

Cognitive Adjustments & Network Interactions

A Dissertation
Presented to
The Academic Faculty

by

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In Partial Fulfillment
of the Requirements for the Degree
Doctor of Philosophy in the
School of Psychology

Georgia Institute of Technology
May 2019

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Cognitive Adjustments & Network Interactions

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In Memory of Martin (Marty) Smith

ACKNOWLEDGEMENTS

I would like to thank my parents for their unconditional love and support. Also, I would like to thank Eric Schumacher for his guidance over the past few years and the members of my dissertation committee for their time and advice. In addition, I would like to thank all of the outstanding individuals that have lent me a helping hand over the course of my life.

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LIST OF SYMBOLS AND ABBREVIATIONS

Anterior Cingulate Cortex (ACC)

Anterior Insula (AI)

Anterior Prefrontal Cortex (aPFC)

Bayes Information Criterion (BIC)

Cingulo-Opercular Network (CON)

Confidence Interval (*CI*)

Congruent Trial Preceded by a Congruent Trial (cC)

Congruent Trial Preceded by an Incongruent Trial (iC)

Congruent Trial Preceding a Congruent Trial (Cc)

Congruent Trial Preceding an Incongruent Trial (Ci)

Congruency Sequence Effect (CSE)

Default Mode Network (DMN)

Dorsal Anterior Cingulate (dACC)

Dorsal Attention Network (DAN)

Dorsolateral Prefrontal Cortex (DLPFC)

Error Related Negativity (ERN)

Expected Value of Control (EVC)

Frontoparietal Network (FPN)

Functional Magnetic Resonance Imaging (fMRI)

Full Width at Half Maximum (FWHM)

Fusiform Face Area (FFA)

Hierarchical Error Representation (HER)

Hierarchical Reinforcement Learning Model of the Anterior Cingulate Cortex (HRL-ACC)

Inferior Frontal Gyrus (IFG)

Inferior Frontal Junction (IFJ)

Incongruent Trial Preceded by a Congruent Trial (cI)

Incongruent Trial Preceded by an Incongruent Trial (iI)

Incongruent Trial Preceding a Congruent Trial (Ic)

Incongruent Trial Preceding an Incongruent Trial (Ii)

Intertrial Interval (ITI)

Locus Coeruleus (LC)

Medial Prefrontal Cortex (mPFC)

Montreal Neurological Institute (MNI)

Multi-Voxel Pattern Analysis (MVPA)

Orbitofrontal Cortex (OFC)

Predicted Outcome Response (PRO)

Prefrontal Cortex (PFC)

Reaction Time (RT)

Relative Value of Foraging (RVF)

Saliency Network (SN)

SUMMARY

Our understanding of the neural substrates of cognitive adjustments is fairly limited. Given the growing body of work showing that brain connectivity network interactions are behaviorally relevant, more attention should be paid to network interactions when studying adjustments of cognitive control. Both the Frontoparietal Network (FPN) and the Cingulo-Opercular Network (CON) have been associated with elements of cognitive control. The aim of this study was to gain a better understanding of how these networks contribute to cognitive adjustments, specifically the congruency sequence effect, by testing the hypothesis that increased coupling between these networks is associated with more adjustment in behavior. Additionally, it was predicted that CON activity over and above FPN activity would predict both the neural response in the FPN and behavior on the subsequent trial. A significant congruency sequence effect was not observed in this data set. Inter-network connectivity was shown to be greater prior to relatively fast trials for a subset of subjects. In addition, significant negative modulation of current trial FPN was observed but this modulation could not be clearly linked to behavioral adjustments. Overall, the findings suggest that interactions between these networks have some role to play in performance but the primary hypotheses were not supported.

CHAPTER 1: INTRODCUTION

A current trend in the in study of cognitive control has been a progressive move away from tightly compartmentalized homuncular models of control towards non-homuncular models that explain executive functions as emergent properties of a cognitive and/or neurophysiological architecture (Eisenreich, Akaishi, & Hayden, 2017). Beyond this trend the field is ripe with a diverse and rapidly growing orchard of theories. This is in part due to the scope of the concept of cognitive control. Generating a computational model let alone a vague theory that can explain a large fraction of the behaviors that are generally believed to require cognitive control is a herculean task.

1.1 Brain Based Theories of Control

Dialogue between sets of functionally modular brain regions can allow for the emergence of complicated cognitive processes. A landmark neural theory of cognitive control that has inspired a great deal of the subsequent thinking in this subfield is the guided activation theory (Miller, & Cohen, 2001). It was inspired by the biased competition model of visual attention and can be thought of as a general extension of that theory (Desimone, & Duncan, 1995). According to the guided activation theory the prefrontal cortex maintains goals and biases competition occurring in lower order processing regions in under to nudge behavior in a direction that will bring the subject closer to a given goal state (Miller, & Cohen, 2001). A foundational mechanism of this theory, competition, now plays a critical role in many models of cognitive control (Botvinick, et al., 2001).

It has been shown that the neural fingerprint, in terms of the frontoparietal network's connectivity profile, of tasks varies as a function of task rules that determine the processes employed by the task (Cole, Reynolds, Power, Repovs, Anticevic, & Braver 2013). The frontoparietal network is marked by the presence of many regions known as hubs which exhibit a high degree of functional connectivity (Cole, 2017). Features of the frontoparietal network are likely not just indicative of the current task set but likely predictive of performance state. Additionally, the interaction of the frontoparietal network with other intrinsic connectivity networks could play a critical role in the regulation of cognitive control (Dosenbach et al., 2006). In order to further explore the physiological bias of the modulation of cognitive control the behavioral manifestations of these processing adjustments need to be assessed.

1.2 The Adaptation of Control

The degree of control exerted over the course of a task is likely not static and the dynamics of control might be reflected in micro-adjustments in performance (Unsworth, Redick, Spillers, & Brewer, 2012). A great deal of debate has surrounded the neural instantiation of micro-adjustments of cognitive control like the congruency sequence effect and post error slowing in addition to the debate over whether these behavioral phenomena are even manifestations of cognitive control. The most contentious debate in this area concerns the congruency sequence effect (Egner, 2007). The congruency sequence effect, which is commonly found in Stroop, flanker, and Simon paradigms, is defined by a larger congruency effect occurring on trials following congruent trials relative to the congruency effect following incongruent trials (Akçay & Hazeltine, 2008; Egner 2007; Kerns et al., 2004; Kerns 2006; Gratton, Coles, & Donchin, 1992). This modulation of the congruency

effect by the previous trial's congruency status has been proposed to stem from adjustments in attention elicited by cognitive control mechanisms (Botvinick et al., 2001; Gratton et al., 1992). These accounts came under criticism after memory confounds were found to be present in many of the paradigms used to measure the congruency sequence effect (Hommel, Proctor, & Vu, 2004; Mayr, Awh, & Laurey, 2003; Schmidt, & De Houwer, 2011).

The first line of criticism came from those concerned with the effects of stimulus response repetitions present in the paradigms being used to study the congruency sequence effect (Hommel et al., 2004; Mayr et al., 2003). Hommel and colleagues proposed that the co-occurrence of stimuli and responses are cognitively embodied by the integration of features into a transient representation which they labelled an "event file" (Hommel et al., 2004). Complete repetition trials (feature repetition facilitates execution on these trials) and complete alternation trials (no feature binding to overcome) are expected to have shorter reaction times (RT's) than partial repetition trials (repeat of a target but an alternation of the distractor or vice versa leads to previous feature binding that need to be overcome). The standard letter flanker (the central letter is the target and the flanking letters are the distractors that must be ignored; the letters are either S or H) is a prime example of a task that contains stimulus response repetitions. In this paradigm congruent trials preceded by congruent trials (cC) and incongruent trials preceded by incongruent trials (iI) are always complete repetitions or complete alternations. The relatively slow trials (slow relative to the trial of their congruency status preceded by the trial of the opposite congruency status) incongruent trials preceded by congruent trials (cI) and congruent trials preceded by incongruent trials (iC) are always partial repetitions. When

Mayr and colleagues (2003) analyzed complete alternations separately congruency sequence effects were not found but since these initial findings were reported numerous studies that have restricted analysis to complete alternations or used paradigms that did not contain feature repetition trials and observed significant congruency sequence effects (Egner, 2007; Hazeltine, Lightman, Schwarb, & Schumacher, 2011; King, Korb, & Egner, 2012; Ullsperger, Bylsma, & Botvinick, 2005; Weissman, & Carp, 2013).

Tasks like the four-choice color Stroop were used to avoid the feature repetition confound but these paradigms included another type of potential confound (viz., a contingency bias; Schmidt, & De Houwer, 2011). Four choice Stroop tasks usually have an equal number of congruent and incongruent trials. Balancing the trials by congruency status leads to a contingency bias. Assuming an even congruency split, in a Stroop task with four choices green, yellow, red, and blue the word green would have to appear in the color green more often than in the other three colors. This is the result of the word green being congruent on half of the trials. Participants can pick up on these contingencies and respond faster and with greater accuracy to high contingency trials (Schmidt, Crump, Cheesman, & Besner, 2007). Also, it has been shown that the contingency effect is larger for trials occurring after high contingency trials relative to trials preceded by low contingency trials. In a congruency balanced four-choice Stroop task congruent trials are high contingency trials and incongruent trials are low contingency trials. This contingency sequence effect yields the same pattern in the trial type means as the congruency sequence effect. Schmidt and De Houwer controlled for both feature repetitions and contingency bias and did not find a congruency sequence effect (Schmidt & De Houwer, 2011). Prior to the publication of these findings only one study reported a significant congruency

sequence effect in the absence of both featuring binding and contingency bias confounds (Freitas, Bahar, Yang, & Banai, 2007). Schmidt and De Houwer's work evoked a swift response from the cognitive control research community and within a few years significant congruency sequence effects had been found using multiple confound minimized paradigms (Blais, Stefanidi, & Brewer, 2014; Duthoo, Abrahamse, Braem, Boehler, & Notebaert, 2014; Freitas & Clark, 2014; Kim & Cho 2014; Weissman, & Carp, 2013; Weissman, Colter, Drake, & Morgan, 2015; Weissman, Jiang, & Egner, 2014).

One feature of the congruency sequence effects found with these confound minimized paradigms is that the difference between cI and iI trials is less robust to the removal of the confounds than the difference between cC and iC trials (Duthoo et al., 2014; Weissman et al., 2015; Weissman et al., 2014). The portion of the interaction potentially related to the up regulation of control (cI-iI) might be more robust in some confound minimized paradigms (Freitas et al., 2007; Freitas & Clark, 2014; Kim & Cho 2014). This is especially important since much of the neuroimaging literature on sequential control modulations has focused on the up regulation of control (Egner, Delano, & Hirsch 2007; Egner & Hirsch 2005; Kerns et al., 2004; Kerns, 2006).

Unfortunately most of the neuroimaging work focusing on congruency sequence effects predates the discovery of the contingency bias. Despite the serious limitation of not taking this confound into account imaging work has resulted in findings that were in line with what was predicted by computational modeling (Botvinick et al., 2001). Kerns and colleagues put the conflict monitoring account of the anterior cingulate to test with a Stroop task (stimulus and response repetitions removed from analysis) that was completed in the scanner (Kerns et al., 2004). Activity in the anterior cingulate was lower on iI trials relative

to cI trials. Anterior cingulate activity was tied to behavioral adjustments. Trials were partitioned into groups defined by the degree of behavioral adjustment on the subsequent trial. The high adjustment groups corresponded to the fastest iI trials and the slowest iC trials. The low adjustment groups corresponded to the slowest iI trials and the fastest iC trials. Post error trials were divided into high and low adjustment groups based on the degree of post error slowing. High adjustment iI trials exhibited greater anterior cingulate activity on the previous trial relative to low adjustment trials. In addition, error trials exhibiting a high degree of post error adjustment were marked by greater anterior cingulate activity relative to those with less post error adjustment (Kerns, et al., 2004).

Another interesting finding reported by Kerns and colleagues involves the interaction of the anterior cingulate and the prefrontal cortex. They found that anterior cingulate activity on the previous trial predicted activity in a prefrontal cortex region of interest (ROI) on the current trial. This effect remained even after partialling out variance shared with activity in the left temporal lobe, another task related region (Kerns et al., 2004). These findings were replicated in a Simon task (Kerns et al., 2006). The original Kerns and colleagues study had several limitations. First, they used a fixed intertrial interval of 1.5 seconds. This is problematic considering that jittered ITIs mitigate the influence of between trial bleeding stemming from the sluggish nature of the BOLD response thereby leading to better estimates of the task related activation to different event types (Ollinger, J. M., Shulman, G. L., & Corbetta, M. 2001a; Ollinger, J. M., Shulman, G. L., & Corbetta, M. 2001b).

Congruency sequence effects have been observed with jittered ITIs ranging between 3 and 5 seconds averaging 4 seconds (Egner & Hirsch, 2005). This investigation

of conflict adaptation, that employed jittering, made use of the functional specificity of the fusiform face area (FFA). Subjects completed a Stroop like task while in the scanner (Egner & Hirsch, 2005). The task consisted of pictures of famous actors and political figures with words overlaid on them. The words were either the names of famous actors or political figures and congruency status was determined by the compatibility of the category of the word and the category of the face (Egner & Hirsch, 2005). In one condition faces were the target dimension in another faces were the distractor condition. Trials occurring after incongruent trials were considered periods of high cognitive control. When the face was the target greater activity was found in the FFA for high control trials relative to low control trials suggesting amplification of the target. When the face was the distractor FFA activity was not lower in high control trials relative to low control trials suggesting cognitive control was not inhibiting the distractor. In addition, it was found that functional connectivity between the dorsolateral prefrontal cortex (DLPFC) and the FFA was greater on high control trials when the face was the target but connectivity between these regions was not context dependent for the face distractor condition (Egner & Hirsch, 2005). This study not only provided evidence in favor of a target stimulus amplification account of cognitive control but demonstrated that congruency sequence effects can be observed with jittered ITIs (Egner & Hirsch, 2005).

As of this point in time imaging studies of the congruency sequence effect need to be replicated with confound minimized paradigms (Egner & Hirsch 2005; Kerns et al., 2004; Kerns, 2006). Considering the attenuated congruency sequence effects present in confound minimized paradigms and the fact that the congruency sequence effect derogates

as the ITI increases it is not clear if these effects will replicate (Egner, Ely, and Grinband, 2010).

1.3 The Medial Prefrontal Cortex and the Interaction of Networks

The cingulo-opercular network (CON) a set of regions comprised of the anterior cingulate cortex, anterior insula, anterior thalamus and the anterior prefrontal cortex has been shown through the use of a mixed block/event design to be associated with the initiation of a task, the maintenance of a task, and error processing (Dosenbach, Fair, Miezin, Cohen, Wenger, Dosenbach, Fox, Snyder, Vincent, Raichle, Schlaggar, & Petersen, 2007). Dosenbach and colleagues have proposed two hypotheses for how this network interacts with the frontoparietal network (FPN) which is associated with error adjustments and task initiation (Dosenbach et al., 2007; Dosenbach, Fair, Cohen, Schlaggar & Petersen 2008). The first hypothesis posits that information on task initiation and error feedback is passed from the FPN to the CON which is used to inform task configuration. The second hypothesis has the two networks working in parallel rather than being intimately linked (Dosenbach et al., 2007; Dosenbach et al., 2008). This is not the only area of uncertainty concerning the functionality of the CON. Other theories view the CON as a salience network that detects regions processing salient information (Menon & Uddin 2010; Seeley, Menon, Schatzberg, Keller, Glover, Kenna, Reiss, & Greicius 2007). The resting state connectivity of the dorsal anterior cingulate cortex (dACC) has been shown to be positively related to a pre-scan anxiety, a trait associated with placing an excessive degree of salience on certain stimuli, but this relationship was not found for any FPN nodes (Seeley et al., 2007). Unlike Dosenbach's CON what Seeley and colleagues call the salience network includes some limbic regions like the temporal pole and the amygdala but

more importantly it includes many deep subcortical components like the periaqueductal gray, hypothalamus, substantia nigra, and the ventral tegmental area to name a few (Seeley et al., 2007). The extension of this network into limbic/subcortical regions implies that it is involved in the processing of value (Seeley et al., 2007).

Effective connectivity methods have provided evidence that the salience network might trigger switching between activation of the default mode network (DMN) and the FPN. More specifically Granger causality analysis revealed a causal role of the right anterior insula in the deactivation of the DMN and the activation of the FPN (Sridharan, Levitin, & Menon 2008). These findings were interrupted as the salience network directing attention in an internal (DMN) or external (FPN) direction and that the AI is the critical hub of the salience network with the dACC providing quick access to the motor system (Menon & Uddin 2010). Essentially these findings suggest that this network may judge if external or internal information is more salient and drive the switching between inward and outward attention.

The salience network (SN) and CON views of cingulo-opercular function are not mutually exclusive. Dosenbach and colleagues (2007) reported error related effects in the CON as would be predicted by the salience account. The key difference is that the theories put forward by the Petersen group are more expansive in terms of proposed functionality than the account put forward by Menon's group (Dosenbach et al., 2007; Menon & Uddin 2010; Seeley et al., 2007). There is evidence that a dorsal (CON) ventral (SN) divide might separate functional associations highlighted by the two groups (Power, Cohen, Nelson, Wig, Barnes, Jessica, Church, Vogel, Laumann, Miezin, Schlaggar, & Petersen, 2011). The coordinates reported by the Dosenbach et al., (2006) were dorsal to those reported by

Seeley et al., (2007) and graph theory based methods show the two sets to have different connectivity profiles (Power, et al., 2011). The SN and the CON might be separate networks but additional research on this potential partition is needed.

Another proposed function of the CON is the maintenance of tonic alertness (Sadaghiani & D'Esposito 2014). Pre-stimulus CON activity predicts detection in a continuous simple detection task and during resting state scanning spontaneous CON activity was positively associated with a common marker of alertness upper alpha band power (Sadaghiani, Hesselmann, & Kleinschmidt 2009; Sadaghiani, Scheeringa, Lehongre, Morillon, Giraud, & Kleinschmidt 2010). Additionally, performance on a pitch discrimination task that factorially manipulated the alertness demand (High: jittered intervals; Low: fixed interval) and attention demand (High: Hard to discriminate pitches; Low: Easy to discriminate pitches) showed a dissociation between the dorsal attention network (DAN) and the CON. Activity in the CON and CON intra-network connectivity were greater when alertness demand was high but were not responsive to attention demand. Activity in the DAN was inversely related to attention demand but not related to alertness demand (Sadaghiani & D'Esposito 2014). The authors of this study emphasized that they believe that tonic alertness is just one function of the CON but stressed that it differs from task maintenance in that tonic alertness extends to situations without a well-defined task that require vigilance. Also, they noted that tonic alertness differs from salience since the latter concept is dependent on homeostatic importance but tonic alertness scales with effortful engagement (Sadaghiani & D'Esposito 2014).

When it comes to the individual components of the CON considerable debate surrounds the function of the anterior cingulate cortex (ACC). In the early 2000's the

conflict monitoring model was the dominant explanation for the function of the dACC (Botvinick et al., 2001). This architecture for simulating interference paradigms was grounded on a connectionist network with two input layers, one for the relevant dimension & the other for the irrelevant dimension, a response layer, an attention layer and the conflict monitor (Botvinick et al., 2001; Botvinick, Cohen, Carter 2004; Botvinick 2007). Conflict is defined as co-activation of mutually inhibitory units in the response layer (motor conflict) which is quantified as Hopfield energy of the response layer (Botvinick et al., 2001). This is recorded by the conflict monitor which was proposed to be the ACC. The ACC sends a conflict signal based on an exponentially weighted average of conflict on previous trials to the attention layer which is generally believed to be physiologically instantiated in the DLPFC. The attention layer amplifies the activity of target stimuli units relative to the distractor stimuli units to an extent determined by the strength of the control signal. This model is able to account for the proportion level congruency effect, post error slowing, speed accuracy tradeoffs, the error related negativity (ERN), the N2, and the CSE (Botvinick et al., 2001; Yeung, Botvinick, & Cohen, 2004).

Despite its explanatory power the conflict monitoring model has its weaknesses (Alexander & Brown, 2011; Botvinick 2007; Brown & Braver, 2005; Burle, Roger, Allain, Vidal, & Hasbroucq, 2008; Heilbronner & Hayden, 2016; Weissman, Egner, Hawks, Link, 2015). In confound minimized paradigms the CSE tends to be more likely if the distractor precedes the target but the conflict monitoring model defines conflict as simultaneous activation of mutually inhibitory units (Duthoo et al., 2014; Weissman et al., 2015). Simultaneous presentation of incompatible stimuli should be ideal for eliciting conflict if conflict is defined as it is by the conflict monitoring model. Also, the magnitude of the

ERN is not predicted by the degree of temporal overlap of responses (measured by EMG) as would be predicted by the conflict monitoring account (Burle et al., 2008). The ERN might reflect conflict but given these findings if the ERN reflects conflict it is likely more cognitively upstream than the level of response processing (Burle et al., 2008).

