other probes (the letters Q, F, I, M and U) with a "no" response. AY sequence trials (10% frequency) occurred when an A cue was followed by a Y probe. The AY sequence theoretically results in both a violation of expectation and the inhibition of a prepotent motor response due to the preponderance of AX sequences (which sets one up to expect an X following an A), and thereby maximizes the demand for reactive CC (Cohen et al., 1999).

In contrast, participants theoretically always know to make a "no" response to any probe that follows the presentation of a B cue, which should maximally engage proactive CC relative to AX and AY trials. Specifically, while participants must still inhibit a prepotent motor response following a BX sequence (10% frequency), the proactive utilization of information from the B cue should prepare them to make a "no" response (Cohen et al., 1999). BY sequence trials (10% frequency) were included to generate the expected cognitive set based on cue/probe probabilities used in previous studies, but were not of primary interest in data analyses. Letter sequences were presented in a pseudorandom order, but always maintained the same probability structure within each run (i.e., AX = 70%; AY = 10%; BY = 10%; BX = 10%), resulting in the following trial counts: AX = 112; AY = 16; BX = 16; BY = 16. Participants received instructions and completed practice (until performance indicated understanding of task) prior to entering the scanner.

Behavioral Analyses

Accuracy (percent correct), median RT for correct trial data and response variability were computed for cues (A, B) and three of the probe trial types (AX, AY, and BX). Within subjects t-tests examined reaction time differences across the following contrasts: A vs. B cues; AX vs. AY probes; AX vs. BX probes; and AY vs. BX probes. Wilcoxon signed-rank tests examined non-normally distributed accuracy data. Finally, Pitman tests were chosen to examine within subject response variability across conditions. Specifically, a correlation coefficient was computed between the sum (e.g., Probe X + Probe Y) and difference (e.g., Probe X – Probe Y) between two conditions and assessed for significance (Piepho, 1997).

A series of three multiple regressions were conducted using separate behavioral metrics from the AX-CPT task (behavioral shift index [BSI], AY and BX RTs) as the dependent variable and MCCB factors (vigilance, working memory, and planning) as the independent variables. The BSI represents the most typically used metric from the AX-CPT task (Paxton et al., 2006; Paxton et al., 2008) for determining whether the individual is responding in a highly proactive (i.e., large positive index score) or reactive (i.e., small or negative index) manner. The BSI was computed using RT as follows:

$$BSI = \frac{AY - BX}{AY + BX}$$

Imaging, Processing and Statistical Analyses

High resolution 5-echo multi-echo Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) T_1 [repetition time (TR) = 2530 ms; echo times (TE) = 1.64, 3.5, 5.36, 7.22, 9.08 ms; inversion time (TI) = 1200 ms; flip angle = 7°; number of excitations (NEX) = 1; slice thickness = 1 mm; field of view (FOV) = 256 mm; matrix size = 256 x 256; isotropic voxels = 1 mm] were collected for structural images on a 3T Siemens Trio Tim scanner. Echo-planar

images were collected for four runs of the AX-CPT task using a single-shot, gradient-echo echoplanar pulse sequence with simultaneous multi-slice technology [TR = 460 ms; TE = 29 ms; flip angle = 44°; multiband acceleration factor = 8; NEX = 1; slice thickness = 3 mm; FOV = 248 mm; matrix size = 82 x 82; 56 interleaved slices; 3.02 x 3.02 x 3.00 mm voxels]. The first three images of each run were eliminated to account for T_1 equilibrium effects, resulting in a total of 3116 images for the final analysis. A single band reference image (SBREF) was also acquired to facilitate registration with the T_1 image. Two EPI distortion mapping pre-scan sequences [TR = 7220 ms; TE = 73 ms; flip angle= 90°; refocus flip angle = 180°; slice thickness = 3 mm; FOV = 248 mm; matrix size = 82 x 82; 56 interleaved slices; 3.02 x 3.02 x 3.00 mm voxels] with reversed phase encoding directions (A → P; P → A) were also collected to correct for susceptibility related artifacts in the task data.