Additionally, although evidence for the ACC's relationship to conflict is abundant in the functional magnetic resonance imaging (fMRI) literature many failures to replicate these findings at the single neuron level have been reported (Amiez, Joseph, Procyk 2005; Cai & Padoa-Schioppa 2012; Hayden, Heilbronner, Pearson, & Platt, 2011; Ito, Stuphorn, Brown, & Schall 2003; Nakamura, Roesch, & Olson 2005; Quilodran, Rothe, & Procyk 2008). Nevertheless neurons responsive to task conflict have been observed in non-human primates (Ebitz, & Platt 2015). Additionally, a small subpopulation of ACC neurons that were not responsive to reaction time have been shown to be responsive to conflict on a Stroop like task in a non-human primate sample (Michelet, Bioulac, Langbour, Goillandeau, Guehl, Burbaud 2015). Evidence for the conflict monitoring model in the animal literature was considered non-existent for a long period of time but it can be said now that the animal literature lends the conflict monitoring model some support.

Single cell recording evidence for conflict processing in the ACC comes from humans as well. Obsessive compulsive patients that were given surgical lesions of the ACC exhibit an absence of the CSE during the period immediately after surgery a result predicted by the conflict monitoring account (Sheth, Mian, Patel, Asaad, Williams, Dougherty, Bush, & Eskandar, 2012). Single cell recordings taken prior to the production of the lesion showed higher firing rates in ACC neurons during conflict trials relative to non-conflict trials a result that is in obvious accordance with the conflict monitoring model

(Sheth, et al., 2012). The general discrepancy between the single cell recording findings and the fMRI literature might stem from there being a small population of conflict responsive ACC neurons, interspecies differences, and/or BOLD conflict signals stemming not from cellular firing rate increases but from the activation of a greater number of neurons in the ACC (Heilbronner & Hayden 2016; Michelet et al., 2015; Nakamura et al., 2005). Given that BOLD signal reflects metabolic activity it would not be surprising if the number of units activated explanation has the most weight (Logothetis, 2008; Nakamura et al., 2005). Another way of thinking about this issue is that the degree of input to the ACC might be the true basis of conflict signals detected with fMRI. Local field potentials are better predictors of BOLD than firing rates and maybe the amount of input the ACC receives is the real driving force behind conflict effects rather than the number of neurons that undergo a change in firing rate (Logothetis, 2008).

Some have criticized the conflict monitoring account on the grounds that conflict is confounded with reaction time (Fan 2014; Grinband, Savitskaya, Wager, Teichert, Vincent, Ferrera, & Hirsch 2011). Both contrasting slow congruent trials against fast congruent trials and slow congruent trials against fast incongruent trials yield activation similar to that found for contrasts of incongruent trials against congruent trials (Grinband et al., 2011). Others have performed similar procedures and replicated these results and some have been able to demonstrate conflict effects in the ACC after controlling for reaction time (Neta, Schlaggar, & Petersen, 2014). It was suggested that the ACC's conflict signal might simply be a time on task signal (Grinband et al., 2011).

The time on task account is not only theoretically underwhelming but it stems from a fundamental misunderstanding of the conflict monitoring model (Yeung, Cohen, &

Botvinick 2011). The conflict monitoring model does not distinguish between conflict generated by incongruent stimuli and conflict that is a product of noise that is built into the model (Yeung et al., 2004; Yeung et al., 2011). In psychological terms this noise may be a manifestation of response biases, breakdowns of attentional lapses, perceptual noise, or other factors that influence processing (Yeung, et al., 2011). Years prior to the publication of Grinband and colleagues when describing simulations of the ERN it was explicitly mentioned that the conflict signal was high on slow congruent trials due to noise (Yeung et al., 2004; Yeung, et al., 2011). Also, the time on task account fails to explain conflict related activity that has been reported in the ACC when controlling for reaction time and the findings of Michelet and colleagues (Neta, Schlaggar, Petersen, 2014).

Another challenge facing the conflict monitoring model is that it does not explain the ACC's responsiveness to error likelihood (Brown & Braver 2005). The change detection task (based on the stop signal paradigm) has been used to demonstrate the ACC's role in the processing of error likelihood. At the start of a trial a colored cue indicated whether the upcoming trial was high or low in error likelihood. The trials consisted of an arrow stimulus which indicated the direction of the response and on 33% of trials a larger second arrow appeared above the initial arrow. The presence of the second arrow indicated the need to change the direction of the response and error likelihood was manipulated by the timing of the second arrow which was determined by a staircase method (Brown & Braver 2005). The change signal trials were conflict trials in this task. Activity in the ACC was greater for high error likelihood change trials relative to low error likelihood change trials and ACC activation was greater for high error likelihood no change trials when compared to low error likelihood trials (Brown, & Braver, 2005). These findings are by no

means fatal but somewhat problematic for the conflict monitoring account since the ACC showed that error likelihood effects trumped conflict.

A new family of models inspired by reinforcement learning, models of agent environment interaction in which agents' actions are guided by adaptive predictions of reward, are able to explain the error likelihood effects present in the ACC not to mention other effects not explained by the conflict monitoring account (Sutton & Barto, 1998). The predicted response outcome model, PRO, has become quite popular in the cognitive control field in recent years (Alexander, & Brown, 2011). PRO is grounded on reinforcement learning algorithms but differs from them in a number of important ways. The model is instantiated with rate coded neurons. PRO learns to connect action plans to predictions of responses and outcomes, what Alexander and Brown call, "response-outcome learning", as opposed to learning stimulus-response mappings as is typical in reinforcement learning. Basically PRO learns to associate stimuli with response-outcome conjunctions and will generate predictions proportional to conditional probabilities for the conjunctions given the conditions of the current trial (Alexander, & Brown, 2011). The predictions and information regarding the desirability of outcomes are used determine inhibition to response units. The response units compete with each via mutual inhibitory connections and are biased by top down control. The model also makes timing predictions of when an outcome should occur. The first response unit to pass an activation threshold acts as the chosen response. Comparison of the predicted and actual outcomes yields a prediction error when predictions are discrepant from actual outcomes and the prediction error is used to update the model's subsequent predictions (Alexander, & Brown, 2011). The ACC is proposed to act as a response-outcome predictor. There are two types of prediction errors:

unexpected occurrences and unexpected non-occurrences. Unlike in reinforcement learning, these prediction errors are not positive or negative in the sense that they are rewarding or aversive, rather they simply reflect unexpected occurrences and non-occurrences respectively. Another key difference from canonical reinforcement learning models is that PRO makes use of vector-valued prediction and prediction errors instead of scalar values thus allowing multiple outcomes to be predicted simultaneously (Alexander & Brown 2011). The model does not have a single prediction on a given trial. This factor explains PRO's ability to account for conflict effects. On incongruent trials the correct response is highly predicted but given that the inappropriate response is more likely on incongruent trials than congruent trials the prediction for the inappropriate response is greater on an incongruent trial relative to a congruent thus there is more overall outcome prediction on incongruent trials (Alexander and Brown 2011). This is true of high error likelihood vs. low error likelihood trials as well. Essentially this model is generally compatible with Nakamura and colleagues speculation that conflict signals in the ACC are a manifestation of the number of units activated (Alexander & Brown 2011; Heilbronner & Hayden 2016; Nakamura et al., 2005).

PRO is capable of explaining conflict effects, the ERN, feedback related negativity (FRN), error likelihood effects, the ACC's sensitivity to reward prediction errors, the N2 component, speed accuracy tradeoffs and other effects (Alexander & Brown 2011; Vassena, Holroyd, & Alexander 2017). Given that PRO's "conflict" effect stems from greater prediction related activity on incongruent trials instead of the extent of co-activation of mutually inhibiting response units the model is compatible with the idea that conflict merely reflects the number of potential responses (Alexander & Brown 2011; Brown 2009;

Fan 2014). Additionally, there is evidence that stimuli associated with multiple responses can produce congruency sequence effects in the absence of response conflict suggesting control adjustments commonly associated with ACC related conflict signals might simply depend on the degree of response prediction/number of potential responses (Weissman, Colter, Grant, & Bissett 2017).

The general idea that the ACC's association with conflict is a byproduct of a relationship with uncertainty is a core tenet of some theories of cognitive control. Jin Fan has proposed that the ACC might be responsible for general information processing speed and demands on this function are determined by the degree of response entropy (Fan, 2014). Reaction times have long been associated with the amount of information conveyed by the stimulus. A paradigmatic example is the Hick-Hyman law in which reaction time increases logarithmically with the number of choices (Hick, 1952; Hyman, 1953). Uncertainty is the basis of the information processing demands and is manifested in reaction time. Fan points out that conflict is a special case of increased entropy (Fan 2014). He cites studies showing that the ACC is more active during random compared to fixed sequences and research showing its lesions are associated with overall increases in reaction time as evidence supporting the entropy/uncertainty determined processing demand account of ACC activation (Di Pellegrino, Ciaramelli, & Ladavas, 2007; Fellows & Farah, 2005; Koechlin, Corrado, Pietrini, & Grafman, 2000; Vendrell, Junque, Pujol, Jurado, Molet, & Grafman, 1995).

Fan does note that there are potential problems in many of the ACC lesion studies. Many of the lesion studies made use of ratio scoring procedures ($\text{ConflictRT} - \text{NoConflictRT} / \text{OverallRT}$ or $\text{ConflictRT} - \text{NoConflictRT} / \text{NoConflictRT}$) which might

mask group differences in the congruency effect assuming the effect is correlated with overall RT which is often the case. Unfortunately, Fan does not point out specific studies that made use of ratio scores but more importantly it seems that Fan fails to realize that this pattern of results might be trouble for his own theory of ACC function (Fan, 2014). If conflict trials differed from non-conflict trials simply in terms of information entropy it is reasonable to assume both trial types would be equally affected by a decrease in processing capacity. Nevertheless, it is not necessarily the case that a processing capacity deficit would be present at all processing demand levels. An entropy threshold might serve as a delimiter of the presence or absence of a deficit. In addition, Fan downplays the importance of human single cell recording work that is incompatible with the lesion research showing an overall greater RT in subjects with ACC lesions (Fan, 2014; Sheth et al., 2012).

Research has shown that the ACC is involved in the biasing of sensory information relevant to the task at hand (Crottaz-Herbette, & Menon, 2006; Fan, 2014; Egner & Hirsch, 2005). Fan frames these findings as manifestations of the ACC's ultimate function manipulating the precision of option choice "beliefs", with greater precision comes with wider gaps between the likelihood of the most likely choice vs. all of its competitors. Essentially the ACC attempts to minimize the uncertainty of which choice will be made (Fan, 2014).

1.4 The Cingulate and Decision Making

PRO is a much better specified conception of ACC function compared to Fan's account but PRO has limitations as well. A major shortcoming of the original PRO model

was that it did very little to incorporate affective factors into the model despite abundant evidence that the ACC seems to have a role in motivational processing (Holroyd, & Yeung, 2012). The ACC is involved in reward processing and is part of a pain circuit (Bush et al., 2000). These factors should be taken into consideration by modelers. The ACC's proximity to the limbic system makes it a natural nexus of affect and cognition. Severe lesions of the ACC produce apathy and akinetic mutism (Paus 2001). For example, a patient that recovered from akinetic mutism, induced by a stroke that affected the left ACC, described her experience as that of having an "empty mind". Despite being aware of her surroundings, including the conversations of her doctors, she had no will to respond (Allman, Hakeem, Erwin, Nimchinsky, & Hof 2001; Damasio & Van Hoesen, 1983). Electrical stimulation of the anterior midcingulate cortex has been shown to elicit autonomic responses not to mention what was described as a need to overcome, and the will to persevere (Parvizi, Rangarajan, Shirer, Desai, and Greicius 2013). Additionally, patients with intractable pain treated with 5mm in diameter bilateral ACC lesions exhibited less spontaneous behavior and reported that they still experienced pain but they were less bothered by it (Allman, et al., 2001; Cohen, Kaplan, Zuffante, Moser, Jenkins, Salloway, & Wilkinson, 1999).

New incarnations of PRO have been developed that attempt to better incorporate the ACC's role in foraging decisions, choice difficulty processing, and effort exerted (Brown and Alexander, 2017; Vassena, Deraeve, & Alexander 2017). The PRO-Control model has the ACC acting as a minimizer of losses and a maximizer of gains (Brown & Alexander, 2017). According to the model the ACC does this by basing decision making

on cost signals from multiple time scales. This model marks a general trend towards a decision making conception of ACC function.

Animal research and recent research in human subjects has mustered up support for a decision making view (particularly foraging decisions) of ACC function (Kolling, Behrens, Wittmann & Rushworth, 2016). Foraging theory explains choosing to search for new sources of reward and engaging with the current source in terms of the search value and the engage value (Kolling et al., 2016). Human work in this area has come under criticism since the relative value of foraging (the value of a behavioral change vs. exploiting the default course of action, simply put, is the difference between the search value and the engage value) is often confounded with task difficulty as indexed by RT (Shenhav, Straccia, Cohen, Botvinick, 2014). According to theory at the point of indifference (relative value of foraging equal to zero, no difference between the value of searching and engaging) subjects should be equally likely to choose to forage or engage but Shenhav and colleagues observed a bias, in their subjects, to engage leading to a subjective indifference point that was rather high in terms of the objective relative value of foraging. This leads to a confounding of the relative value of foraging (RVF) and task difficulty since points near the subjective indifference point are the most difficult given the small differences in reward and RT is positively related to the RVF (Kolling et al., 2016; Shenhav, et al., 2014). Even though an equal number of trials on each side of the objective indifference point were used the greater subjective indifference point did not allow many trials that were high in search value but were not difficult (Kolling et al., 2016). These issues were addressed by Kolling and colleagues who made use extensive training and detailed task instructions in order to close the gap between the subjective and objective

indifference points (Kolling, Behrens, Mars, Rushworth, 2012). With only 2% of the variance in the search value, and the engage value shared with difficulty it can be safely said that this confound was minimized (Kolling et al., 2012; Kolling et al., 2016). Choice difficulty indexed by the distance from the indifference point and RT both were shown to produce ACC activation around the time of the decision. Also, these effects were located around the border of the dorsal ACC and the pre-supplementary motor area (Kolling et al., 2016). Search value yielded sustained ACC activation and engaged value had a negative effect on the ACC that occurred later in the trial (Kolling et al., 2016). These results parallel non-human primate work in a patch-leaving task showing that the firing of neurons in the dACC is associated with the value of searching (Hayden, Pearson, Platt, 2011).

Another interesting study investigated the ACC's role in model updating as opposed to the processing of surprise (Kolling et al., 2016). The PRO model conceives error related activity in the ACC as a product of surprise but Rushworth's group was interested in ACC activity driven by a change in the full set of expectancies (the model) as opposed to activity driven by deviations from prediction (Alexander & Brown 2011; Kolling et al., 2016; O'Reilly, Schuffelgen, Cuell, Behrens, Mars, & Rushworth, 2013). They looked into the differences between surprise and model updating with a saccade task involving a circle with a fixation cross placed in its center. On each trial a dot appeared at some point on the circle indicating where subjects had to make a saccade and the location of a dot's appearance was predictable since dots were mostly contained to a certain vicinity during and extended series of trials (O'Reilly et al., 2013). Surprise trials significantly deviated from the current trend. When a dot in a special color appeared a change in the model was signaled. Future dots would now appear in the vicinity of this dot. The degree

of model updating was measured by the Kullback-Leibler divergence which captures the discrepancy between two probability distributions (O'Reilly et al., 2013; Kolling et al., 2016). ACC activity was predicted by model updating but not by surprise (O'Reilly et al., 2013).

Intentionality is fundamentally related to decision making and the ACC and the mPFC more broadly seem to have a crucial role in intention. The ACC has been shown to be more active during voluntary task switching relative to explicit task switching (switching between tasks in accordance with some procedure like alternating runs or presentation of a cue that determines the task to execute on the upcoming trial) and the medial prefrontal cortex has been shown to be predictive of free task choices (Forstmann, Brass, Koch, & von Cramon, 2006; Demanet, De Baene, Arrington, Brass 2013; Haynes, Sakai, Rees, Gilbert, Frith, & Passingham, 2007; Orr & Banich, 2014; Soon, Brass, Heinze & Haynes, 2008; Soon, He, Bode, & Haynes, 2013). In a study that established response bias during a training session it was shown that the ACC in a voluntary task switching paradigm was more active when making an unbiased choice relative to when a biased choice was made (Demanet et al., 2013). Also, ACC activity was greater for trials without bias relative to trials that resulted in a biased choice. The authors admitted that the ACC activity could stem from the monitoring of conflict between internally driven and biased task choices but they favored interrupting the results in terms of intentional control related activity since the ACC was equally elicited by trials that were not biased by prior experience and when unbiased decisions were made (these trials were biased but the bias was properly countered). Also, biased choices were found to be more likely during periods of mind wandering (Demanet et al., 2013). On the other hand Orr and Banich did not find

that the ACC was involved in overcoming bias. They made use of a paradigm that had a separate decision phase where a task was chosen when a question mark appeared on the screen and then a task execution phase that occurred after a brief interstimulus interval (Orr & Banich, 2014; Orr, & Weissman, 2011). The paradigm included voluntary trials where subjects made a free choice during the decision phase keeping in mind that they should switch in a random fashion while keeping proportion of each task choice balanced as is customary in voluntary task switching paradigms and explicit switching trials where a task cue was given in the place of a question mark. The question marks and cues were flanked by two distractors which were either associated with one of the two tasks or neither (neutral). The contrast of voluntary and explicit trials showed activity in the lateral frontal pole, the AI, and the medial prefrontal cortex/dACC (mPFC) the key frontoparietal network regions the DLPFC and the inferior parietal lobule. These were regions marked by greater activation during voluntary trials relative to explicit trials but only the bilateral AI and the bilateral lateral frontal pole showed activation that was unique to the voluntary condition (Orr, & Banich, 2014). Contrary to the findings of Demanet and colleagues only the AI and lateral frontal pole were found to be involved in overcoming bias (Orr, Banich, 2014). Despite the disagreements in the results of Orr and Banich and the findings of the Demanet group both studies point to a role of the CON in intentional control.

The application of pattern classification methods to free choice paradigms has generally yielded results that supports a role of the ACC (more clearly the medial PFC) in decision making (Haynes et al., 2007; Soon et al., 2008; Soon et al., 2013). Haynes and colleagues noted the importance of ensuring that prediction of a decision must not stem from confounding factors like specific motor preparations. In order to prevent prediction

driven by specific response preparations the word select was presented to subjects and subjects were required to pick a task at this point in time but no overt response was required. The select signal was followed by a delay period which was followed by two numbers that could be added or subtracted based on the choice the subject made and then a set of four possible answers were presented (Haynes et al., 2007). MVPA (Multi-Voxel Pattern Analysis) revealed that voxels in the mPFC including the ACC during the delay period were predictive of the choice to engage in the addition or subtraction task. When MVPA was applied to a modified Libet paradigm that required subjects to make spontaneous decisions to press a left or right button, followed by a report of when the decision was made, while viewing a string of letters that were updated every 500ms (a replacement for the clock in the Libet paradigm the time of the intention was reported by the subject via selecting the letter that was present at point of the decision) the period up to 10 seconds prior to the reported awareness of the intention to action was predictive of the decision (Soon, et al., 2008). The precuneus extending into the posterior cingulate cortex and a region stretching from the frontal pole into the mPFC were predictive of the decision (Soon et al., 2008). In addition, subsequent research showed that these results can be partially replicated (predictive 4 seconds prior to the reported intention) in an addition subtraction task switching paradigm (Soon et al., 2013). The authors interpreted these findings as evidence for unconscious decision making processing but this is by all means a premature conclusion. The predictive power of these regions might reflect a conscious deliberation process that is taking place during the delay period or stochastic neural activity as opposed to an unconscious decision process (Schurger, Sitt, Dehaene, 2012). Nevertheless, this line of research adds to the case that the CON is critical for the formation of intentions.

Neural recordings taken from 12 epileptic patients during the performance of a Libet task showed ACC, and SMA activity prior to the reported moment that an intention entered conscious awareness (Fried, Mukamel, & Kreiman, 2011). Support vector machine classification provided superior accuracy when predicting finger movement based on SMA recordings as opposed to those taken from the ACC. The SMA has significant anatomical connectivity to the ACC and considering the increase in spiking observed in ACC neurons prior to the awareness of intention this study provides additional evidence in favor of its role in the formation of intentions (Fried et al., 2011).

1.5 Anatomy of the Anterior Cingulate

The anatomy of the ACC makes it well suited to act as a monitor and a regulator of cognition. Parcellation of the cingulate cortex via K means clustering based on structural connections has uncovered an interesting connectivity structure (Beckmann, Johansen-Berg, & Rushworth 2009). Clusters located in the midcingulate cortex were defined by strong connectivity to motor areas and clusters in the vicinity of the dACC extending into the midcingulate were marked by connectivity to the dorsal prefrontal cortex (Beckmann et al., 2009). Clusters in the ventral portion of the ACC were marked by connectivity to the medial and lateral orbitofrontal cortex, amygdala, hippocampus, and hypothalamus many of which are regions sometimes associated with the SN (Beckmann et al., 2009; Seeley et al., 2007). The connectivity parcellation of ACC fits Bush Luu, and Posner's dorsal/cognitive ventral/affective ACC divide quite well (Bush, Luu, & Posner, 2000). The dACC seems to be critical for interfacing with the environment given its roles in cognitive

control and motor responding. When it comes to the ACC's role in the initiation of actions the strongest anatomical support comes from the fact that the ACC's motor area projects directly to the spinal cord (Dum & Strick, 1991; Vogt, Finch, & Olson, 1992). Additionally, a hallmark symptom of seizures occurring in the ACC are automatisms (Devinsky, Morrell, & Vogt, 1995). Automatisms are common in temporal lobe epilepsy as well but the automatisms of ACC seizures tend to be more complex and occur earlier than those associated with temporal lobe seizures (Devinsky et al., 1995). Early research involving the stimulation of the ACC in human subjects reported the triggering of movements and facial expressions that depended on the environment which suggests a role action formation (Devinsky et al., 1995; Escobedo, Fernandez-Guardiola, & Solis, 1973; Talairach, Bancaud, Geier, Bordas-Ferrer, Bonis, Szikla, & Rusu, 1973).

Two key anatomical features of the ACC are the lack of cortical layer IV a major target of thalamic input and the presence of a large layer V a source of subcortical outputs (Allmann et al., 2001). It shares these features with nearby motor areas. The size of layer V might be indicative of wide reaching regulatory role mediated in part through the ACC's interactions with subcortical nuclei responsible for neuromodulation. Another factor that defines both the ACC and the AI is that they are home to large neurons known as spindle, or von Economo neurons (Allman et al., 2001; Allman, Tetreault, Hakeem, Manaye, Semendeferi, Erwin, Park, Goubert, & Hof, 2010; Von Economo, & Koskinas, 1925). These neurons are only found in humans, great apes, and macaque monkeys and some cetaceans and elephants (Evrard, Forro, & Logothetis, 2012; Fan 2014; Hakeem, Sherwood, Bonar, Butti, Hof, & Allman, 2009; Hof, & Van der Gucht, 2007; Nimchinsky, Vogt, Morrison, & Hof, 1995; Nimchinsky, Gilissen, Allman, Perl, Erwin, & Hof, 1999).

In the ACC these cells are present in layer Vb of BA 24. The concentration of Von Economo neurons is greatest in humans and the concentration of these cells is inversely related with phylogenetic distance from humans (Allman et al., 2001; Nimchinsky et al., 1995; Nimchinsky et al., 1999). Given that cell body size is likely positively related to the degree of axonal arborization it has been proposed that these cells have widespread connections spanning across many brain regions and the dendritic trees of Von Economo neurons have been shown to be narrow (Allman et al., 2001; Allman et al., 2010; Watson, Jones, & Allman, 2006). The speculation of far reaching connectivity is supported by widespread connections of Von Economo neurons found in macaque monkeys (Evrard, et al., 2012). The Von Economo neurons have a high level of symmetry between the apical and basal dendrites and it has been suggested that this is indicative of an input comparison function for the Von Economo neurons (Allman et al., 2010; Watson et al., 2006). This fits well with the literature linking the ACC and decision making which is by its nature a comparative process. It is likely that Von Economo neurons may have a key role to play in maintaining the functional integration of the CON and its communication with other networks but a precise understanding of their function remains elusive.

The hierarchical reinforcement learning model of the ACC (HRL-ACC) has a fairly well informed physiological grounding (Holroyd & McClure, 2015). The model proposes that the ACC controls extended goal directed behavioral sequences rather than the fine grain details of action (Vassena et al., 2017). Basically, the key distinction is strategy vs. tactics. This line of thinking is compatible with speculations of the Petersen group regarding the function of the wider CON (Dosenbach et al., 2007). HRL-ACC breaks the ACC into caudal and rostral components but unlike Bush and colleagues, Holyroyd and

McClure have a well specified description of the interaction between these components. The caudal component selects tasks, monitors lower level actions and provides a control signal that will reduce the amount of effort needed to complete the task (Holroyd & McClure, 2015). The caudal component is monitored and regulated by the rostral component. This component allows for switching between task strategies by reducing the cost of switching at the level of the caudal component. Tonic dopamine levels which represent reward modulate the degree of control (Holroyd & McClure, 2015). The ACC is heavily innervated by dopamine and dopaminergic agonists have been used to treat akinetic mutism induced by Parkinson's implying that dopamine might play a critical role in ACC functioning (Allman et al., 2001; Kuenig, Leenders, Martin, Magyar, & Schultz, 1999; Gaspar, Berger, Febvret, Vigny, & Henry, 1989). HRL-ACC was designed to explain rodent behavior and it accounts for foraging by associating exploiting a current patch with increased caudal control and switching/searching with increased rostral control (Vassena, et al., 2017).

The physiology of the ACC implies that it might have a special place in the upper echelon of a cognitive hierarchy. The scope of the ACC's functional associations is tremendous and a simple account of this region's functionality remains out of grasp. Theories that have attempted to capture the behavioral correlates of the ACC under one function have come close but consistently fall short of covering the full span of its functionality (Alexander, & Brown, 2011; Botvinick et al., 2001; Holroyd, & McClure, 2015). Multifunctionality is a real possibility and if this the case a unifying model might forever elude scholars.

1.6 *The Need for Synthesis*

Despite the challenges facing the field of ACC research the quest for a unifying theory is far from hopeless. Multifunctionality is not unlikely but the connections between the functions associated with the ACC implies that this region might embody some kind of process common to all of the proposed functions. In the modeling literature there seems to be a general move towards synthesis. PRO has a wide scope of predictive ability and is branching off into many new theories (Vassena, et al., 2017). Botvinick was early to point out the need to create a synthesis of choice accounts of the ACC and monitoring accounts (Botvinick 2007). This new perspective has not been embodied in a fully detailed computational model as of this point in time but the cost benefit analysis view that attempts to unify decision making and monitoring meta-accounts of the ACC has plenty of room to incorporate the factors that have the focus of the clinical neuropsychologists and physiologists (Shenhav, Botvinick, & Cohen 2013). The expected value of control (EVC) theory views the ACC as an aggregator of signals. The ACC integrates expected costs and expected rewards in order to determine the value of the implementation of control on a trial. The model assumes that engaging control processes is intrinsically costly. The EVC is defined as the sum of the probability of each outcome given the current state (e.g., degree of motivation, difficulty of the task at hand, and other factors) and the current control signal (e.g., task representation intensity, alertness level, degree of attentional focus, and other factors) times the corresponding outcome value all minus the cost of the control signal (Shenhav et al., 2013). Value can be positive or negative and is based on the immediate reward plus the product of a discounting factor and the maximum EVC given the outcome and all feasible levels of the control signal. The control signal specification process was

proposed to be the maximization of the EVC given the current state. Conceptually the cost benefit analysis framework of the EVC account is appealing although it lacks the sublime simplicity of PRO. Nevertheless, a computational model based on the EVC needs to be fully developed. PRO-Control is a computationally well specified attempt to bridge different accounts of ACC function that, like the EVC theory, views the ACC functionality through the lens of cost benefit analysis (Brown, Alexander, 2017). This model through further evolution might develop into a unifying account of ACC functionality.

Another pathway towards a unitary model of the ACC/mPFC function might come from the predictive coding literature (Friston, 2008). This hierarchical framework for understanding cognition and its neural embodiment was originally applied to the perceptual processes but it has been used to explain motor control by replacing motor commands with motor “predictions” (Edwards, Adams, Brown, Parees, & Friston, 2012; Friston, 2008). Each level of these hierarchies contains prediction units and error units. The “beliefs” of a lower level are predicted by the prediction units of an adjacent higher level. The error units of the lower level receive the predictions of the higher level and compare them to the state of the prediction units on its level thereby calculating a prediction error. The predictions of the upper level are adjusted based upon the prediction error of the lower level (Friston, 2008). The goal of predictive coding modeling is to minimize the prediction error. Alexander and Brown have introduced a new model that attempts to unify theories of the prefrontal cortex and the mPFC by creatively applying the predictive coding framework (Alexander, & Brown, 2015; Alexander, & Brown, 2016). The hierarchical error representation (HER) model replicates many empirical findings and has demonstrated faster learning than standard machine learning methods (Alexander, & Brown, 2016). The

HER model builds off of PRO which assumes prediction errors are calculated in the mPFC and that a processing hierarchy stretches posterior to anterior regions (Alexander, & Brown, 2011; Alexander, & Brown, 2015; Alexander, & Brown, 2016). According to HER the DLPFC attempts to predict the prediction errors calculated by the mPFC. Higher levels attempt to minimize the residual error of the lower levels. In psychological terms the model proposes that the contents of working memory are those that help minimize prediction error (Alexander, & Brown, 2016).

When it comes to motivations and goals predictive coding can account for these factors as priors at the upper levels of a hierarchy (Friston, 2008; Friston, 2013). Outside of HER is another path to applying predictive coding to understand the interaction of the ACC with other brain regions. Given the ACC's well developed layer V and projects to subcortical nuclei it might have a role in determining a statistical factor of vital importance in predictive coding hierarchies, precision (Allman et al., 2001; Aston-Jones, & Cohen, 2005; Feldman, & Friston, 2010; Verguts, & Notebaert, 2008). Precision is defined as the inverse variance and the precision of the prediction errors determines the weight given to the errors when updating predictions. If the precision is high at low levels relative to higher levels ascending prediction errors will have more influence on higher level predictions but if the relative precision is greater at higher levels prior "beliefs" will dominate (Edwards, et al., 2012; Friston, 2008; Lawson, Rees, & Friston, 2014). In terms of physiology precision is believed to be a function of attention and instantiated by the synaptic gain of the error neurons which is affected by neuromodulators (Feldman, & Friston, 2010; Mumford, 1992). ACC might through a proxy like the locus coeruleus (LC) manipulate the relative precision of different processing regions in the cortex. This is an idea similar to one put

forth by Fan but he failed to emphasize that changes in relative precision could be manifested in the neocortex's connectivity profile (Fan, 2014). How a precision imbalance would impact the functional connectivity between the regions of a predictive coding hierarchy is ambiguous since the predictions in levels with weaker relative precision would still be influenced by stronger levels, implying that functional connectivity, but important changes are made to the structure of effective connectivity. The effective connectivity of a high precision level may increase, given its increased influence on predictions at other levels, relative to a situation where precision was roughly equivalent across levels. On the other hand, the effective connectivity of relatively weaker regions would decrease relative to a more even playing field. In one sense, you have decoupling since information flow is less bidirectional. This scenario is speculative but it illustrates a point that it is easy to conceive of the ACC as having a role in the regulation of communications between different brain regions. Thinking about the ACC from a connectivity perspective might help integrate ideas regarding the many different processing signals observed in the ACC/mPFC. Cost benefit analysis and predictive coding accounts of the ACC have great prospects but they are in their infancy. Unfortunately thinking about the ACC functionality from a connectivity perspective is limited and deserves greater attention.

1.7 The Physiology and Functions of the Anterior Insula

The AI, like the ACC, has been associated with the pain circuit not to mention the “feeling of knowing” and insightful problem solving of anagrams (Allman, et al., 2010; Aziz-Zadeh, Kaplan, Iacoboni, 2009; Craig, 2011; Kikyo, & Ohki, 2002). The AI is also

active at moment of recognition when visual stimuli presented to subjects slowly emerge from noise (Ploran, Nelson, Velanova, Petersem, Wheeler, 2007). The AI has also been implicated in error processing (Klein, Endrass, Kathmann, Neumann, Von Cramon, & Ullsperger, 2007; Klein, Ullsperger, Danielemeier, 2013; Ullsperger, Harsay, Wessel, Ridderinkhof, 2010). After each trial of an antisaccade task subjects made a response that indicated if they believed they made an error (Klein, et al., 2007). Both the ACC, pre-SMA, and the AI were associated with errors. Only the AI showed greater activation for a contrast of aware vs. unaware errors (Klein, et al, 2007). In line with previous research post error slowing only occurred after errors subjects were aware of and the extent of post error slowing was positively related to activity in the rostral cingulate zone (Debener, Ullsperger, Siegel, Fiehler, Von Cramon, & Engel, 2005; Garavan, Ross, Murphy, Roche, & Stein, 2002; Hester, Foxe, Molholm, Shpaner, & Garavan, 2005; Klein, et al., 2007; Kerns et al., 2004; Nieuwenhuis, Ridderinkhof, Blom, Band, & Kok, 2001). Error awareness seems to be a key factor that allows the ACC's error signal to lead to performance adjustments and the AI might mediate this relationship. In a meta-analysis of 55 fMRI the AI was active during all conditions associated with cognitive adjustments (Klein et al., 2010). Decision uncertainty, errors, negative feedback and conflict all elicited AI responses. The AI has a well-established role in autonomic awareness as well and its role in error awareness might be linked to this function (Klein, et al., 2010). A prime example of the linkage between AI and autonomic effects is the positive relationship between AI activity and galvanic skin response (Critchley, Elliott, Mathias, Dolan, 2000). Norepinephrine is a driving force behind sympathetic excitation and the down regulation of parasympathetic tone. Baseline pupil diameter a popular index of tonic LC

norepinephrine tone before and after aware errors was correlated with AI activity not to mention regions associated with error processing (Aston-Jones, & Cohen, 2005; Harsay, Cohen, Spaan, Weeda, Nieuwenhuis, Ridderinkhof, 2010; Klein, et al., 2010).

The AI has been proposed to play a key role in general homeostatic awareness. Craig (2011) pointed out that the mid-insula a structure only found in humans is activated by more than just interoceptive demands, the traditional function ascribed to the insula, but mechanoreceptive, and proprioceptive stimulation also evoke responses in this region. He proposed that the mid-insula aggregates many sources of information in order to relay a unitary representation of homeostatically salient features to the AI. Craig (2010) dubbed this global representation “the sentient self”. This proposed representation of one’s current bodily/affective state is associated with an opponent process. A long line of research has implicated the right insula with negative emotions and the left insula with positive emotions allowing for bivalent feelings in Craig’s model (Craig, 2005; Craig, 2009; Craig, 2010). The right and the left insula are also affiliated with sympathetic and parasympathetic tone respectively (Craig, 2005).

An anterior to posterior gradient in the insula’s connectivity profile has been observed in monkeys (Cerliani, Thomas, Jbabdi, Jeroen, Siero, Nanetti, Crippa, Gazzola, D’Arceuil, Keysers, 2012). AI is mainly connected to the amygdala, OFC, and rostral inferior frontal gyrus (IFG). The posterior insula is connected primarily with the caudal IFG, posterior temporal, and parietal regions (Cerliani, et al., 2012; Klein, et al., 2013). The structural connectivity between the insula and the IFG makes sense when considering the CON’s proposed role in task maintenance. The inferior frontal junction (IFJ) is in close proximity to the AI, not to mention the IFG, and it exhibits greater activity on task

switching relative to repeat trials, trials that require working memory updating, and greater conflict related activity (Sakai, 2008).

Like the ACC the AI has Von Economo neurons and they are concentrated in the inferior AI (Allman et al., 2010). Comparison of human brains to the brains of great apes showed that, across species, Von Economo neurons were more frequent in the right hemisphere for both the ACC and the AI (Allman et al., 2010). Allman and colleagues inspired by Craig proposed that the role of the right hemisphere in sympathetic mobilization had something to do with the discrepancy in Von Economo neuron representation arguing that the rapid relaying of error feedback information which would likely require sympathetic activation was more important due to downside risk than the speed of information transfer related to positive outcomes that evoke an increase in parasympathetic tone. Another interesting finding from this study, that happens to be rather pertinent to functional brain networks, comes from a structural connectivity analysis. Diffusion tensor imaging conducted on a gorilla uncovered connections between the Von Economo containing region of the AI and the frontal pole, another key node of the CON, not to mention the amygdala (Allman, et al., 2010).

Like the ACC, the AI has a unique neural infrastructure that can serve as a foundation for a far reaching regulatory system. Cognitive adjustments might be dependent on awareness states that related to the functioning of the AI. Like the ACC it has the potential to help bridge cognition and affect.

1.8 *The Fluidity of Networks*

The relations between brain networks have been shown to be context dependent (Cocchi, Zalesky, Fornito, & Mattingley, 2013). For example, using a special correlation psychophysiological interaction analysis Fornito and colleagues examined the task dependence of correlations of the time courses of ICA defined networks. Greater task related connectivity between DMN and FPN components was found during a recollection task the faster RTs were related to greater task related positive connectivity between these networks (Fornito, Harrison, Zalesky, & Simons, 2012). Typically, performance is hindered by a breakdown in the antagonistic relationship between these networks but many paradigms are heavily dependent on externally orientated (Thompson, Magnuson, Merritt, Schwarb, Pan, McKinley, Tripp, Schumacher, & Keilholz, 2013).

A recent meta-analysis of 5 studies that made use of slow reveal tasks uncovered differing trends in the left FPN, right FPN, and the CON (Gratton, Neta, Sun, Ploran, Schlaggar, Wheeler, Petersen, & Nelson, 2017). Analysis of the time course of the hemodynamic response showed that the right FPN not only showed late onsets but prolonged responses suggesting that these regions might be involved post-recognition processing possibility including cognitive adjustment (Gratton et al., 2017). The prolonged effect might represent some sort of updating process. Given that Kerns and colleagues found that previous trial ACC activity was predictive of current trial activity in the right DLPFC this is not an unreasonable hypothesis. The left FPN on the other hand was marked by an early accumulator like response strongly suggesting a role in pre-decision processes (Gratton, et al., 2017). The CON exhibited a transient response with a late onset. The authors concluded that this decision event linked CON signal likely reflects what they

called performance reporting (Gratton, et al., 2017). An alternative account that is not mutually exclusive with performance reporting is that the CON might be integrating the FPN information (accumulated evidence) relevant to a decision and possibly carrying out the actual decision making process. This fits well with the literature on the ACC's role in intentional control and decision making (Allman, et al., 2001). Before trying to determine the exact types of processes being conducted by the FPN and CON it is necessary to better understand the context dependence of functional connectivity within and between these networks.

Situations involving sequential adjustments of cognition would be ideal for gaining a better understanding the potential trial by trial interactions between the CON and the FPN. Although the precise mechanisms behind the CSE can be debated it is likely the case that the confound minimized CSE reflects the adjustment of cognitive control. Confound minimized CSE paradigms have been shown to replicate the event related potential effects associated with the CSE (Larson, Clayson, Kirwan, Weissman, 2016). It remains to be seen if the findings of Kerns and colleagues can be replicated with a confound minimized CSE procedure. Given what is known about the CON/SN it is certainly plausible that performance adjustments are dependent on its connectivity with the FPN and that it may somehow manipulate the information sharing between the nodes of the FPN based on performance demands. Context dependent, more specifically adjustment dependent, connectivity between the CON and the FPN merits investigation.

1.9 *Outline of Predictions*

Given what is now known about the interaction of functional networks the parallel processing hypothesis of the CON and the FPN is likely unsound (Dosenbach et al., 2007). The alternative account that the FPN feeds the CON task initiation and feedback related information that can be used to adjust task parameters is more likely (Dosenbach et al., 2007). Also, the CON is in an excellent position to modulate the information sharing between the nodes of the FPN. The proposed study is intended to test two predictions the first being that connectivity between the FPN and the CON will be greater on trials preceding high behavioral adjustment trials and the second being that previous trial activity in the CON will modulate task related activation in the FPN over and above the influence of previous trial FPN activity. The second hypothesis is not directional. A high level of CON activity on the preceding trial could lead to a mobilization of the FPN that could manifest itself as greater responsiveness to the stimulus on the subsequent trial. Alternatively, greater CON activity on the previous trial could lead to weaker responses to the stimulus on the subsequent trial due to greater cognitive preparation. Additionally, previous trial CON activity should predict current trial reaction time over and above previous trial FPN activity. If the FPN and CON share performance based information that is pertinent to behavioral adjustments then functional coupling should be greater prior to high adjustment trials. Also, if the CON makes unique contributions to performance monitoring it may modulate subsequent trial FPN activity. Given the evidence showing that the FPN is involved in feedback processing and the presence of autocorrelation in the BOLD time series it is imperative to account for previous trial FPN activity when testing this prediction. Granted the FPN has been proposed to relay feedback related information to the CON and

controlling previous FPN might obscure the CON's role in the modulation of subsequent trial activity considering that the shared variance between the two could reflect an exchange of feedback related information (Dosenbach et al., 2007). Nevertheless, a large mass of research has provided evidence that the CON regions are involved in performance monitoring and this network's monitoring functions may not be completely dependent on information processed in the FPN. The general goals are to both see if the findings of Kerns and colleagues generalizes to a network perspective and test for functionally relevant interactions of the CON and FPN.

CHAPTER 2: METHODS

2.1 *Subjects*

The study made use of the SONA subject pool and subjects were compensated with either 1 credit per hour or \$10 per hour. Data was collected from 39 subjects (20 males) with an age range of 18 to 30. Of these 39 subjects two chose to drop out. Two subjects were removed from the imaging analysis due to excessive motion (15% or more of TR's censored based on AFNI's censoring procedure with a motion threshold of .3mm) and two subjects were removed due to differences in the field of view cutting off certain regions of interest. All subjects were right handed, at least 18 years of age and had normal or corrected to normal vision. Individuals with neurological or psychiatric disorders were excluded from the study. Additionally, those with medical conditions that increase the risk of aversive effects in the scanner environment were not be admitted into the study.