Anomalous time-series data were first identified and replaced based on values from the previous and subsequent image using AFNI's despiking protocol (Cox, 1996). All time-series data were then temporally interpolated to the first slice to account for differences in slice acquisition and spatially registered in two- and three-dimensional space to the SBREF to reduce the effects of head motion. Susceptibility-induced field distortion was estimated and corrected using FSL Topup (Andersson et al., 2003; Smith et al., 2004). Task data were converted to standard stereotaxic coordinate space (Talairach and Tournoux, 1988) using a non-linear algorithm (AFNI 3dQwarp) and spatially blurred using a 6-mm Gaussian full-width half-maximum filter. A voxel-wise deconvolution analysis generated a single hemodynamic response function for each trial-type relative to the baseline state (visual fixation plus gradient noise) based on the first 14.26 seconds post-stimulus onset. Error trials were modelled separately for each trial-type to eliminate error variance (Mayer et al., 2011).

As our a priori hypotheses posited sustained DLPFC activity, two separate percent signal change (PSC) windows were calculated by summing the beta coefficients for images occurring between 3.22 and 5.06 seconds (peak activation) and between 5.06 and 6.9 seconds (late peak) post-stimulus onset and dividing by the average model intercept. The time windows of interest were determined a priori based on observed HRF across trial conditions in the motor and sensory regions. A 2 × 2 [Cue (A vs. B) × Time (Peak Activation vs. Late Peak)] repeated-measures ANOVA was conducted to examine functional activation across cue types. A similar 2 × 2 analytic strategy was utilized to examine the difference amongst probes (AX vs. AY, AX vs. BX, and AY vs. BX). "Sustained" activation was operationally defined as regions exhibiting significant Condition × Time interactions in which the difference was being driven by differential activity in the late peak phase. The main effects of Time were not of interest to current analyses. Following standard statistical conventions, only the interaction terms were evaluated for any regions exhibiting both a significant effect of Condition and a Condition × Time interaction. All voxel-wise results were corrected for false positives at $p < 0.05$ based on 10,000 Monte-Carlo simulations ($p < 0.001$ and minimum cluster size = 602 microliters).

Results

Behavioral Analyses

Results indicated that participants exhibited significantly (t_{45}=-4.68, $p < 0.001$) faster RT for A relative (611.44 ± 187.16 ms) to B (664.44 ± 167.85 ms; Figure 1C) cues in conjunction with a trend for decreased variability in B relative to A cues (Pitman test $r = 0.26$; $p = 0.084$). In contrast, there were no differences in accuracy data for A (97.43 ± 3.80%) and B (96.58 ± 5.60%) cues. RTs (Figure 1C) for AY probes (809.64 ± 145.11 ms) were significantly slower than to both AX (610.58 ± 129.67 ms; t_{45} = -16.17, $p < 0.001$) and BX (633.76 ± 251.84 ms; t_{45} =

-6.21, $p < 0.001$) probes. There were no significant differences in RT between AX and BX probes. RT variance was significantly greater for BX relative to both AX ($r = -0.71$; $p < 0.001$) and AY ($r = -0.61$; $p < 0.001$) probes, with similar amounts of variance observed for AX and AY probes ($p > 0.10$) in spite of differences in RT. Finally, accuracy for BX probes (93.23 ± 7.83%) was significantly lower than both AX (96.57 ± 4.64%; Z = -2.57, $p = 0.01$) and AY probes (96.45 ± 5.39%; Z = -2.62, $p = 0.01$).

Secondary analyses were also conducted to examine the relationship between the BSI and the individual RT scores (BX = proactive CC; AY = reactive CC). Results (Figure1D) indicted a strong inverse correlation between the BSI and BX RT (r = -0.90; 81.0% of total variance; $p < 0.001$), with a weaker relationship present between BSI and the AY RT (r = -0.31; 9.5% of total variance; $p = 0.04$).

Regression analyses indicated significant relationships between the working memory score and both the BSI RT ($\beta = 0.44$, $t_{42} = 2.70$, $p = 0.01$) and BX RT ($\beta = -0.37$, $t_{42} = -2.19$, $p = 0.03$). Results from the AY RT (reactive CC measure), planning and vigilance variables were not significant. Exploratory correlation analyses were conducted between the MCCB measures and median RT for the remaining cues and probes given the negative results with vigilance and planning measures. The working memory factor was significantly inversely correlated with RT on the A and B cues (all p's < 0.05). In contrast, the vigilance and planning measures were not related to RT data from either cues or probes (all p's > 0.10).

Functional Task Results: Cue-Related Activity

Results from the 2 × 2 [Condition (A vs. B cue) × Time (Peak Activation vs. Late Peak)] repeated-measures ANOVA indicated increased activation in the right VLPFC extending into the anterior insula (aI/VLPFC; BAs 13/44/45; µl = 751) for B relative to A cues (Figure 2A). There

was a significant Condition × Time interaction in the bilateral ACC and medial frontal gyrus (anterior default mode network [DMN]; BAs 10/24/32; µl = 3230) and the posterior cingulate/precuneus (posterior DMN; BAs 23/31; µl = 1043; Figure 2B). Simple effects tests indicated greater activation in the DMN regions in response to A cues relative to deactivation following B cues during the late peak compared to peak phase.

Functional Task Results: Probe-Related Activity

A similar series of 2 × 2 ANOVAs were used to test our a priori hypotheses about differential activation for reactive CC (AY probes) and proactive CC (BX probes) probe trials across the peak and late peak phases. The first analyses compared AY vs. AX probes, with a main effect of Probe (AY > AX for both peak and late peak phases) observed within the thalamus (µl = 10119) and left caudate (µl = 1062). Significant interactions indicated sustained activation (i.e., greater AY relative to AX activation in late peak phase only) within the right (BAs 9/10; µl = 1801) and left (BAs 10/46; µl = 2989) superior frontal gyrus/DLPFC, bilateral precuneus (BA 7; µl = 3432), left claustrum/putamen (BAs 13; µl = 602), and right (µl = 10165) and left (µl = 10527) cognitive regions (i.e., lobule VIIa Crus I and II) of the cerebellum (Figure 3). There was also a larger difference in the magnitude of activation during the late peak compared to the peak phase (sustained activation; AY > AX) within the right (BAs 6/8/9; µl = 6124) and left (BAs 6/8/9/44/45; µl = 10279) premotor/frontal eye fields/DLPFC, bilateral dACC/preSMA (BAs 6/8/32; µl = 4997), right (BAs 13/22/38/44/45/47; µl = 8168) and left (BAs 13/22/38/44/45/47; µl = 9087) aI/VLPFC, right (BAs 7/19/39/40; µl = 12369) and left (BAs 7/19/39/40; µl = 13559) posterior parietal cortex, and the right (BAs 21/22; µl = 17748) and left (BAs 13/21/22/39/40/41/42; µl = 19058) primary and secondary auditory cortices extending into the inferior, middle, and superior temporal gyrus.

Results of the 2 × 2 repeated-measures ANOVA examining AX and BX probes indicated significant interactions in five different clusters. Simple effects testing of the interaction indicated sustained activation for the right (BAs 13/44/45/47, μl = 2038) and left (BAs 13/45/47, μl = 1213) aI/VLPFC for the BX relative to AX probes during the peak phase (Figure 4A). In contrast, the right posterior aspect of the middle temporal gyrus (BAs 19/39; μl = 791) demonstrated greater activation for BX relative to AX probes during the peak phase only (suggesting brief, rather than sustained activation). Finally, although significant interactions were observed in the right precuneus/posterior cingulate gyrus (BAs 29/30/31; μl = 789) and secondary auditory cortex/middle temporal gyrus (BAs 21/22 μl = 915), follow-up simple effects tests were negative.

The ANOVA examining the AY and BX probes indicated significant interactions within the left sensorimotor cortex extending into inferior parietal lobe (BAs 2/40/42/43, μl = 2628), right lobule VIIIa of the cerebellum (motor region; μl = 757) and left lobule VIIa Crus I and II of the cerebellum (cognitive regions; μl = 849; Figure 4B). Simple effects tests indicated that the interaction in these areas resulted from sustained activation during the AY relative to BX trails. A significant interaction was also present within the secondary auditory cortex (BAs 6/13/22; μl = 797); however, testing of all simple effects within this cluster were not significant.