2.2 *Behavioral Task & Analysis*

The confound minimized paradigm used in this study is derived from the work of Kim and Cho (2014). Three circles were presented at the center of the screen for 2,000ms. Subjects had 2,000ms to respond. The target was the central circle and the flankers acted as distractors. The circles appeared in different colors and on every trial, alternated between horizontal or vertical orientations. There was a total of four colors which were grouped into pairs, red-blue, and green-yellow. Each color set only appeared in one stimulus orientation. All ITIs consisted of a fixation cross and a black background. For

each block each stimulus appeared an equal number of times. In addition, the trial order was pseudo-randomized with the constraint that an approximately equal number of congruency sequences (iI, iC, cC, cI) were presented in each block. Because the first trial of each block had no preceding trial one sequence occurred one trial less often than the other sequences.

Pilot testing was employed in an attempt to determine the optimal task design. The confound minimized CSE paradigm was piloted in behavioral testing rooms over two sessions. In one session, it included blocks with 50% of the ITIs lasting 2,000ms, 25% lasting 4,000ms, and the 25% lasting 8,000ms. This distribution of ITIs has been shown to allow proper estimation of event related BOLD response (Ollinger et al., 2001a; Ollinger et al., 2001b). The other session had ITIs of 2,000ms, 4,000ms, and 6,000ms uniformly distributed. Both versions included stimulus durations of 2,000ms and blocks of 96 trials with a duration of 9.6 minutes (not including four seconds of block level feedback at the end of the block). Subjects completed 6 blocks with each ITI distribution not including a 48 trial practice block with trial level feedback that was given prior to the scan in a testing room during the actual study. Both of the versions of the task were coded in Psychology Software Tools' E-prime software. Subjects responded via MR compatible button boxes using their index and middle fingers of their right hand. Subjects were told to work as quickly and as accurately as possible.

The pilot testing was necessary considering that the CSE has been shown to attenuate with response to stimulus interval duration (Egner et al., 2010). The CSE was shown to be significant in a 500ms-1,000ms bin, a 1,500ms-2,000ms bin, and a 2,500ms-3000ms bin but statistically insignificant in 4,000-5000ms, and 6,000-7000ms bins. The

4,000ms-5000ms bin was not statistically significant but it did exhibit a CSE of a little less than 10ms while the 6,000-7000ms bin clearly did not contain a CSE (Egner et al., 2010). The authors noted that imaging studies have yielded CSE's with relatively long ITIs (Egner et al., 2005; Egner et al., 2007; Egner et al., 2008). Reanalysis of Egner et al., (2008) which made use of a uniform ITI distribution of 4,000ms, 5,000ms, and 6,000ms ITIs showed a trend of CSE attenuation but the interaction of ITI duration and the CSE was not significant (Egner et al., 2010). It was not clear what the ITI distribution should have looked like for this study given the inconsistent findings regarding the time course of CSE attenuation and the challenges imposed by the sluggish nature of the BOLD response on event related designs (Dale, 1999). If the Kim and Cho task did not produce trending CSEs with the afore mentioned jittering regiments another paradigm like the face Stroop task used by Egner et al., (2010) would have been adapted to suit the proposed studies aims.

Alternatives to the Kim and Cho task had certain shortcomings given the aims of this study. For example, the face Stroop task requires subjects to respond to the gender of a face when a black and white picture of a face is presented as the underlay to a gender word (male or female) written in red font in either upper or case letters. The case of the font switches each trial and the same face never appears on successive trials ensuring an absence of stimulus repetitions. When it comes to response repetitions the trial order is arranged so that half of trials are complete alternations and half are partial repetitions (due to a response repetition and stimulus alternation). In order to remove the stimulus response repetition confound only the complete alternation trials can be analyzed thus eliminating half of the data collected from analysis (Egner et al., 2010). This task was undesirable for this reason.

Another alternative was using one of the many paradigms with distractors preceding the target given that these tasks produce more robust confound minimized CSEs than task with simultaneous presentation of the distractor and the target (Weissman et al., 2015). The problem with these tasks is that Kerns et al., (2004) made use of a task with simultaneous distractor-target presentation. A confound minimized Stroop paradigm was another potential course of action but this task has the serious shortcoming of the Stroop task, vision blurring strategies (Bertone, Bettinelli, & Faubert, 2007). Subjects were encouraged to work as quickly and as accurately as possible, as would have been the case if any other paradigm previously discussed was chosen, in order to help homogenize the emphasis placed on speed and accuracy (Pachella et al., 1974).

The RT and accuracy data were analyzed using SPSS, Excel, and MATLAB. The presence of the CSE was tested by a previous trial congruency by current trial congruency ANOVA. An arcsine transform was applied to the accuracy data.

2.3 fMRI Preprocessing & Analysis

The scanning was conducted at the Center for Advanced Brain Imaging with a 3T Prisma^{fit} scanner. Subjects started the session by completing practice trials outside the scanner. In total the scan time was approximately 90 minutes. The session included six functional runs (T2*Weighted Echo-planar multiband sequence) with a TR of one second, TE of 30ms, multiband factor of 2, 32 slices, 4mm slice thickness, and a 220mm field of view, lasting 9.7 minutes (582 TR's per functional run) each and a voxel size of (3.4×3.4×4.0). A structural scan (roughly 6 to 7 minutes) and field mapping were

conducted prior to the functional runs. Subjects were in the scanner for a little short of 90 minutes.

The NIH's AFNI package and custom MATLAB code were used for fMRI data preprocessing and analysis. The preprocessing started with despiking of the data. AFNI does this by computing the difference between each voxel time series and a smooth curve and then obtaining the mean absolute difference of the residual series. A transform was applied when the standard deviation of a voxel's residuals from the mean absolute difference was greater than a threshold of 2.5. Despiking was followed by motion correction. This step was carried out by aligning functional scans to a base (the 3rd scan) using cubic interpolation. This was followed by registration of the functional scans to the anatomical scan with a localized Pearson correlation cost function. The data was then transformed to the Montreal Neurological Institute (MNI) template space and voxels were spatially smoothed with a full width at half maximum (FWHM) Gaussian kernel of 6 mm. Each voxel time series was then scaled to have a mean of 100.

This study required more than one regression model. All models included a constant, a linear, quadratic, cubic, and quartic trends in addition to 6 motion regressors. The first analysis was based on the beta series correlation approach (Rissman, Gazzaley, & D'esposito, 2004). Each trial had its own individual predictor. This method has been used to model adjacent stages of a trial (cue, delay, probe) thus offering a detailed description of the changing connectivity landscape across processing stages (Rissman, et al., 2004). The other models included traditional trial type predictors as opposed to individual trial predictors.

Each correct trial with the exception of the last trials in a run were modeled as separate predictors. The model included a single regressor for error trials and single regressor for the last trial in each block since these trials do not precede any trials. The individual trial predictors were labelled based on their status as the first trial in sequence (Ii, Ic, Cc, Ci, & pre-error trials). Average beta time courses, for each trial type, were calculated for the nodes belonging to the CON (40 nodes) and the FPN (24 nodes) in Gordon and colleagues' ROI set (Gordon, Laumann, Adeyemo, Huckins, Kelley, & Petersen, 2016). For each trial type each ROI beta time course was Z scored. In order to remove periods marked by extreme movement global outlier time points were removed. Global outliers were defined as time points where at least 80% of the ROI's had Z scores of greater than or equal to an absolute value of 2. Incongruent trials were separated based upon if they preceded high and low adjustment trials. High and low adjustment was based off a median split of trials based on RT (Kerns et al., 2004). For Ii, high adjustment trials were defined as relatively fast trials while for Ic high adjustment was defined as relatively slow trials. Kerns and colleagues relied on median splits and top and bottom quartiles for defining high and low adjustment. A slightly different approach was taken here. Instead of using a global median split (based on all trials across blocks) a local median split was carried out for each block. This was intended to mitigate the effects of global performance adjustments stemming from factors like fatigue (Dutilh, van Ravenzwaaij, Nieuwenhuis, van der Maas, Forstmann, & Wagenmakers, 2012).

All pairwise correlations between the nodes of the two networks were obtained for high adjustment Ii trials, low adjustment Ii trials, high adjustment Ic trials and low adjustment Ic trials. Fisher's Z transform was applied to the correlation values and paired

t-tests were performed between incongruent trials preceding high adjustment and those preceding low adjustment trials. Group level analyses of the inter-network connections were conducted via single sample t-tests corrected by the Benjamini-Hochberg procedure for determining the false discovery rate (Benjamini, & Hochberg, 1995).

In order to study the modulation of current trial stimulus evoked FPN responses by previous trial CON activity, for each subject the residuals of a multiple regression were used as an index of CON specific activity. The beta series for each node of the FPN served as predictors of the average beta series across all CON nodes. Residual series were obtained for each subject. A separate model that simply predicted a right ACC (overlapping with the Kerns et al., 2004 1,10,40 Talairach region) node's beta series was fit as well. The residuals were used as parametric modulators of current trial activity. Four parametric modulation models were analyzed. Two used the residuals of the average preceding trial CON signal residuals and the other two used the dACC ROI preceding trial residuals as a parametric modulator of current trial activity. For each residual series one model collapsed across adjustment level and the other had separate predictors for high and low adjustment (iI high, iI low, iC high, & iC low). These models included a predictor for error trials, five sequence predictors (9 when based on onsets for the second trial in a sequence (iI, iC, cC, cI, & _post error trials), and a junk predictor for the first including the first trial in each run and trials classified as global outliers. TR censoring was carried out as an additional safeguard against the influence of motion. This was not implemented for the individual trial regression model since it would not permit the modeling of certain trials. The motion censoring removed time points based on a Euclidean norm of the backward difference with a .3mm as a threshold. The residuals of preceding incongruent trials were

expected to influence the amplitude of the subsequent trial response. A positive or a negative relationship could be expected. Positive modulation might reflect increased readiness and a negative relationship might reflect neural efficiency stemming from preparation.

When it comes to the influence of preceding congruent trials on current trial activity the outcome was even harder to anticipate. On average incongruent trials preceded by congruent trials should exhibit greater activation than incongruent trials preceded by incongruent trials. It might be the case that CON activity on congruent trials may still have a modulatory role given that attentional lapses and other forms of interference may occur on congruent trials (Yeung, et al., 2004). If FPN-CON connectivity is greater for incongruent trials residual variance in the CON should be greater for the preceding congruent trials. This is a potential key difference between the two trial types.

Also, considering the CON's potential role in cognitive adjustments, these residuals were expected to have a negative relationship with subsequent trial reaction time. A multilevel modeling approach was chosen given that trials are nested within subjects. Two modeling streams were assessed one for the CON residuals and the other for the dACC residuals. Models were constructed in a stepwise fashion and the Bayes information criterion (BIC) was compared between models. A model with a minimum BIC is generally considered ideal. The BIC rewards model fit but also penalizes based on the number of parameters thus discouraging overfitting (Schwarz, 1978). Parameters were estimated via maximum likelihood estimation. The first incarnation of the model included only a fixed intercept and a random intercept, and the second incarnation added a fixed slope for previous trial residual. The third incarnation included three additional fixed slopes. Three

dummy coded trial type predictors (cC serving as the reference) were added to the model. The fourth incarnation added three fixed interaction effects (residual x cI, residual x iI, & residual x iC). Other interactions were not included in the model in order to avoid excessive complexity. The fifth stage added a random slope for previous trial residual. In the event that the parameter estimation process failed to converge the random effects were constrained to be unrelated. For both the CON and ACC residuals the model with the minimum BIC was chosen. After model selection restricted maximum likelihood was employed in order to obtain better estimates of random parameters.

CHAPTER 3: RESULTS

3.1 Pilot Sessions

A total of 11 subjects (4 males) took part in the pilot study. The practice was given prior to each session. Sessions took place within a week of each other. The ITI schedule presentation order was counterbalanced between subjects. One subject did not complete the uniform distribution ITI schedule session.

A three factor within subjects ANOVA (Previous trial congruency x current trial congruency x ITI) on the RTs of the exponential ITI distribution schedule only revealed significant main effects for current trial congruency, $F(1, 10) = 30.367, p < .001, \eta_p^2 = .752$, and ITI, $F(1.243, 12.429) = 4.440, p < .05, \eta_p^2 = .307$. The Greenhouse-Geisser correction was applied to effects vulnerable to violations of the sphericity assumption. Post hoc comparisons showed that the main effect of ITI was driven by a difference in the means of the trials following two second ITI's (the relatively slow RT trials) and those after four second ITI's, $t(10) = 2.494, p < .05$, but this effect was not significant after Bonferroni correction. Despite the previous trial congruency x current trial congruency interaction that defines the congruency sequence effect being insignificant, $F(1, 10) = .624, p = .448, \eta_p^2 = .059$, figure 1 shows a trend towards a CSE driven by an adjustment in iC trials (as is common in many confound minimized paradigms) and despite the lack of a three way interaction between previous trial congruency, current trial congruency and ITI, $F(1.641, 16.405) = .508, p = .609, \eta_p^2 = .048$, it seems that the trend is only present for trials preceded by two second ITIs.

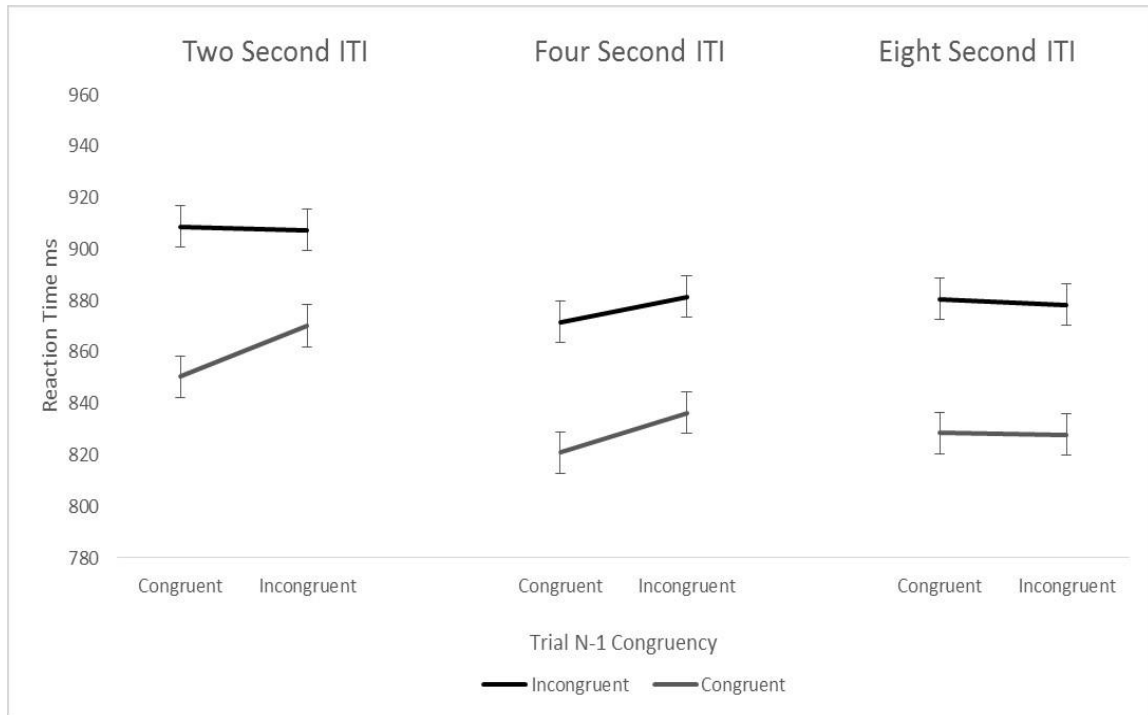


Figure 1-Congruency sequence effect by ITI for the exponential ITI schedule session. The error bars represent the standard error for the interaction of current trial congruency, previous trial congruency and the preceding interval.

Analysis of the uniform distribution ITI schedule session's RTs only revealed significant effects for current trial congruency, $F(1, 9) = 7.888, p < .05, \eta_p^2 = .467$, and ITI, $F(1.210, 10.888) = 15.041, p < .05, \eta_p^2 = .626$. The main effect of ITI was driven but a statistically significant difference between trials following two second ITI's and those following four second ITI's, $t(9) = 5.293, p < .001$. The effect survived Bonferroni correction. As with the other ITI schedule the CSE was not significant, $F(1, 9) = .328, p = .581, \eta_p^2 = .035$. Despite the lack of a significant previous trial congruency, current trial congruency, and ITI interaction, $F(1.178, 10.604) = .647, p = .647, \eta_p^2 = .067$, figure 2 shows that a pronounced CSE is present for the six second ITI a weak one for the four

second ITI but a negative CSE (more interference after incongruent trials) was present after two second ITIs.

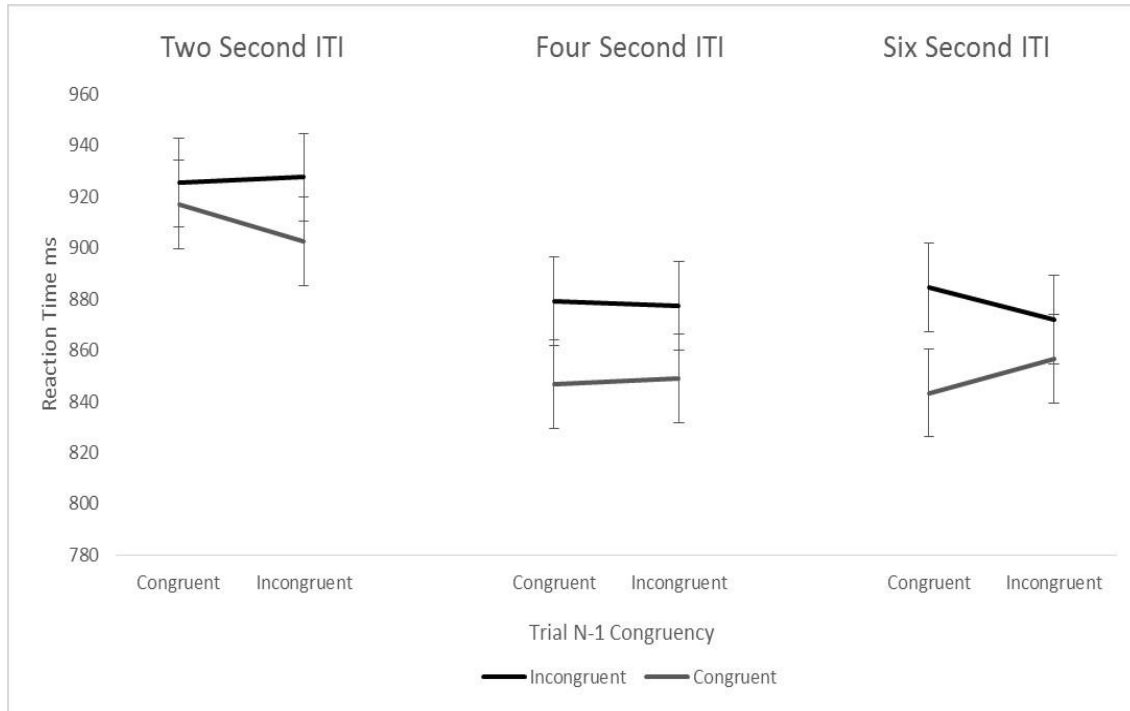


Figure 2-Congruency sequence effect by ITI for the uniform ITI schedule session. The error bars represent the standard error for the interaction of current trial congruency, previous trial congruency and the preceding interval

An ANOVA of the arcsine transformed accuracy proportions simply yielded a significant main effect of current trial congruency, $F(1, 10) = 8.929, p < .05, \eta_p^2 = .472$, for the exponential distribution ITI schedule session. The same analysis applied to the uniform distribution ITI schedule session only yielded a significant main effect of current trial congruency, $F(1, 9) = 17.678, p = .05, \eta_p^2 = .663$, as well. This was driven by higher

accuracy for congruent trials as would be expected. The means and standard deviations of the reaction time and accuracy data from exponential and uniform sessions can be found in tables 1 and 2 respectively.

Table 1-Exponential Distribution Session Means (Standard Deviations)

Trial Type	Two Second Interval	Four Second Interval	Eight Second Interval
cC Reaction Time	850 (171)	821 (127)	829 (150)
cI Reaction Time	909 (157)	872 (137)	881 (132)
iC Reaction Time	870 (172)	836 (154)	828 (149)
iI Reaction Time	907 (179)	882 (165)	878 (148)
cC Accuracy	.98 (.02)	.99 (.01)	.98 (.03)
cI Accuracy	.96 (.04)	.95 (.04)	.97 (.03)
iC Accuracy	.98 (.03)	.98 (.02)	.98 (.03)
iI Accuracy	.96 (.03)	.98 (.03)	.98 (.03)

Table 2- Uniform Distribution Session Means (Standard deviations)

Trial Type	Two Second Interval	Four Second Interval	Six Second Interval
cC Reaction Time	917 (175)	847 (178)	843 (147)
cI Reaction Time	925 (161)	879 (137)	885 (139)
iC Reaction Time	903 (177)	849 (141)	857 (161)
ii Reaction Time	928 (177)	878 (144)	872 (136)
cC Accuracy	.98 (.03)	.98 (.02)	.97 (.03)
cI Accuracy	.97 (.01)	.98 (.01)	.98 (.02)
iC Accuracy	.96 (.04)	.98 (.02)	.97 (.02)
ii Accuracy	.96 (.03)	.97 (.02)	.96 (.04)

Two of the subjects had fairly slow reaction times (averaging over one second). When they were removed from the analysis a stronger trend towards a CSE is present for the exponential distribution ITI schedule. This effect is not statistically significant, $F(1, 8) = 1.452$, $p = .263$, $\eta_p^2 = .154$. After the removal of the slow subjects from the uniform distribution ITI schedule session a significant CSE was observed, $F(1, 7) = 11.558$, $p < .05$,

$\eta_p^2 = .623$. It should be noted despite the lack of a significant three-way interaction the CSE was not present for trials preceded by two second ITI's (see figure 3 & 4).