A series of three follow-up regression analyses were conducted to determine if differences in functional activation during cues (i.e., calculated A - B PSC for regions in Figure 2) or behavioral metrics (i.e., AY, BX) were associated with differences in functional activation (i.e., calculated AY - BX PSC for regions in Figure 4B) during the late peak phase of probes. The BSI was excluded due to evidence of strong multicollinearity with its RT components. Results indicated the difference in activation within the right aI/VLPFC during cues (A-B) was

significantly and inversely related to the difference in activation during probes (AY-BX) in the sensorimotor cortex (β = -0.58, t_{40} = -4.59, $p < 0.001$), left lobule VIIa Crus I and II of the cerebellum (β = -0.47, t_{40} = -3.85, $p < 0.001$), and right lobule VIIIa of the cerebellum (β = -0.58, t_{40} = -4.96, $p < 0.001$; Figure 5). In addition, activation in the DMN (averaged across both regions) was significantly related to the difference in activation during probes in the left (β = -0.31, t_{40} = -2.55, p = 0.02) and right (β = -0.25, t_{40} = -2.14, p = 0.04) lobules of the cerebellum (Figure 5). The three behavioral indices were not associated with differential activation on AY versus BX probes (all p's > 0.10).

Secondary Analyses: Baseline Contrasts and Variability Analyses

Our principal analyses did not support a priori predictions of increased DLPFC activity for B relative to A cues or during BX probes. Secondary analyses were therefore performed to examine cue and probe activation relative to baseline state during the peak phase. In addition to the regions found to significantly differ between cues during direct comparisons (i.e, right aI/VLPFC and the anterior/posterior nodes of the DMN), the bilateral DLPFC (BAs L = 9/46, BAs R = 9) demonstrated significant activation during B cues relative to baseline, which was absent during A cues (Figure 6A). Results also indicated common activation across both cue conditions in the bilateral preSMA/SMA/premotor cortex (BA 6), visual cortices (BAs 18/19/37), posterior cingulate (BAs 23/31), lobule VI of the cerebellum and left sensorimotor cortex (BAs 2/3/4).

Both probes following A cues (AX and AY trials) elicited widespread activation relative to baseline in the bilateral pre-SMA/SMA/premotor cortex (BA 6), DLPFC (BAs 9/10), aI/VLPFC (BA 13/44), auditory cortices extending into the temporal lobe (BAs 22/40/41/42), thalamus, lobule VI and lobule VIIIa of the cerebellum and left sensorimotor cortex (BAs 2/3/4)

during the peak phase (Figure 6B). In contrast, probes following B cues (BX and BY trials) elicited relatively sparse activation relative to the baseline state, with activity limited to the bilateral auditory cortex extending into the temporal lobe and insula (BAs 13/21/22/41/42). BX probes showed additional activation within the left sensorimotor cortex (BAs 3/4; Figure 6C).

Region of interest-based Pitman Tests were then conducted to examine if HRF variability across participants partially explained the null findings versus baseline in the BX probes relative to the large degree of activation observed following AY probes (see larger error bars in Figures 2 – 4). These analyses focused on left primary motor cortex (PMC; 12 mm diameter sphere around Talaraich coordinates -39, -38, and 54) and supplementary motor area (SMA; -2, -7, and 55) based on the assumption that participants at a minimum had to press a button to ensure a correct response for both BX and AY trials. Results indicated increased variability for BX relative to AY probes during both the peak and late peak phases within the PMC (r's = -0.55 and -0.60, respectively) and SMA (r's = -0.65 and -0.66; all p's < 0.01; Figure 6D). These analyses were extended to the pre-peak HRF (1.38 – 3.22s) phase, with results again indicating that variability was greater for BX relative to AY probes in both motor regions (PMC r = -0.53; SMA r = -0.69) during this early window (all p's < 0.01; Figure 6D).

Pitman tests were therefore also conducted to determine whether HRF variability was greater within the PMC and SMA during the peak, late peak, and an after peak phase (encompassing 6.90 – 8.30 s) following cues (Figure 6E). There were no differences between A and B cues in the peak and late peak phases for either motor region. However, significantly greater variability was observed within both the PMC (p = 0.014; r = -0.36) and SMA (p = 0.008; r = -0.38) during the after peak phase for B relative to A cues.

Discussion

In the current study, reactive CC (AY vs. AX probes) resulted in increased reaction times and neural activation within the bilateral dACC/pre-SMA, DLPFC, aI/VLPFC and posterior parietal cortex. Contrary to predictions of sustained DLPFC activation, measures of proactive CC resulted in activation of the right aI/VLPFC during the cue period (B relative to A cues) and activation of the bilateral aI/VLPFC during the probe period (BX vs. AX). Finally, high levels of both behavioral and neural variability characterized proactive CC, suggesting large individual differences in actual implementation. Considered collectively, these results highlight a common and potentially flexible role of the aI/VLPFC for instantiating both reactive and proactive CC across multiple phases of the AX-CPT task.

Behavioral results from our intermodal paradigm (visual cues with auditory targets) were consistent with previous AX-CPT studies that utilized visual stimuli only (Barch et al., 2001; Barch et al., 2003; Paxton et al., 2008; Braver et al., 2009; Paxton et al., 2006), suggesting that proactive and reactive CC function in a supramodal fashion. Reaction times were slower for B relative to A cues and for AY relative to AX and BX probes, consistent with designs with longer (Paxton et al., 2008; Braver et al., 2009) rather than shorter (Barch et al., 2001; Poppe et al., 2016) cue-probe delays. BX probes were associated with both decreased accuracy and increased RT variability, which subsequently captured the majority of BSI variance relative to AY trials. Although the latter finding was likely driven by the increased range of RT during BX trials, it suggests that direct comparisons of AY and BX trials represents a more parsimonious approach for characterizing reactive versus proactive CC rather than the BSI.

The 100% predictive nature of B relative to A (70%) cues has been suggested to proportionally increase the degree of proactive CC and subsequent need for DLPFC engagement

(Blackman et al., 2016; Braver et al., 2009; Braver, 2012). However, in the current experiment B cues resulted in activation of right aI/VLPFC rather than the DLPFC, as well as deactivation of the DMN. The aI/VLPFC has classically been associated with both reactive response inhibition (Aron et al., 2014; Cieslik et al., 2015; Rae et al., 2014; Swick et al., 2011) and bottom-up orienting to salient environmental stimuli (Levy and Wagner, 2011; Uddin, 2015), both of which could potentially be triggered due to the infrequent nature of B cues (20% of trials). However, activation of the medial aI and more posterior aspects of the VLPFC (BA 44) rather than the inferior frontal junction suggests a greater role for response inhibition rather than bottom-up orienting in the current task (Levy and Wagner, 2011).

Probe-related reactive CC (AY > AX) resulted in widespread activity of the classical CC network including bilateral DLPFC, VLPFC, dACC/pre-SMA, and posterior parietal cortex. In contrast, probe-related proactive CC (BX > AX) resulted in isolated activity within the bilateral aI/VLPFC, the same region identified during both B versus A cue comparisons and during reactive CC (compare Figures 2, 3 and 4). The bilateral aI/VLPFC activation across both types of probe trials likely results from a common requirement to reactively inhibit prepotent responses due to violations in expectations (AY trials) or from the appearance of a habitual stimulus (BX trials). Surprisingly, the direct comparison of AY versus BX probes resulted in increased activation (AY > BX) in the left sensorimotor cortex/inferior parietal lobe, right motor and left cognitive regions of the cerebellum (Buckner, 2013) rather than within the traditional CC network. The differential activity in motor circuitry between AY and BX probes was unexpected given that both trials minimally required a button press to indicate a correct trial.

Similar to behavioral results, subsequent analyses suggested that increased neural variability (i.e., individual differences) was a driving factor behind the different patterns of

activity observed during AY and BX trials. Specifically, quantitative analyses (Pitman tests) focused on motor circuitry (primary motor cortex and SMA) indicated increased inter-subject variability for the pre-peak (encompassing 1.38-3.22s post probe onset), peak and late peak phases of the HRF during BX relative to AY probes. The increase in HRF variability began after the late peak phase (encompassing 6.90-8.30s post cue onset) of B cues, with no statistical differences in variability between peak and late peak phases for A and B cues. Although quantitative analyses focused on motor circuitry, qualitative examinations of HRF (Figures 2-4) suggest that increased variability was robustly present across all brain regions following B cues. A further result of this neural variability was the relatively sparse activation (common activation of auditory cortex only) for B probes (BX and BY) relative to the baseline state in comparison to robust activation of prefrontal (aI/VLPFC, DLPFC, dACC/pre-SMA), motor, auditory and posterior parietal cortex relative to baseline during both A probes.