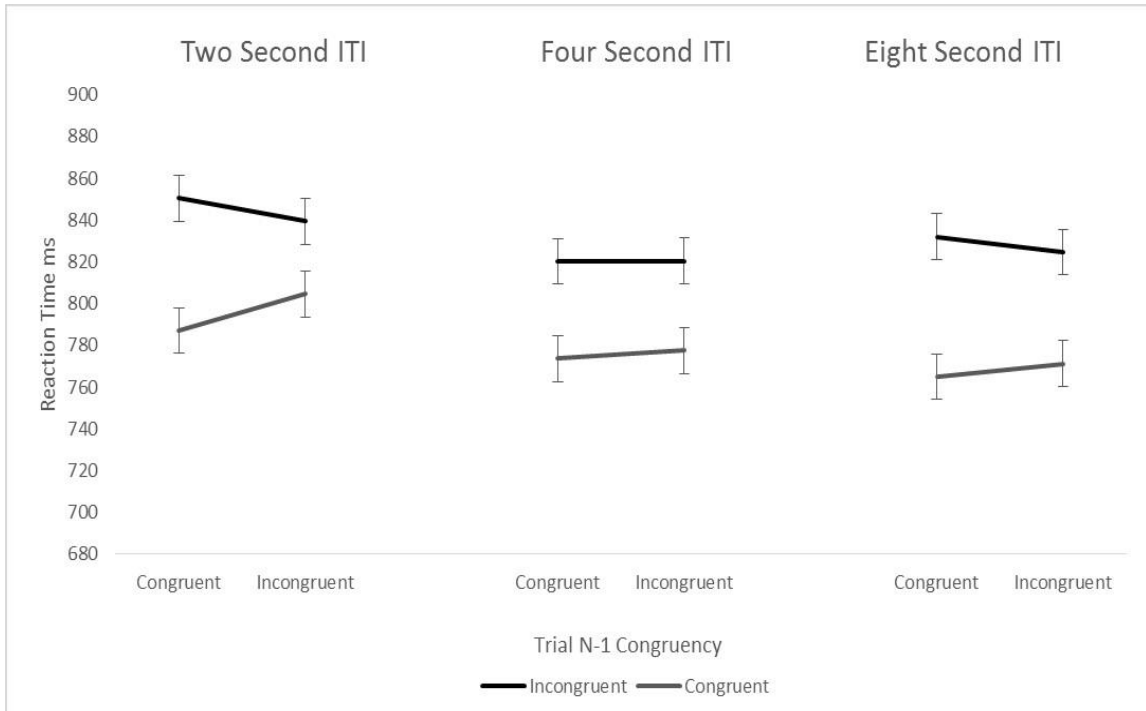


Figure 3-Congruency sequence effect by ITI for the exponential ITI schedule session when excluding RT outlier subjects. The error bars represent the standard error for the interaction of current trial congruency, previous trial congruency and the preceding interval

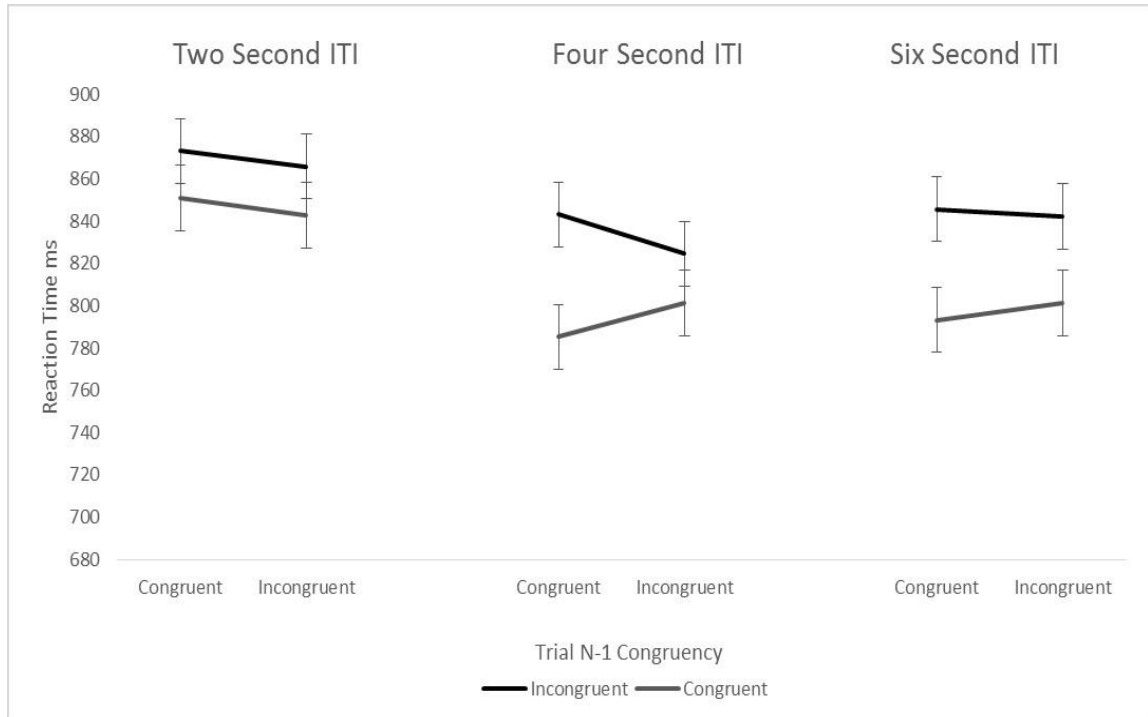


Figure 4-Congruency sequence effect by ITI for the uniform ITI schedule session when excluding RT outlier subjects. The error bars represent the standard error for the interaction of current trial congruency, previous trial congruency and the preceding interval

3.2 Experimental Behavioral Data

A three factor (previous trial congruency x current trial congruency x ITI) within subjects ANOVA showed a significant main effect of congruency, $F(1, 36) = 96.816, p < .001, \eta_p^2 = .729$, and ITI, $F(1.717, 59.331) = 4.954, p < .05, \eta_p^2 = .121$. The congruency effect was 44 ms. All other effects including the critical interaction that defines the CSE, $F(1, 36) = .114, p = .738, \eta_p^2 = .003$, were statistically insignificant. The CSE indexed by the difference in the congruency effect between trials following congruent trials and those following incongruent trials ($[cI-cC]-[iI-iC]$) was 2.23ms. The lack of a CSE is clearly

illustrated in figure 5. Only trials preceded by a four second ITI exhibit a trending CSE. Post hoc paired sample t-tests revealed that trials following two second ITI's had longer RT's than those following four, $t(36) = 2.528, p < .05$, and eight second, $t(36) = 2.399, p < .05$, ITI's but the difference between two and eight second preceding ITI trials did not survive Bonferroni correction. Due to the lack of a significant three-way interaction between previous trial congruency status, current trial congruency status, and ITI in addition to the lack of a robust CSE for all ITI durations imaging analyses were conducted on all trials regardless of preceding ITI status.

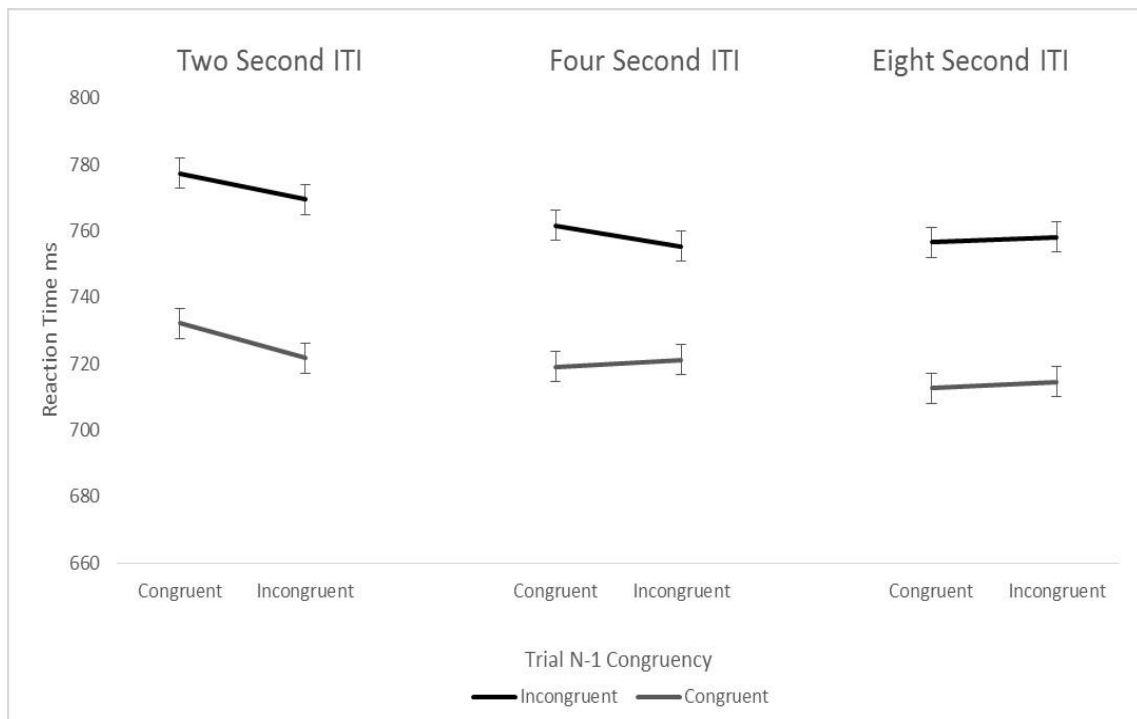


Figure 5-Congruency sequence effect by ITI for the final sample. The error bars represent the standard error for the interaction of current trial congruency, previous trial congruency and the preceding interval.

A trimming procedure was not employed in order to preserve as many trials as possible. Nevertheless, given the long stimulus duration and the liberal response deadline of two seconds the RT data were reanalyzed with a trim that removed all trials 200ms or faster and those 1200ms or slower. The CSE for the trimmed data was 6.06ms. This effect was statistically insignificant and imaging analyses were conducted on untrimmed data.

Analysis of the arcsine transformed accuracy proportions only showed a significant interaction effect between previous trial congruency and ITI, $F(1.731, 62.311) = 4.554$, $p < .05$, $\eta_p^2 = .112$. This interaction was driven by accuracy being greater for trials preceded by congruent trials when the interleaving ITI was four seconds. The main effects of current trial congruency, $F(1, 36) = 3.803$, $p = .059$, $\eta_p^2 = .096$, and ITI, $F(1.548, 55.730) = 2.905$, $p = .076$, $\eta_p^2 = .075$, were marginally significant. In addition, accuracy for all subjects was near ceiling. Means and standard deviations for the untrimmed behavioral data are presented in table 3

Table 3- Behavioral Data Means (Standard Deviations)

Trial Type	Two Second Interval	Four Second Interval	Eight Second Interval
cC Reaction Time	732 (129)	719 (125)	713 (123)
cI Reaction Time	777 (141)	762 (125)	757 (144)
iC Reaction Time	722 (120)	721 (121)	715 (129)
iI Reaction Time	769 (134)	755 (131)	758 (143)
cC Accuracy	.95 (.04)	.97 (.03)	.95 (.07)
cI Accuracy	.95 (.04)	.96 (.04)	.96 (.05)
iC Accuracy	.96 (.04)	.96 (.05)	.97 (.06)
iI Accuracy	.95 (.04)	.95 (.04)	.95 (.06)

3.3 *Beta Series Correlation Analysis (Analysis 1)*

The imaging analyses were conducted on data from 32 subjects. Connectivity between the CON and the FPN was universally positive for trials preceding high and low adjustment (see figure 6 for average correlations between the nodes of the two networks). A FPN node located in the left anterior prefrontal cortex (aPFC) exhibited connectivity

with both the CON and the other nodes of the FPN that was consistently relatively low in magnitude. On the other hand, a narrow node of the FPN located dorsal to the ACC in the vicinity of the SMA and the frontal eye fields had relatively high magnitude correlations with most CON nodes. Figures 6, 7 & 8 show that the average connectivity pattern was rather similar between trial types. None of the high versus low adjustment differences survived FDR correction. For all connectivity comparisons FDR was conducted for a family of tests with a family being defined as the conjunction of a trial type (Ic & Ii) and a connection type (CON-FPN, CON-intra, FPN-intra).

It should be noted that effects at a liberal threshold of a p value of .05 followed a clear pattern. The vast majority of the correlation differences that survived this threshold are negative when comparing Ic trials preceding high versus low adjustment trials thus indicating that connectivity tended to be weaker prior to high adjustment (relatively slow) iC trials. This was true of CON-FPN inter-network connections, CON intra-network connections and FPN intra-network connections. The vast majority of differences crossing this threshold when comparing Ii trials preceding high versus low adjustment trials (relatively fast trials) were positive indicating that connectivity tended to be greater prior to high adjustment iI trials. This was true of CON-FPN inter-network connections and FPN intra-network connectivity but only half of the intra-CON connectivity differences were positive (see Appendix A). Two CON-FPN inter-network connections both including a right aPFC FPN node showed a difference in the same direction (negative) for the Ii and Ic adjustment comparisons. The CON nodes exhibiting reduced connectivity with the right aPFC region prior to high adjustment trials were right and left ACC nodes. Only one pair of FPN nodes exhibited a negative difference and was beyond the threshold for both Ii and

Ic trials but no conjunctions were observed for CON intra-network connectivity differences.

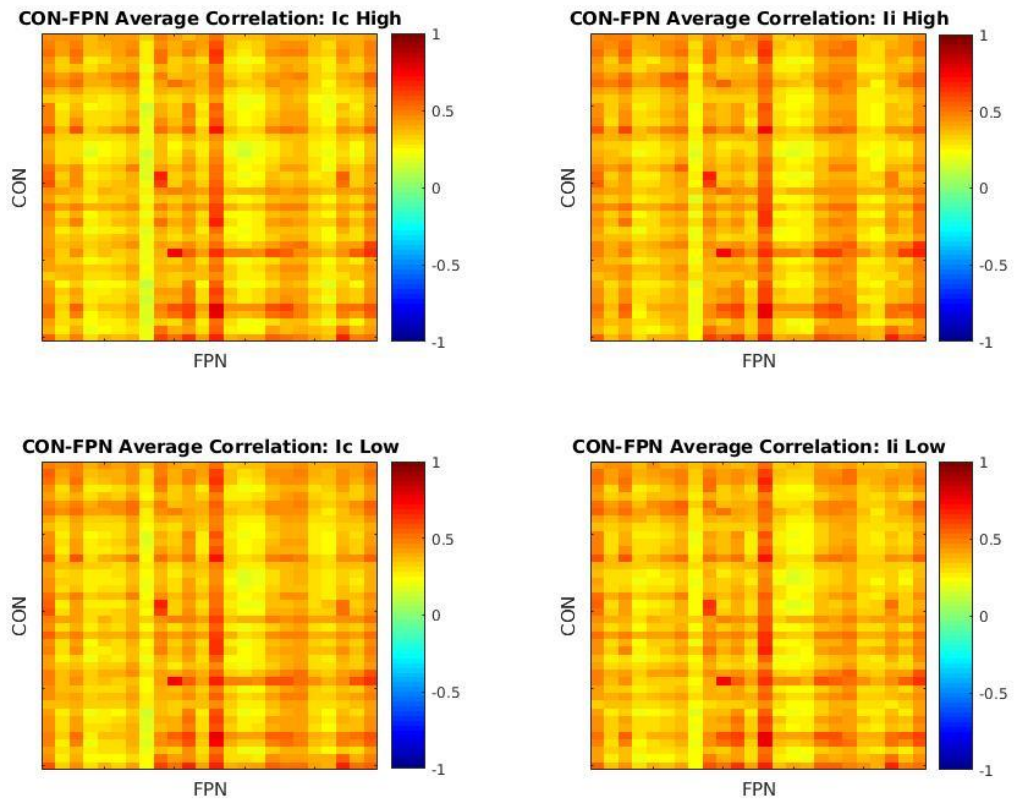


Figure 6-Average correlations between CON and FPN nodes for Ic and Ii trials split by subsequent trial adjustment (defined by a median split)

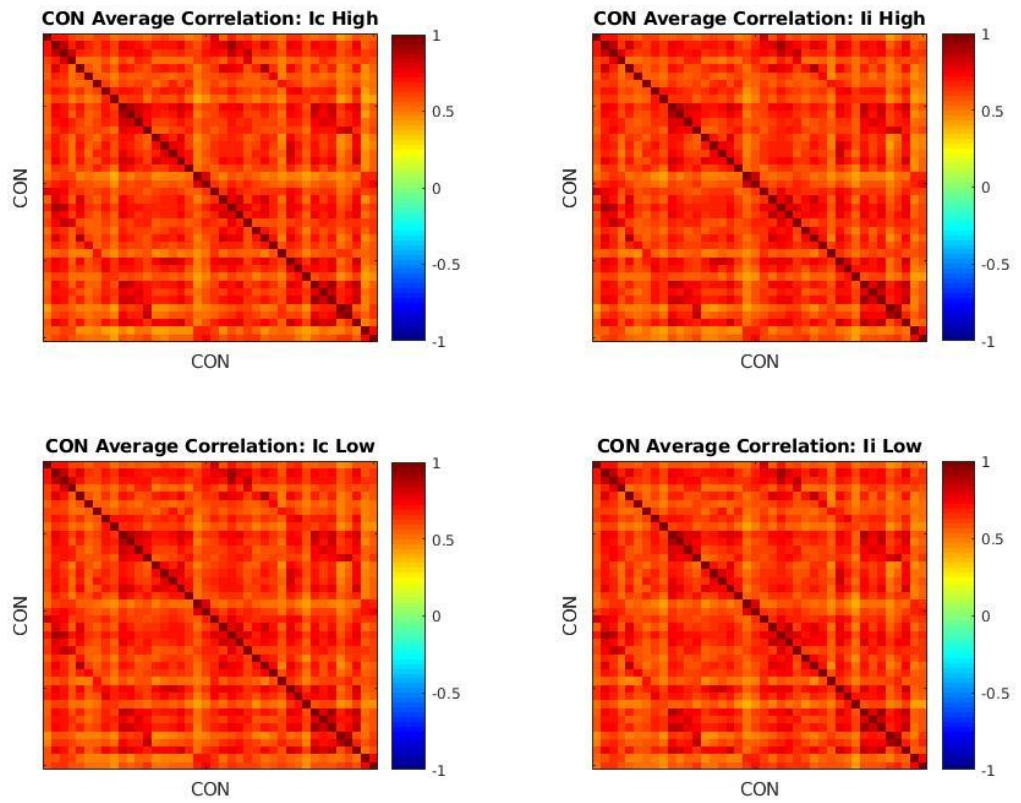


Figure 7-Average correlations between CON nodes for Ic and Ii trials split by subsequent trial adjustment (defined by a median split)

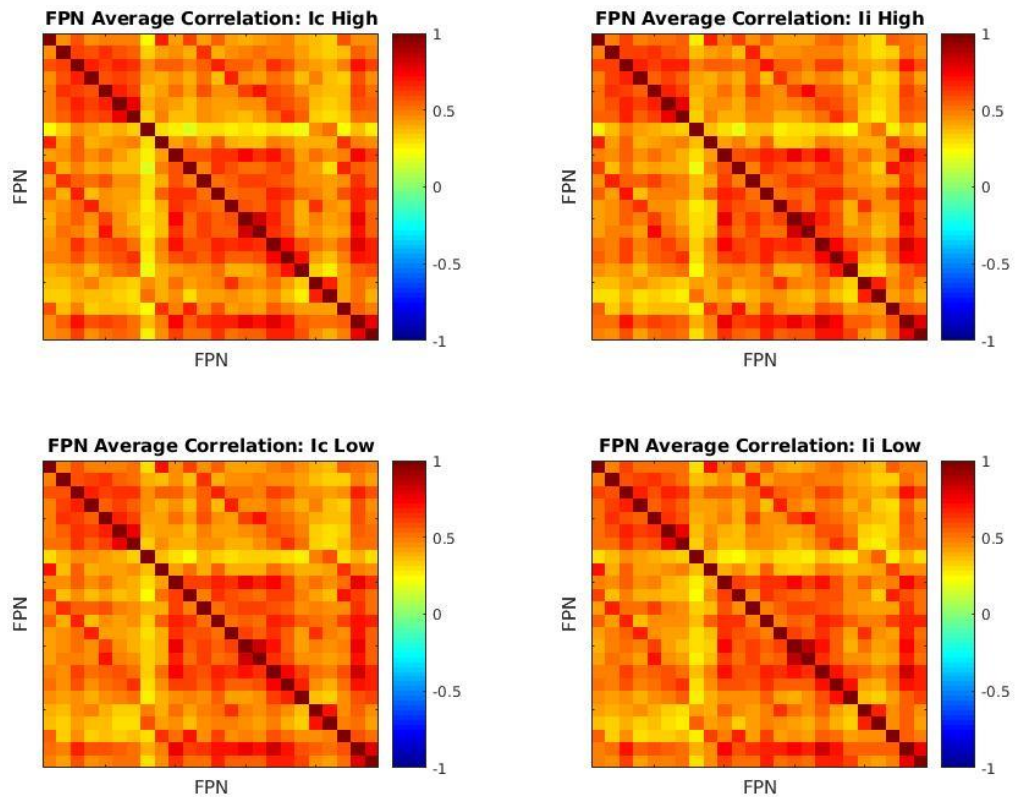


Figure 8-Average correlations between FPN nodes for Ic and Ii trials split by subsequent trial adjustment (defined by a median split)

Median splits might be inadequate at detecting differences since cases near the median may increase the similarity between the sets being compared. When using the first and fourth quartiles to define adjustment level the results are similar as can be seen in the average connectivity maps depicted in figures 9, 10, & 11. Only one connection significantly differed between high and low adjustment trials and survived FDR correction. For Ic trials two CON nodes, a right SMA node and a right precentral gyrus node, were less correlated when preceding high relative to low adjustment trials. The pattern of

connection differences with p values below .05 was similar to what was observed with median split defined adjustment but no conjunctions were present.