Finally, regression analyses demonstrated that neural variability observed during AY vs. BX comparisons (left sensorimotor cortex, right and left cerebellum) was associated with cue-related activity in the aI/VLPFC. Specifically, individuals who exhibited stronger aI/VLPFC activation for B cues also exhibited weaker BX neural responses within motor circuitry (i.e., most data localized to upper right quadrants in Figure 5). Thus, these findings provide preliminary evidence that the aI/VLPFC proactively modulates or potentially suppresses subsequent neural activity (motor programs) during B probe periods in some individuals (Aron, 2011; Chikazoe et al., 2009; Jahfari et al., 2010), leading to a high degree of variability in neural responses when the group is examined as a whole. Although behavioral metrics of proactive CC were related to working memory capacity (Kane and Engle, 2002; Redick and Engle, 2011; Redick, 2014), behavioral performance was not associated with neural variability.

The lack of DLPFC activity during both cue and probe proactive CC conditions in the current study is notable and may be the result of several factors. First, proactive CC has been operationally defined several different ways, even within the AX-CPT task. For example, previous studies (Braver et al., 2009; Paxton et al., 2008; Paxton et al., 2006) have compared cues (A + B; proactive) to probes (AY + BX; reactive). However, current results suggest very different patterns of activity across AY versus BX probes, which would necessarily skew resultant contrasts towards the more active AY condition. Second, behavioral results indicated that similar relationships existed between both A and B cue RT with an independent measure of working memory, suggesting that both cues utilized proactive CC to some degree. Third, the current experiment utilized a voxel-wise approach with rigorous corrections to eliminate false positives (Eklund et al., 2015) whereas previous studies have focused on ROI approaches (MacDonald and Carter, 2003). The latter may be more appropriate for capturing the weak DLPFC activity that was observed during comparisons of B cues to baseline. Finally, variations in task design (e.g., longer inter-stimulus intervals, differences in the frequency of BX probes) also influence how participants utilize cue information (Lesh et al., 2013; Lopez-Garcia et al., 2016) and may ultimately alter DLPFC recruitment.

In spite of our use of advanced acquisition (rapid TR) and analytic techniques, the current experiment was limited by several factors. First, the temporal nature of the HRF inherently eliminates more fine-grained analyses of neuronal spiking available with electroencephalography or magnetoencephalography, and potentially confounds increased activation (i.e., higher peak) with duration (i.e., increased PSC in late peak phase) due to the sluggish nature of the vasculature and hemodynamic response (Buxton, 2012). Thus, fMRI may be limited in the ability to truly assess sustained versus transient activity during proactive/reactive CC (Braver et

al., 2009; Irlbacher et al., 2014), even with the more rapid sampling scheme utilized in the current experiment. Second, the inherent nature of the AX design (low probability B cue followed by low probability BX probe) ensures that the hemodynamic parameters associated with B probes are more challenging to reliably estimate relative to AX counterparts. However, 1) AY probes are also infrequent events and 2) increased variability for BX trials was also present in the behavioral data, suggesting that the source of neural variability for B probes is not purely statistical in nature.

In summary, current results highlight the flexible role of the aI/VLPFC in implementing both proactive and more reactive cognitive processes during the AX-CPT task. Increased activation of the right aI/VLPFC during the cue period was associated with reduced neural activity during the probe period, potentially suggested individual differences in neural suppression. However, the instantiation of proactive CC following B cues exhibited a high degree of individual variability, contrasted with relatively more consistent cognitive strategies (i.e., lower behavioral and neural variability) following the presentation of A cues. Future studies are required to both replicate current findings and to better determine the individual differences that contribute to the variable pattern of neural responses observed during proactive CC.

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Figure Legends

Figure 1. Diagrammatic representation of task and behavioral results. The required correct response (CR) was "yes" (Y) when the letter X followed the letter A (target sequence AX; denoted with an asterisk; 70% of trials; Panel A left). The three remaining conditions (AY, Panel A right; BX and BY, Panel B) all require a "no" (N) response to both cue and probe and each occurred on 10% of trials. The inter-stimulus interval (ISI) was 3220 ms jittered by one TR (460 ms). Box-and-whisker plots depict reaction times (RT) for all task conditions (Panel C). Scatter plots (Panel D) depict relationships between behavioral measures of proactive and reactive cognitive control (BSI = behavioral shift index, AY RT, and BX RT).

Figure 2. Panel A presents regions exhibiting a main effect (M.E.) for cues, with greater activation ($p < 0.001$: blue; $p < 0.0001$: cyan) for B relative to A cue trials in the right anterior insular/ventrolateral prefrontal cortex (aI/VLPFC). Panel B presents regions exhibiting a significant interaction between time (T) and condition (C) for A and B cue trials ($p < 0.001$: red; $p < 0.0001$: yellow) in the bilateral anterior (aDMN) and posterior default mode network (pDMN). Locations of sagittal (X) and axial (Z) slices are given according to the Talairach atlas for the left (L) hemisphere. Percent signal change (PSC) data are plotted over the entire hemodynamic response function for A (red) and B (blue) cue conditions, with error bars reflecting the standard error across participants. Shaded bars indicate peak (P; dark grey) and late peak (LP; light grey) phase of hemodynamic response function (HRF).

Figure 3. Regions exhibiting a significant interaction between time (T) and condition (C) for AX relative to AY trials ($p < 0.001$: red; $p < 0.0001$: yellow). Locations of the sagittal (X) and axial (Z) slices are given according to the Talairach atlas for the left (L) and right (R) hemispheres. Percent signal change (PSC) data are plotted over the entire hemodynamic response function (HRF) for AY (red) and AX (green) probe conditions, with error bars reflecting the standard error across participants. Shaded bars indicate peak (P; dark grey) and late peak (LP; light grey) phase of HRF. Selected regions include left and right posterior parietal cortex (PPC), anterior insular/ventrolateral prefrontal cortex (aI/VLPFC), dorsolateral prefrontal cortex (DLPFC), dorsal anterior cingulate cortex/pre-supplementary motor cortex (dACC/preSMA).

Figure 4. Regions exhibiting a significant interaction between time (T) and condition (C) for AX relative to BX trials (Panel A) and AY relative to BX trials (Panel B; $p < 0.001$: red; $p < 0.0001$: yellow). Locations of the sagittal (X) and axial (Z) slices are given according to the Talairach atlas for the left (L) and right (R) hemispheres. Percent signal change (PSC) data are plotted over the entire hemodynamic response function (HRF) for AX (green), BX (blue), and AY (red) conditions, with error bars reflecting the standard error across participants. Shaded bars indicate peak (P; dark grey) and late peak (LP; light grey) phase of the HRF. Selected regions include bilateral anterior insula/ventrolateral prefrontal cortex (aI/VLPFC) for the AX relative to BX contrast and the left sensorimotor cortex (SMC) and the left cerebellum (Cblm) for the AY relative to BX contrast.

Figure 5. Scatter plots depicting relationships between regions showing significant differences in cue (A-B) and subsequent probe (AY-BX) related activity. Results indicated significant inverse

relationships between differential cue-related activation in anterior insula/ventrolateral prefrontal cortex (aI/VLPFC) and differential probe-related activation in the left sensorimotor cortex (L SMC), right (not pictured) and left cerebellum (L Cblm). Specifically, greater differences in right aI/VLPFC during cues were associated with greater differences between AY and BX probe responses, most likely as a result of neural suppression during BX trials. In contrast, a significant inverse relationship was found between differential cue-related activation in the default mode network (DMN) and only the L Cblm. Asterisks denote significant relationships.

Figure 6. Overlay plots depicting activation for Cue conditions (Panel A), A probe conditions (AX and AY, Panel B), B probe conditions (BX and BY, Panel C) relative to baseline. Highlighted regions include anterior insular/ventrolateral prefrontal cortex (VLPFC), dorsolateral prefrontal cortex (DLPFC), primary motor cortex (PMC). Locations of the axial (Z) slices are given according to the Talairach atlas for the left (L) and right (R) hemispheres. Percent signal change (PSC) data are plotted over the entire hemodynamic response function (HRF) for the supplemental motor area (SMA) and PMC regions of interest for probes (Panel D) and cues (Panel E), with error bars reflecting the standard error across participants. Shaded regions of the HRF indicate pre-peak (PP; cyan), peak (P; dark grey), late peak (LP; light grey), and after-peak (AP; orange) phases examined.