The 17 subjects included in the imaging analyses that showed a congruency sequence effect ($[cI-cC]-[iI-iC]>0$) were examined in isolation. As would be expected the average pairwise correlations were similar to those of the entire sample (see Appendix B). Additionally, the average connectivity maps of the no CSE subjects resembled the maps of CSE subjects (see Appendix B). None of the connectivity differences between high and low adjustment trials survived FDR correction for the CSE subjects. When considering differences with p values less than .05 one CON-FPN connection difference of the same sign was present for both Ii and Ic trials (a left DLPFC node and a left aPFC CON node had a more positive correlation preceding high adjustment trials). The positive negative difference pattern for Ii and Ic trials respectively was true of the CON-FPN and CON connections but it did not hold well for the FPN connection differences (see Appendix A).

When using a quartile based adjustment definition the average connectivity maps remained similar to those of the entire group and to the connectivity patterns of subjects not showing a CSE (see Appendix B). Also, none of the high versus low adjustment connection differences were significant after applying FDR correction and no conjunctions were present at the uncorrected ($p=.05$) level. The positive negative difference pattern held for CON-FPN inter-network connectivity and CON intra-network connectivity but as with the median split definition the trend did not hold well for the FPN intra-network connection differences.

In order to compare the connectivity between groups independent sample t-tests (not assuming equal variances) of the Fisher Z-transformed correlations for each pair in a trial type (Ic High, Ic Low, Ii High, Ii Low) were conducted for inter-network and intra-network connections. After FDR correction no group differences were statistically significant.

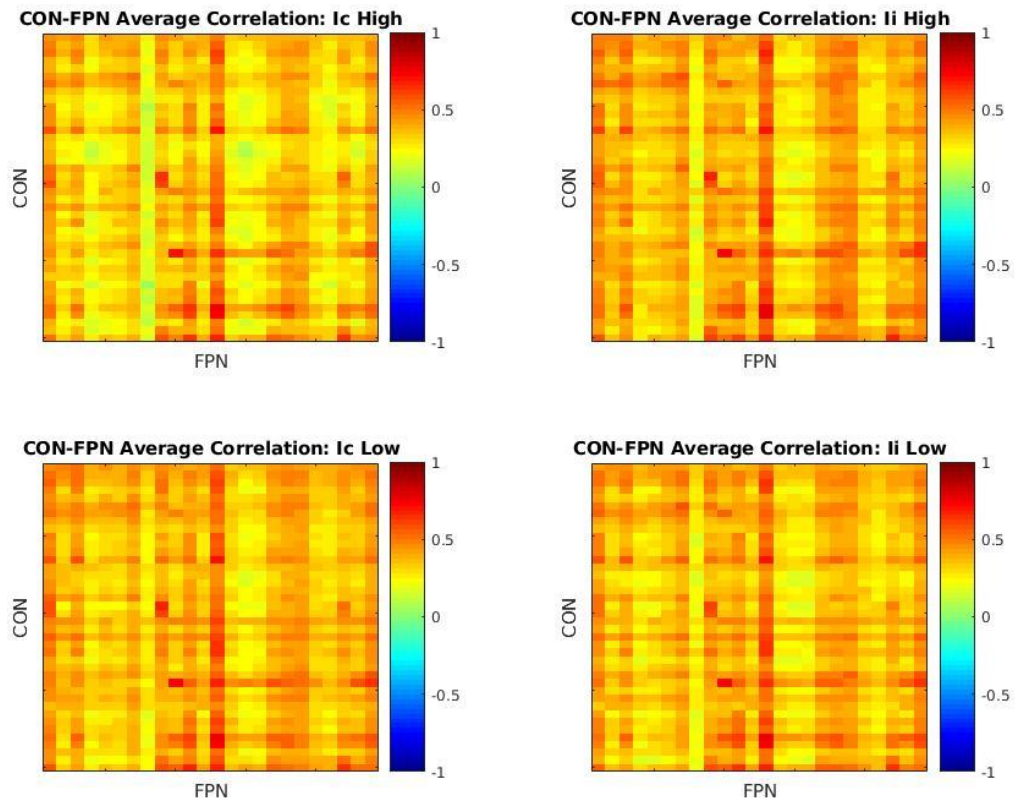


Figure 9- Average correlations between CON and FPN nodes for Ic and Ii trials split by subsequent trial adjustment (defined by bottom and top quartiles)

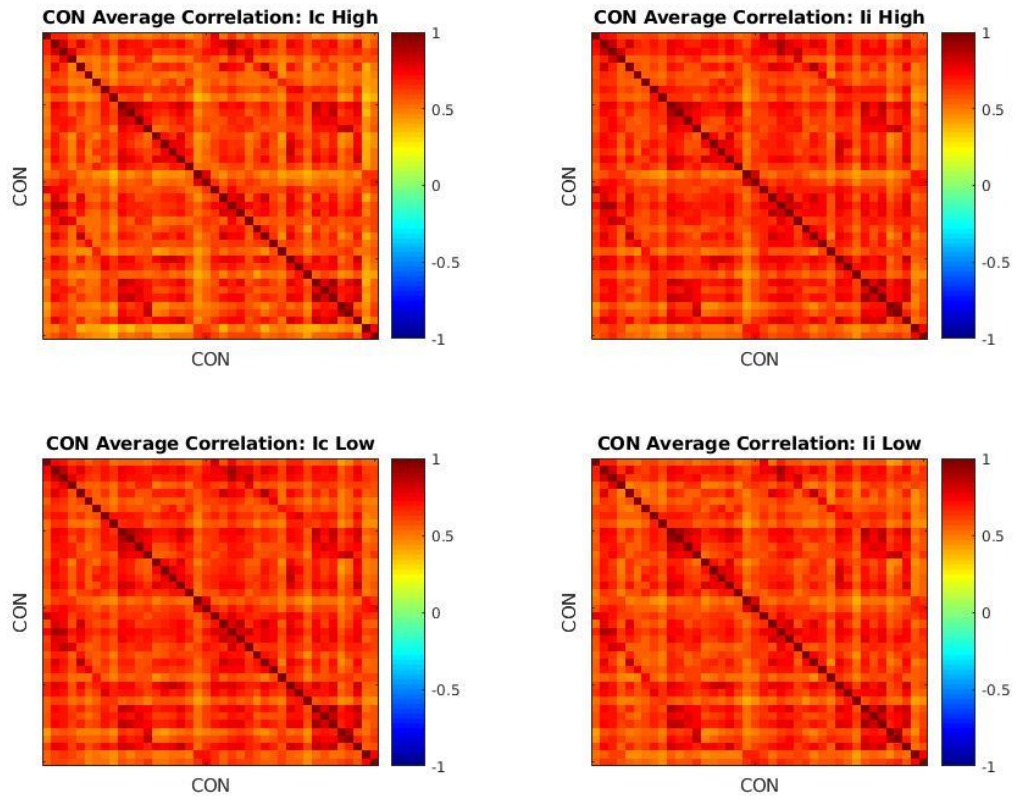


Figure 10- Average correlations between CON nodes for Ic and Ii trials split by subsequent trial adjustment (defined by bottom and top quartiles)

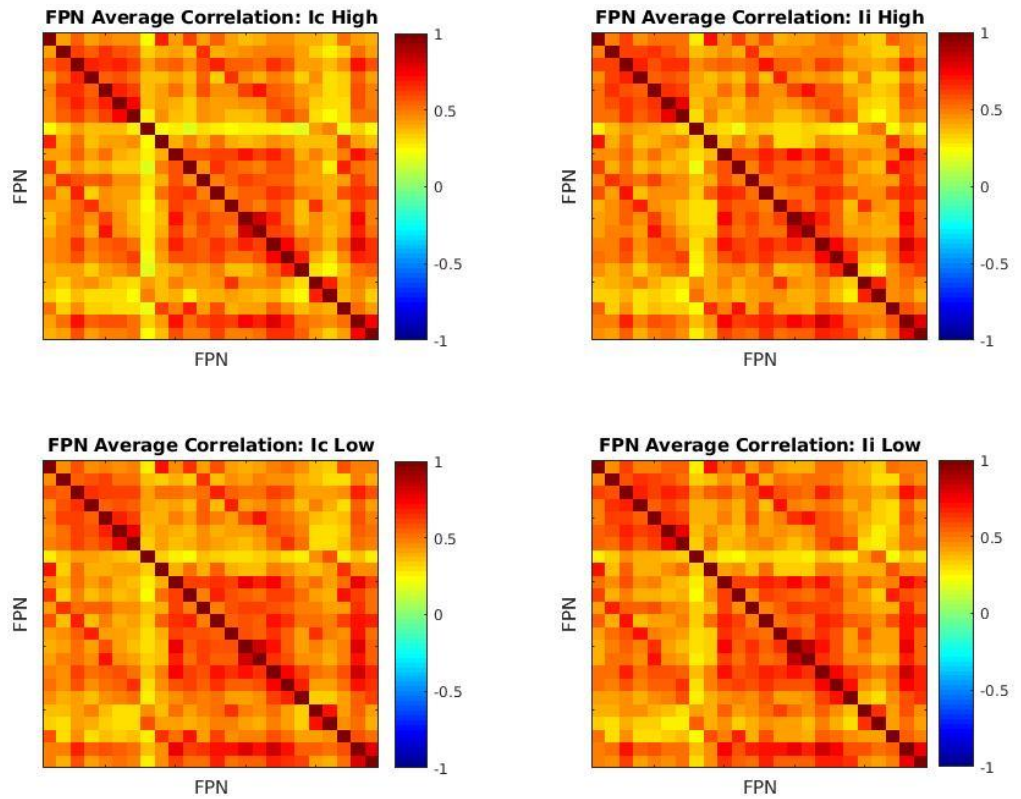


Figure 11-Average correlations between FPN nodes for Ic and Ii trials split by subsequent trial adjustment (defined by bottom and top quartiles)

Pairwise analyses might miss out on aggregate changes in connectivity if these aggregate changes are not founded upon a consistent set of connections across subjects driving an aggregate change. In order to assess aggregate changes in connectivity each subject's average Fisher Z transformed correlations were analyzed. A four-way split plot ANOVA including CSE status (CSE & No CSE), connection category (CON-FPN Inter-network, CON Intra-network, FPN Intra-network), trial type (Ic, & Ii), and adjustment level (High & Low) was conducted with median split defining adjustment level. Levene's test

did not indicate a significant difference in the variance between groups. In addition, to a significant main effect of connection category, $F(1.772, 53.164) = 359.549, p < .001, \eta_p^2 = .923$ (driven by greater intra-network than inter-network connectivity as would be expected), the four-way interaction of CSE status, connection category, trial type, and adjustment level was statistically significant, $F(1.526, 45.765) = 6.295, p < .01, \eta_p^2 = .173$. As can be seen in figure 12 subjects that exhibited a CSE had lower connectivity for high relative to low adjustment Ic trials and the reverse was true of Ii trials. This was not the case for average CON-FPN and CON connectivity in subjects that did not exhibit a CSE.

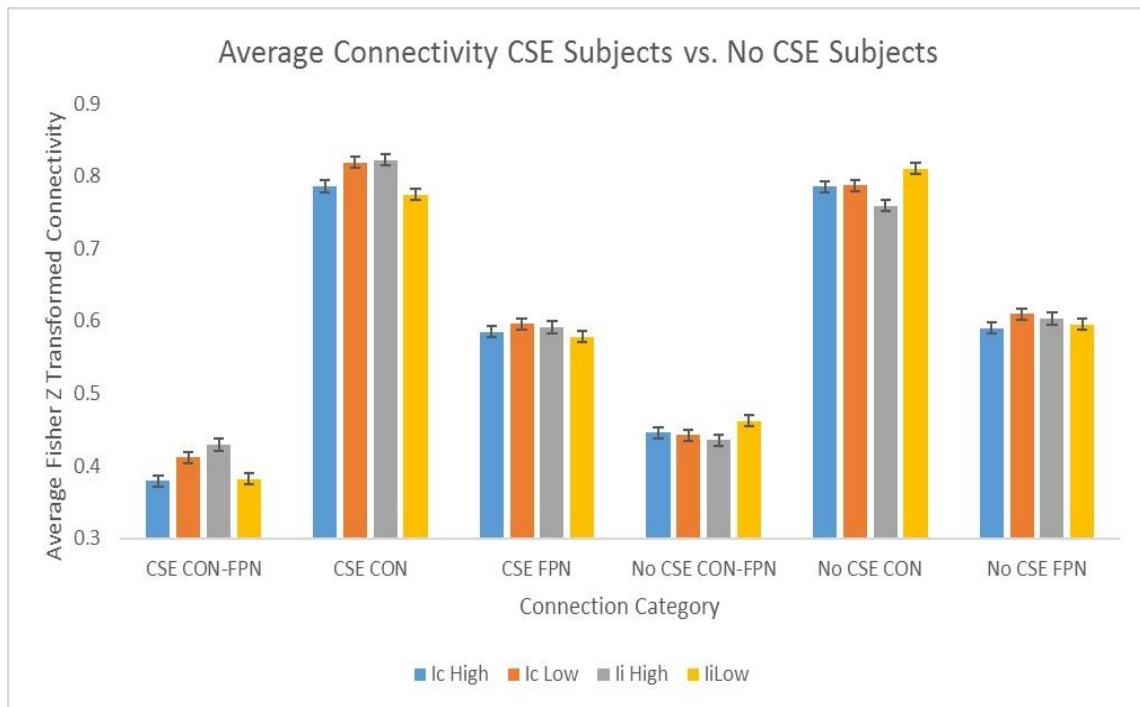


Figure 12-Average connectivity for subjects with a CSE and those without a CSE. Error bars represent the standard error of the interaction of CSE status, connection category, trial type, and adjustment level (Adjustment level defined by Median split).

When conducting the same analysis when defining adjustment by bottom and top quartiles the main effect of connection category, $F(1.803, 54.095) = 353.563, p < .001, \eta_p^2 = .922$, CSE status x trial type x adjustment level interaction, $F(1, 30) = 5.403, p < .05, \eta_p^2 = .153$, and the CSE status x connection category x trial type x adjustment level interaction were statistically significant, $F(1.237, 37.099) = 5.477, p < .05, \eta_p^2 = .154$. Levene's test did not indicate a significant difference in the variance between groups. As can be seen in figure 13 for subjects showing a CSE CON-FPN and intra-CON connectivity was lower for high relative to low adjustment Ic trials and the reverse was true of Ii trials but this was not true of intra-FPN connectivity. In subjects that did not show a CSE connectivity was greater on low adjustment trials regardless of connection category and trial type.

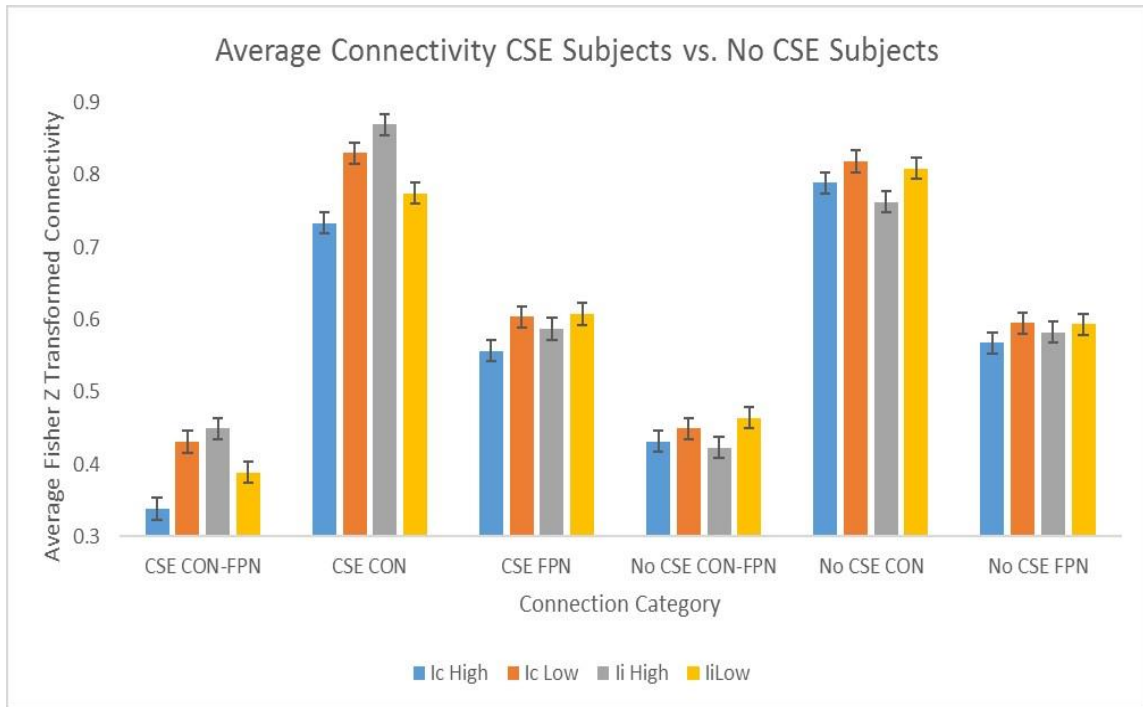


Figure 13-Average connectivity for subjects with a CSE and those without a CSE. Error bars represent the standard error of the interaction of CSE status, connection category, trial type, and adjustment level (Adjustment level defined by bottom and top quartile).

3.4 Parametric Modulation Models (Analysis 2)

A voxelwise analysis of the CON network yielded significant post-FDR correction positive parametric modulation which was expected given the fact that CON residual activity from the preceding trial acted as the parametric modulator. The effects of interest were examined by averaging beta estimates for each node of each network. The congruency effect (incongruent trials – congruent trials for the betas capturing the average effects of a condition) did not reach statistical significance ($p < .05$) let alone survive FDR correction for any CON nodes. Also, when contrasting cI and iI trials as Kerns and colleagues did there were no significant effects for any CON nodes post FDR correction.

Yet, three nodes (two small nodes in the left insula and one in the left inferior parietal lobule, see figure 14) crossed a liberal $p < .05$ uncorrected threshold each exhibiting greater activation for cI than iI trials.

Residual CON network activity from the preceding trial did not significantly modulate current trial responsiveness in the nodes of the FPN when applying FDR correction. This was true when collapsing across adjustment and when separately modeling high and low adjustment trials. A map of effects with an uncorrected p value of .05 can be found in Appendix C. The only region exhibiting positive modulation is a node located in the left middle temporal gyrus and this effect was present on cI trials. Negative modulation was observed on iI trials in right DLPFC, right inferior frontal cortex, and right aPFC FPN nodes. The aPFC node also showed negative modulation on iC trials. The right aPFC node and DLPFC nodes also showed negative modulation when looking at iI high adjustment trials as did a more caudal right DLPFC node. The more rostral right DLPFC node and a right inferior parietal lobule node exhibited negative modulation on low adjustment iC trials as well.

After applying FDR correction, residual previous trial activity in a right ACC node significantly modulated iI trial activity in a right aPFC node of the FPN. Additionally, this is true of this region for iI high adjustment trials but this effect did not survive correction for iI low adjustment trials and iC low adjustment trials (see Appendix C). In both cases the modulation was negative. This region exhibited significant uncorrected negative modulation effects for cC, cI, and iC trials with the right ACC residuals serving as a parametric modulator. On cC trials two right middle frontal gyrus, and a ventral aPFC node exhibited negative modulation. A left aPFC node showed negative modulation on iI

trials and on iC trials this node, another left aPFC, a left DLPFC, a right inferior parietal lobule, and a right DLPFC node exhibited negative modulation. For high adjustment iI trials a right parietal lobule, a right middle frontal gyrus node, and two right DLPFC nodes showed negative modulation. Low adjustment iC trials were marked by negative modulation in the left aPFC, left inferior frontal cortex, right DLPFC, right aPFC, and right middle frontal gyrus. Across trial types modulation was negative and the right aPFC showed the most robust modulation followed by the right DLPFC. Uncorrected modulation effects were more prevalent for trials preceded by incongruent trials.

cI vs. iI Activation in CON Nodes

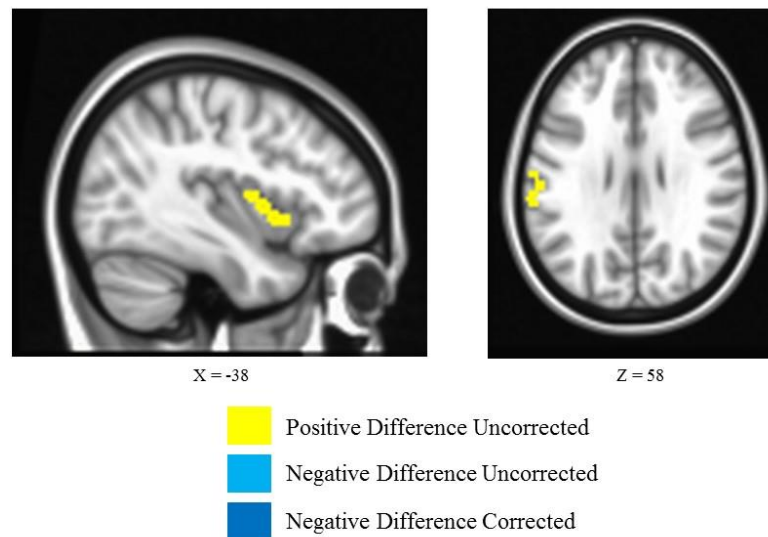


Figure 14-Differences in activation between cI and iI trials in the CON (Corrected is defined as $q=.05$ and uncorrected as $p=.05$).

When comparing parametric modulation on iC and iI trials between subjects with a CSE and those lacking a CSE none of the independent sample t-tests (equal variances not assumed) survived FDR correction for both trial types. For iC trials CSE subjects exhibited more negative modulation with an uncorrected p threshold of .05 in a left DPLFC, a left middle frontal gyrus, and a right middle frontal gyrus node (see Appendix C). As can be seen in Appendix C for iC trials numerous nodes differed when uncorrected but one iC node survived correction. This node is located in the vicinity of the right middle frontal gyrus and exhibited more negative modulation in the CSE subjects.

3.5 *Multilevel Models of Reaction Time*

When modeling RT with the previous trial residual activity in the CON the model containing random intercepts, the fixed effect of CON residuals, and the fixed effects dummy coded trial type held the minimum BIC value as can be seen in table 4. The model had significant variance in intercepts across subjects, $\text{Var}(\mu_{0j}) = 16707.57, p < .001$. The main effect of cI trial status, $F(1, 16611.017) = 102.474, p < .001$, and the main effect of iI trial status, $F(1, 16611.028) = 78.824, p < .001$, were both statistically significant reflecting the congruency effect. The main effect of previous trial CON residual activity was not statistically significant, $F(1, 16610.995) = 1.549, p = .213$, but as can be seen in table 5 there was a negative trend as predicted.

Table 4-Multilevel Model BIC Values

Region	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
CON	225934	225168	224999	225020	225026	225035
Right	225934	225257	225089	225112	N/A	N/A
ACC						

N/A indicates models that did not converge. Model 1: Random Intercept Model 2: Random Intercept, Fixed Effect of Previous Trial Activity Model 3: Random Intercept, Fixed Effect of Previous Trial Activity, Fixed Effect of Trial Type Model 4: Random Intercept, Fixed Effect of Intercept, Fixed Effect Previous Trial Activity, Fixed Effect of Trial Type, Fixed Trial Type Previous Trial Activity Interactions Model 5: Random Intercept, Random Effect of Previous Trial Activity (independent variances assumed), Fixed Effect Previous Trial Activity, Fixed Effect of Trial Type, Fixed Trial Type Previous Trial Activity Interactions Model 6 : Random Intercept, Random Effect of Previous Trial Activity (unstructured), Fixed Effect Previous Trial Activity, Fixed Effect of Trial Type, Fixed Trial Type Previous Trial Activity Interactions

Table 5-Fixed Effects for Multilevel Model-CON

Predictor	b	Standard Error	95% CI
Intercept	730.04	22.72	683.82, 776.26
N-1 Residual	-14.98	12.04	-38.58, 8.61
Activity			
cI Trial	45.85	4.53	36.97, 54.73
iI Trial	40.37	4.55	31.46, 49.29
iC Trial	-3.94	4.54	-12.84, 4.96

CI=Confidence Interval

For the ACC previous trial residual activity, attempts were made to fit models with a random slope for previous trial ACC residual activity but both a version with unstructured covariance and one that assumed independent random effects failed to converge. As with the previous trial CON residuals the model containing random intercepts, the fixed effect of ACC residuals, and fixed effect dummy coded trial type predictors held the minimum BIC value (see table 4). The model had significant variance in intercepts across subjects, $\text{Var}(\mu_{0j}) = 16734.013, p < .001$. Also, the main effect of cI trial status, $F(1, 16617.016) = 102.374, p < .001$, and the main effect of iI trial status, $F(1, 16617.027) = 78.799, p < .001$, were both statistically significant reflecting the congruency effect. The main effect of ACC

residual activity on the previous trial was not statistically significant, $F(1, 16616.995) = .501, p = .479$. The parameter estimates for the fixed effects can be found in table 6.

Table 6-Fixed Effects for Multilevel Model-Right ACC

Predictor	b	Standard Error	95% CI
Intercept	730.02	22.74	683.77, 776.28
N-1 Residual Activity	5.89	8.32	-10.42, 22.20
cI Trial	45.83	4.53	36.95, 54.70
iI Trial	40.38	4.55	31.46, 49.29
iC Trial	-3.75	4.54	-12.66, 5.15

CI=Confidence Interval

3.6 Parametric Modulation & Reaction Time

The lack of a relationship between previous trial residual activity and reaction time does not rule out inter-temporal CON-FPN interactions having a role in behavior. Previous trial activity in the CON or simply the right ACC might influence behavior through its modulation of the FPN on the subsequent trial. The correlations between average

parametric modulation in the right aPFC node that was shown to exhibited significant modulation effects post-correction and mean RT for each trial type and across trial type are displayed in table 7. All of the correlations were very low in magnitude and none reached statistical significance. It should be noted that the correlations for the right ACC based parametric modulation tended to greater in magnitude.

Table 7- Right aPFC Modulation Coefficient-Reaction Time Correlation

Trial Type	CON Residual Activity	Right ACC Residual Activity
All Trials	.01 ($p=.94$)	.16 ($p= .39$)
cC	.03 ($p=.87$)	.27 ($p= .14$)
cI	-.05 ($p= .78$)	.14 ($p= .45$)
iC	-.13 ($p= .47$)	.06 ($p= 0.76$)
iI	.11 ($p= .54$)	-.16 ($p= 0.37$)

CHAPTER 4: DISCUSSION

4.1 *General Findings*

Dosenbach and colleagues proposed two ways of understanding CON-FPN interaction. The closed loop account has feedback related signals from the FPN being fed to the CON in order to inform task set adjustments which are then relayed back to the FPN. The parallel system account assumes that these networks do not interact and work in parallel with the FPN controlling tactical short term control processing and the CON dealing with long term strategic control processing (Dosenbach et al., 2007). Here it was hypothesized that the parallel system account is unlikely and that interaction between the networks is critical for performance adjustments. Additionally, it was proposed that the CSE is dependent on previous trial connectivity between these networks. Specifically, greater inter-network connectivity was predicted to lead to greater performance adjustments. It was hypothesized that previous trial CON activity over and above FPN on the previous trial would modulate the hemodynamic response in the FPN on the current trial.

The CSE was not present in this sample. The lack of a CSE might stem from the ITI schedule but due to a lack of comparison no firm conclusion can be reached regarding the reason behind the CSE's absence. The CSE was not observed when the data were trimmed and when the data were untrimmed. Additionally, a significant congruency effect was not found in the CON despite the fact that this effect has been commonly observed in interference paradigms. This might stem from the relatively small behavioral congruency effect present in the sample. For the accuracy data an interaction between previous trial

congruency status and ITI was observed but there is no apparent interpretation for this result given that it was driven by better accuracy with an intermediate duration (four second) ITI.

When conducting pairwise analyses intra-network and inter-network connectivity did not differ significantly between incongruent trials preceding high and low adjustment. The use of bottom and top quartiles to define adjustment as opposed to a median split did not impact the connectivity profile. Two general trends were present when comparing high and low adjustment trials. Connectivity tended to be weaker prior to high adjustment iC trials and it tended to be stronger prior to high adjustment iI trials. It was predicted that that connectivity would be greater prior to high adjustment trials. Although not significant when corrected for multiple tests the trend in the Ii trials is in accordance with the hypothesis. Yet, Ic trials do not fit with what was expected. It is possible that these results reflect a trend for previous trial intra-network (particularly in the CON) and CON-FPN inter-network connectivity to be negatively related to current trial RT. High adjustment iC trials are relatively slow trials while high adjustment iI trials are relatively fast trials. There was a trend for connectivity to be greater prior to relatively fast trials. The higher level of connectivity observed prior to fast trials might reflect the CON devoting more resources to its proposed tonic alertness function (Sadaghiani, & D'Esposito, 2014). Intra-network CON connectivity has been shown to scale with tonic alertness demands and it was shown to be greater prior to fast trials in this sample. Nevertheless, it is not clear what would be driving tonic alertness demands given that incongruent trials were not less frequent than congruent trials and the CON has been shown to be unresponsive to selective attention

demands (Sadaghiani, & D'Esposito, 2014). One possibility is that the observed connectivity differences stem from stochastic fluctuations in the level of alertness.

When examining average connectivity across all connections, as opposed to pairwise connectivity, in a given connection category the CSE subjects exhibited a pattern marked by weaker connectivity on high adjustment Ic trials relative to low adjustment Ic trials and the reverse trend for Ii trials. This pattern was not found in subjects that did not display a CSE. Also, FPN intra-network connectivity unlike CON-FPN inter-network connectivity and CON intra-network connectivity did not show this pattern. These results suggest that the average previous trial CON-FPN inter-network connectivity and previous trial CON intra-network connectivity predict behavior but not in the predicted manner. Connectivity was hypothesized to be greater prior to high adjustment trials regardless of trial type. Greater connectivity may predict faster RT's as opposed to adjustment at least in the subjects that showed the CSE pattern in their behavioral data. This is somewhat counterintuitive since in subjects that exhibited a CSE it would be expected to find greater connectivity prior to high adjustment (for Ic high adjustment is defined as being relatively slow) trials regardless of trial type. It is not clear what role previous trial connectivity plays in the performance of subjects that did not manifest a long interval CSE. Subjects that did not exhibit a CSE tended to have greater connectivity for low adjustment trials regardless of trial type (especially when using a quartile based adjustment definition).

In the CON there was no post-correction significant differences between cI and iI trials as was observed by Kerns and colleagues (2004) in the ACC. Nevertheless, uncorrected significant activity exclusively in the direction of the Kerns and colleagues' findings ($cI > iI$) was observed. The previous trial residual activity in the CON did not

significantly modulate current trial activity in the nodes of the FPN even when high and low adjustment trials were modeled separately but this was not the case for the residual activity from a right ACC CON node. A right aPFC node showed significant negative modulation on iI trials. This modulation was significant on iI high adjustment trials but not for iI low adjustment trials when adjustment level was modeled separately. This same right aPFC node showed uncorrected significant negative modulation for iI and iC trials when using CON residuals as a parametric modulator. Uncorrected significant negative modulation was present for iC high adjustment and iI high adjustment, when separately modeling trials of the two adjustment levels, for this region as well. Also, when using right ACC residuals as a parametric modulator uncorrected significant negative modulation was observed in this region for cC, cI, and iC trials. When separately modeling high and low adjustment trials uncorrected effects were observed on iI low and iC high adjustment trials. In addition, a right DLPFC node displayed a similar pattern of negative modulation as the right aPFC node. Negative modulation was pervasive across trial types and across FPN nodes. The only case of uncorrected significant positive modulation was a left middle temporal gyrus node during cI trials when both CON and right ACC residuals were used as a parametric modulator. Critically, negative modulation of the FPN was for the most part universal across trial type and was most pronounced in the right aPFC and to a lesser extent the right DLPFC.

When comparing parametric modulation in CSE and no CSE subjects three regions a left DLPFC, a left middle frontal gyrus, and a right middle frontal gyrus node exhibited uncorrected significant differences between the two groups. Greater negative modulation was present in these regions for the CSE group during iC trials.

Multilevel modeling did not reveal a significant influence of either CON or right ACC previous trial residual activity on RT. For both sets of residuals the minimum BIC values belonged to a model that included a random intercept, a fixed effect of previous trial residual activity, and dummy trial type predictors. Both cI and iI trials significantly differed from the baseline case, cC trials, reflecting the congruency effect. This clearly does not rule out the possibility that previous trial residual activity influences RT. The effect of previous trial residual activity on RT might depend on the degree of FPN modulation.

It is possible that the observed negative modulation might be a manifestation of a performance adjustment process. Decreased BOLD signal responsiveness might be indicative of an increase in neural efficiency induced by cognitive preparation stemming from previous trial demands. Additionally, negative modulation seemed to be somewhat more consistent in the right FPN. As stated earlier the right FPN has suggested to be responsible for performance updating (Gratton et al., 2017). Given the outcome of the multilevel modeling strong claims cannot be made regarding the functional nature of previous trial residual activity in the CON and right ACC. When correcting for multiple comparisons a significant effect is present for iI high adjustment trials but this effect did not reach significance for iI low adjustment trials. This alone is not enough to have confidence in a connection between previous trial activity and current trial RT.

4.2 *Data & Design Limitations*

The congruency effect observed in this sample was larger than the one observed by Kim and Cho with a slightly different version of this paradigm (44ms vs. 27ms). Yet, the CSE was not present. One potential cause is the ITI schedule. The results of the pilot study were far from unequivocal but they suggested that with more power a CSE stood a chance of being observed at least at certain ITIs. Kim and Cho used a much shorter stimulus duration than the one used in this study (250ms vs. 2000ms). The longer stimulus time used in this study lead to significantly longer amount of processing time, even at the shortest ITIs, relative to Kim and Cho's study. Other confound minimized paradigms might have been better suited for this study. Paradigms with the distractor preceding the target might have increased the probability of observing a CSE with the ITI schedule used in this study (Weissman et al., 2015). The CSE seems more robust for these tasks but taking this route would have added another difference with the paradigm used by Kerns and colleagues which presented the distractor and the target at the same time (Stroop task). Granted the hypothesis regarding the parallel systems account could still be tested with paradigms that have distractors preceding targets. It is certainly possible that the CSE is simply not a robust effect and the processes underlying it have a very ephemeral nature but it is also possible that the steps taken to ensure confound minimization remove not just non-control related memory based behavioral adjustments but adjustments based on control as well. Memory processes and control might interact in order to produce the CSE (Schmidt, De Houwer, 2011; Verguts, & Notebaert, 2008; Weissman, Hawks, & Egner, 2016).

Another limitation of this study was the use of previous trial residuals. Figure 15 presents a scatter plot of the residuals and RT. For most subjects the activity in the FPN nodes on the preceding trial explained a rather large share of the variance in preceding trial CON activity (70% of the variance was not untypical). The limited unshared variance implies range restriction. Restriction of range limits predictive power. This problem is inherent to the data and is more fundamental than any of the experimental design issues. A more theoretical issue concerns the nature of the CON-FPN correlation on the previous trial. During the execution of a trial these regions might be engaged in dialogue that determines performance adjustments. The FPN and the CON, have a high degree of shared variance in activation. Removing shared variance with the FPN from the CON removes meaningful information. Surely residual activity in the CON might still have a role to play in performance adjustments given that the CON exhibits functional couplings (sustained activation throughout a task, scaling with tonic alertness demands) that are not observed in the FPN (Dosenbach et al., 2006; Dosenbach et al., 2007). Nevertheless, if previous trial coupling between the CON and the FPN plays a role in determining performance adjustments regressing out FPN node activity from the average CON signal reduces the odds of findings a relationship since it restricts previous trial CON to current trial performance and FPN activity relationships to a small amount of the variance remaining in the CON.

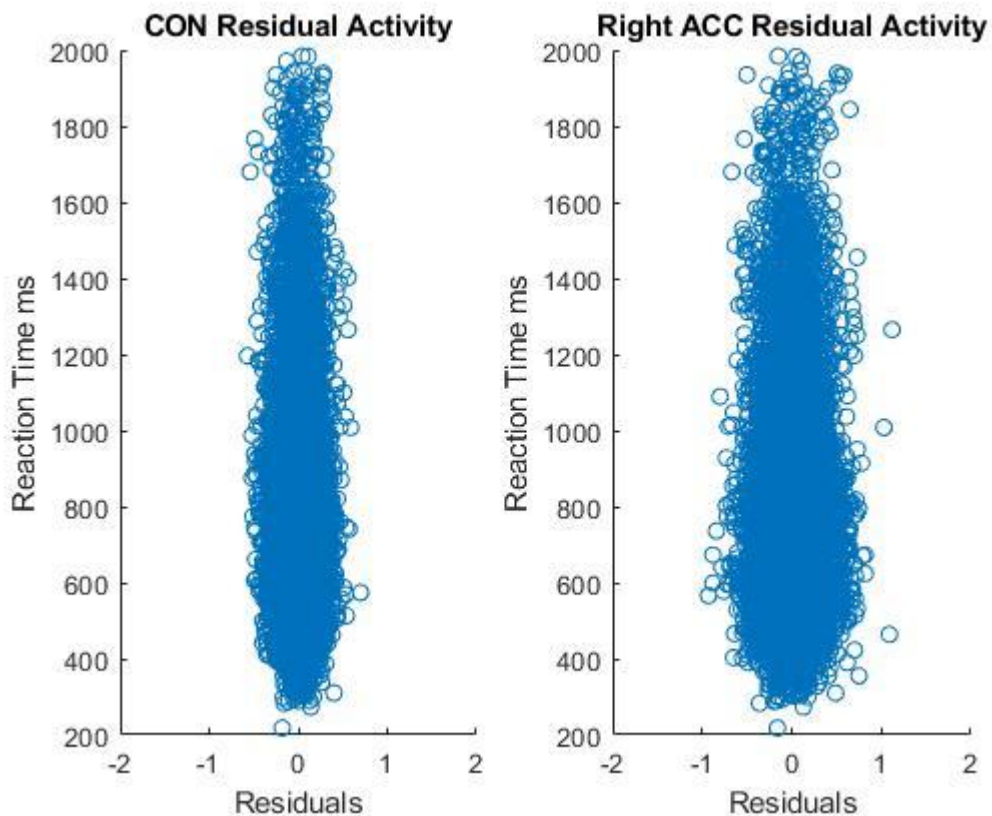


Figure 15-Scatter plots of previous trial residual activity (CON and right ACC) and reaction time.

4.3 *Theoretical Alternatives*

An obvious explanation for the findings is that the hypotheses tested were unsound. The lack of a CSE makes it hard to determine if this was in fact the case. On average connectivity significantly differed between high and low adjustment trials (in an unpredicted manor) when applying FDR correction but the absence of a CSE calls into questions the high and low adjustment distinction. Given the connectivity differences that were observed it seems more likely that CON-FPN inter-network connectivity is simply greater on incongruent trials that preceded fast trials. Parametric modulation of a FPN

node by previous trial right ACC activity lends some degree of support to the network interaction hypothesis but the absence of a firm behavioral connection cast a cloud over these findings. It is not clear if the negative modulation induced by the right ACC node is functionally relevant given that parametric modulation was not correlated with RT. Nevertheless, the lack of post-correction significant modulation in this region for iI low adjustment trials in contrast to a corrected significant effect for iI high adjustment trials hints at a relationship between modulation and RT. The absence of a post-FDR significant effect for the average CON signal residuals is problematic for the modulation hypothesis. In addition, the negative modulation based solely on right ACC residual activity is more potent than that induced by the network as a whole. This does not sit well with the idea that the network is responsible for inducing adjustments in the FPN.

Also, current trial connectivity is not the only means of network interaction. The CON has been implicated in long time scale processing (Dosenbach et al., 2006; Dosenbach et al., 2007). One possibility is that the CON slowly adjust FPN activity over the course of multiple trials. It might even carry out this function in a way that would not necessarily manifest itself in functional connectivity metrics. For example, Aston-Jones and Cohen's account of locus coeruleus (LC) function has the ACC and orbitofrontal cortex regulating LC firing mode (Aston-Jones, & Cohen, 2005). Norepinephrine projections from the LC can modulate adaptive gain in neurons across the cortex. FPN functioning might be influenced by the CON via the LC. The CON could have subtle and long time scale effects on the FPN induced through changes in neuromodulation.

4.4 *Parametric Modulation & Future Directions*

Further investigation into the general relationship, regardless of trial type, between previous trial residual CON activity and RT is warranted. Also, more advanced modeling approaches might produce better results than the use of previous trial CON residuals as a parametric modulator. Another possibility is that the CSE could be reexamined in an imaging context using some sort of trial pairing procedure (short ITIs between trials defines pairs to be analyzed together) but this course of action can end up confounding previous and current trial activity. Also, subjects could be preselected (based on the presence of a CSE) during a behavioral session for participation in scanning session. Granted this path can be criticized on two grounds, one being that the within subject reliability of the CSE (some of the pilot subjects exhibited a CSE on one day and not the other could have stemmed from the different ITI schedules but unreliability in the effect cannot be ruled out) is currently unknown. Another is that the findings would not be generalizable to the population as a whole since it would be based on a non-random sample. This is a sound criticism but it also stems from some very important flaws in the study of human cognition. Heterogeneity is often underappreciated in cognitive neuroscience and cognitive psychology more broadly. Comparisons of those without a CSE and those exhibiting a CSE, assuming the presence of the effect is consistent within subjects, could shed light on subtle individual differences in cognitive control. Another issue worth investigating from an individual differences standpoint is the relationship between the CSE and ITI. Why might the CSE persist through long intervals in some subjects and fade away in other subjects?

4.5 *Summary*

Overall, the hypotheses were not supported. There might be a general effect of CON-FPN connectivity in addition to CON intra-network connectivity on RT given that, at least in subjects showing a CSE behavioral pattern, connectivity was greater prior to the relatively fast trials for each trial type. Another finding was that previous trial right ACC activity over and above previous trial FPN activity negatively modulates the right aPFC and the same might be true for residual activity on the previous trial in the CON. Also, residual activity in the CON and the right ACC do not predict current trial RT. Only future research will be able to provide firm conclusions regarding the relationship between these networks but based on the findings in this sample it can simply be said that network interaction is certainly present but the evidence for its functional significance was equivocal. Nevertheless, the dependence of previous trial connectivity on the adjustment level is a strike against the parallel system account since this relationship suggest that network coupling influences performance. Additional research is needed to understand the functional nature of these network interactions and to assess the scope of individual differences in coupling of these networks.

APPENDIX A: CONNECTIVITY EFFECT MAPS

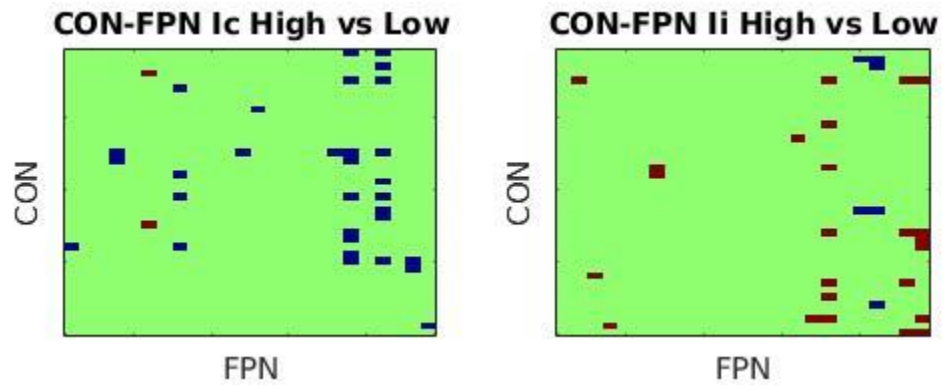


Figure A.1-High vs. low adjustment (defined by median split) CON-FPN connectivity differences with p values below the .05 uncorrected threshold. Blue marks negative differences (High < Low) and red marks positive differences (High > Low).

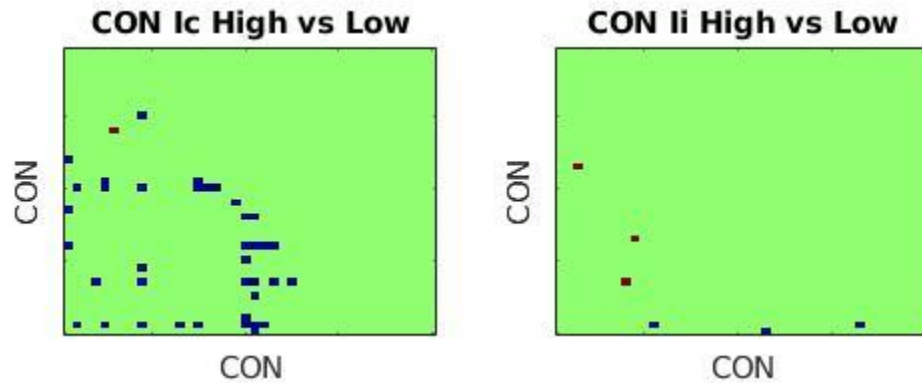


Figure A.2-High vs. low adjustment (defined by median split) CON connectivity differences with p values below the .05 uncorrected threshold. Blue marks negative differences (High < Low) and red marks positive differences (High > Low).

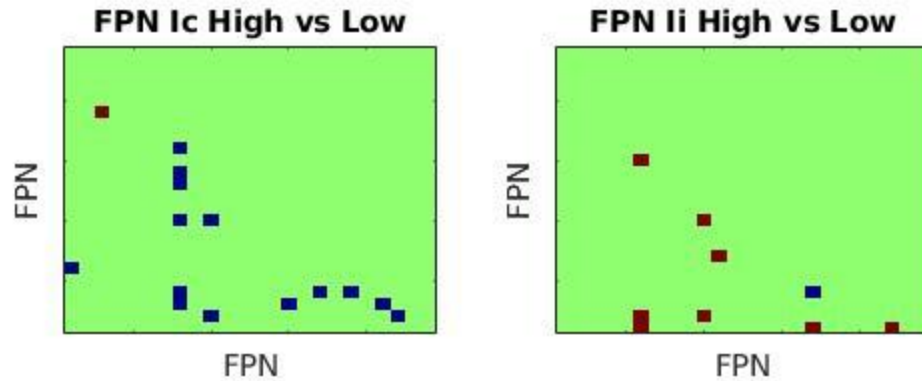


Figure A.3-High vs. low adjustment (defined by median split) FPN connectivity differences with p values below the .05 uncorrected threshold. Blue marks negative differences (High < Low) and red marks positive differences (High > Low).

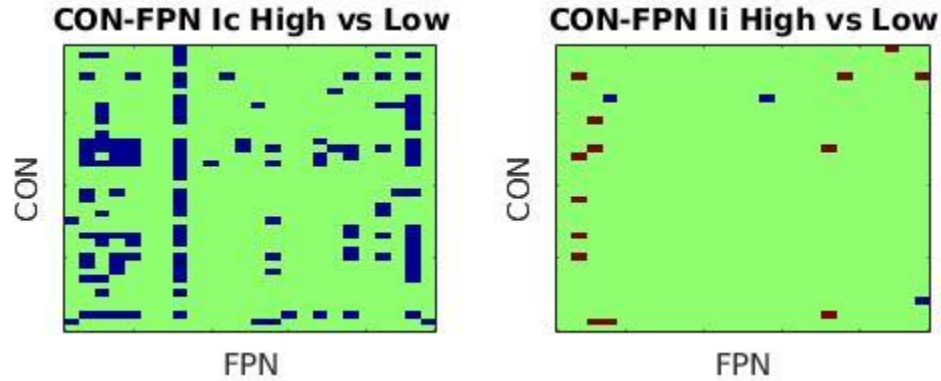


Figure A.4-High vs. low adjustment (defined by bottom and top quartiles) CON-FPN connectivity differences with p values below the .05 uncorrected threshold. Blue marks negative differences (High < Low) and red marks positive differences (High > Low).

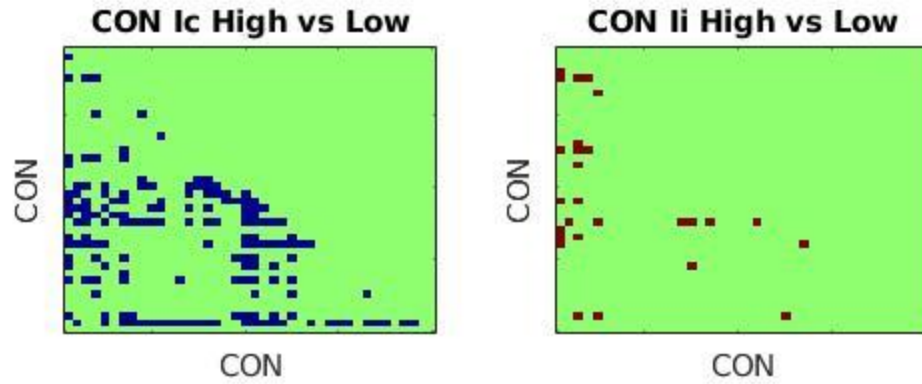


Figure A.5-High vs. low adjustment (defined by bottom and top quartiles) CON connectivity differences with p values below the .05 uncorrected threshold. Blue marks negative differences (High < Low) and red marks positive differences (High > Low).

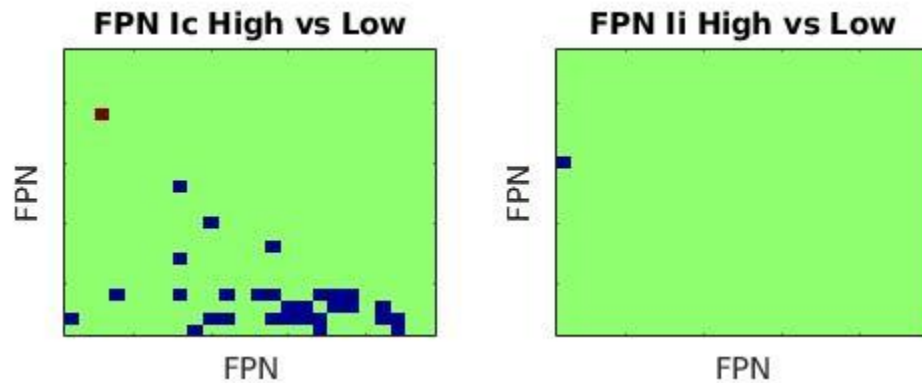


Figure A.6-High vs. low adjustment (defined by bottom and top quartiles) FPN connectivity differences with p values below the .05 uncorrected threshold. Blue marks negative differences (High < Low) and red marks positive differences (High > Low).

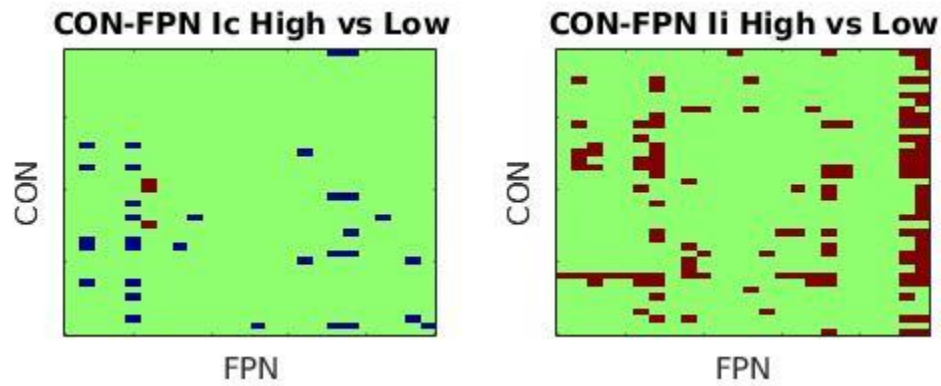


Figure A.7-High vs. low adjustment (defined by median split) CON-FPN connectivity differences with p values below the .05 uncorrected threshold. Blue marks negative differences (High < Low) and red marks positive differences (High > Low) for subjects exhibiting a CSE.

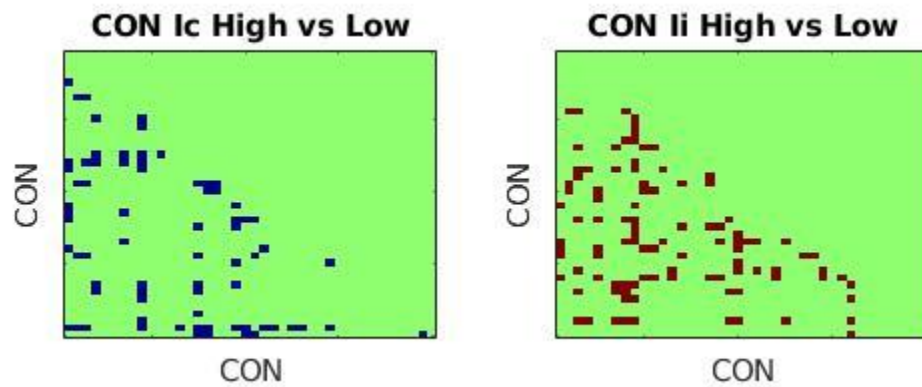


Figure A.8-High vs. low adjustment (defined by median split) CON connectivity differences with p values below the .05 uncorrected threshold. Blue marks negative differences (High < Low) and red marks positive differences (High > Low) for subjects exhibiting a CSE.

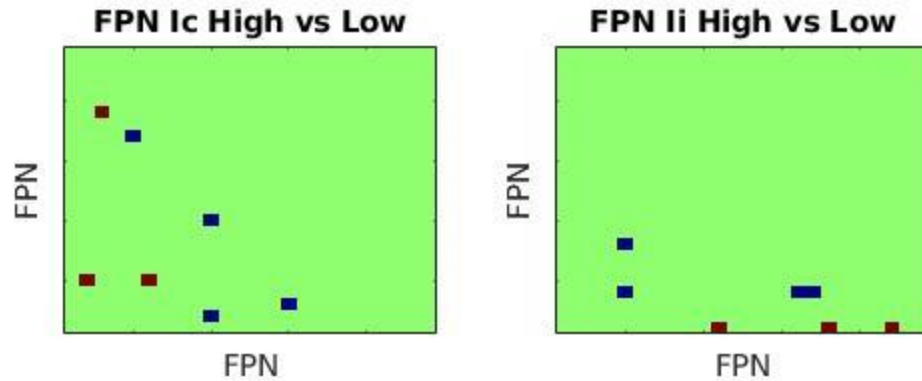


Figure A.9-High vs. low adjustment (defined by median split) FPN connectivity differences with p values below the .05 uncorrected threshold. Blue marks negative differences ($High < Low$) and red marks positive differences ($High > Low$) for subjects exhibiting a CSE.

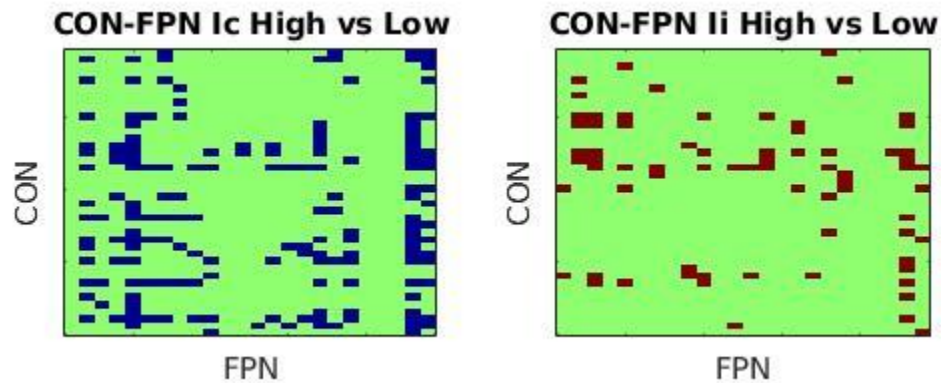


Figure A.10-High vs. low adjustment (defined by bottom and top quartiles) CON-FPN connectivity differences with p values below the .05 uncorrected threshold. Blue marks negative differences ($High < Low$) and red marks positive differences ($High > Low$) for subjects exhibiting a CSE.

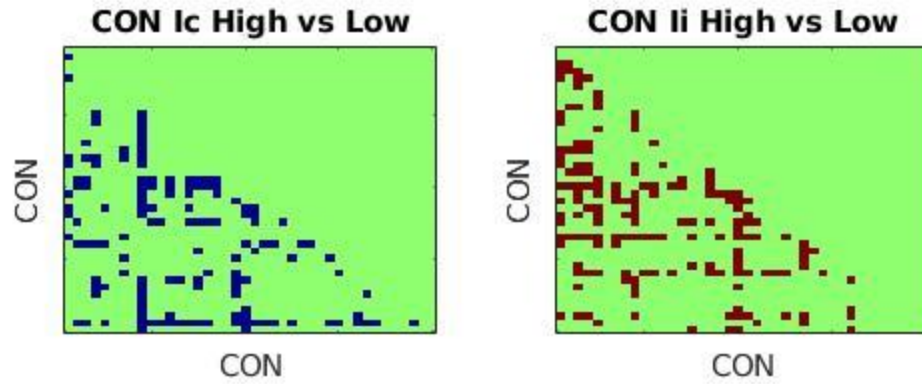


Figure A.11-High vs. low adjustment (defined by bottom and top quartiles) CON connectivity differences with p values below the .05 uncorrected threshold. Blue marks negative differences ($High < Low$) and red marks positive differences ($High > Low$) for subjects exhibiting a CSE.

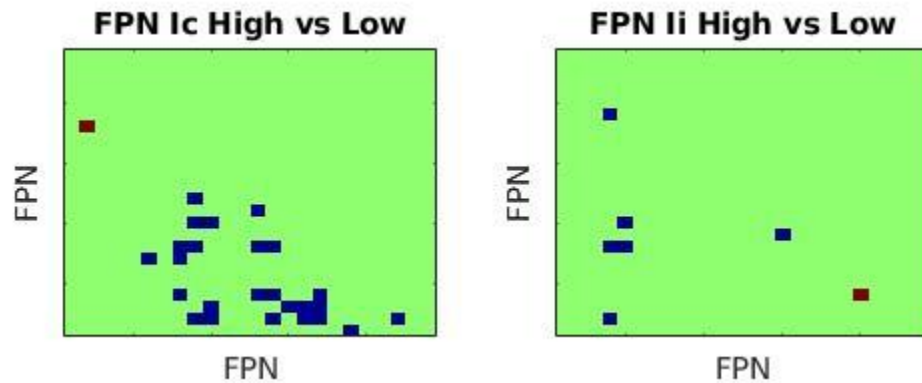


Figure A.12-High vs. low adjustment (defined by bottom and top quartiles) FPN connectivity differences with p values below the .05 uncorrected threshold. Blue marks negative differences ($High < Low$) and red marks positive differences ($High > Low$) for subjects exhibiting a CSE.

APPENDIX B: CSE VS NO CSE CONNECTIVITY

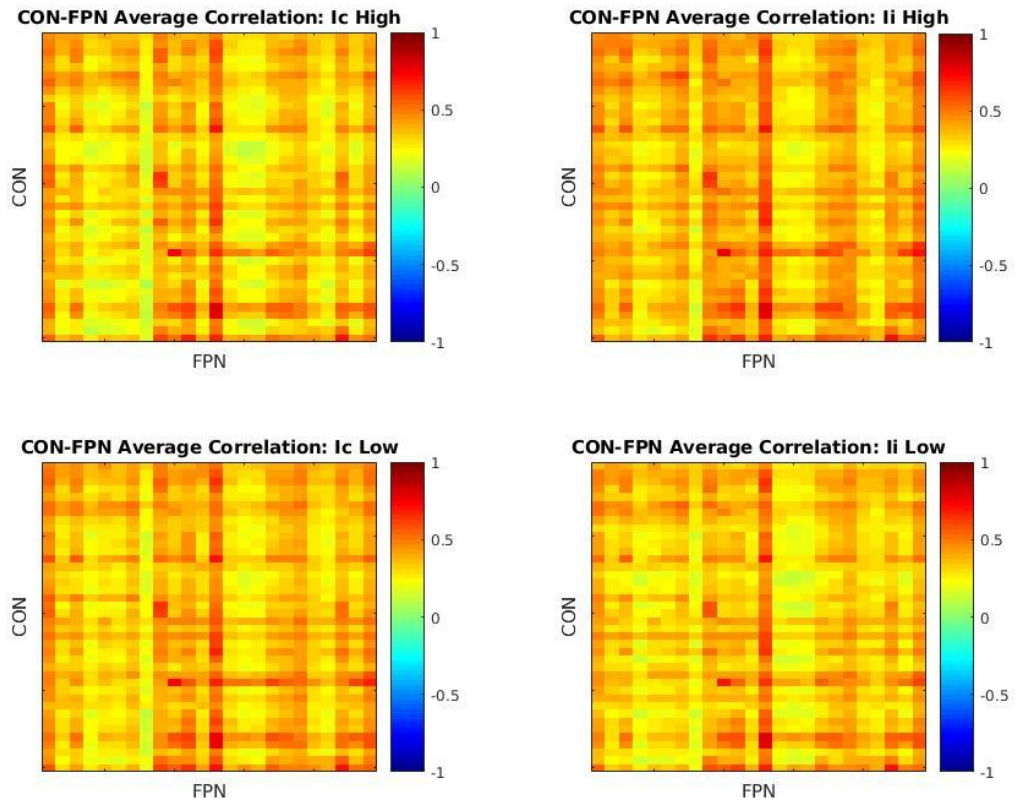


Figure B.1-Average correlations between CON and FPN nodes for Ic and Ii trials split by subsequent trial adjustment (defined by a median split) for subjects exhibiting a CSE.

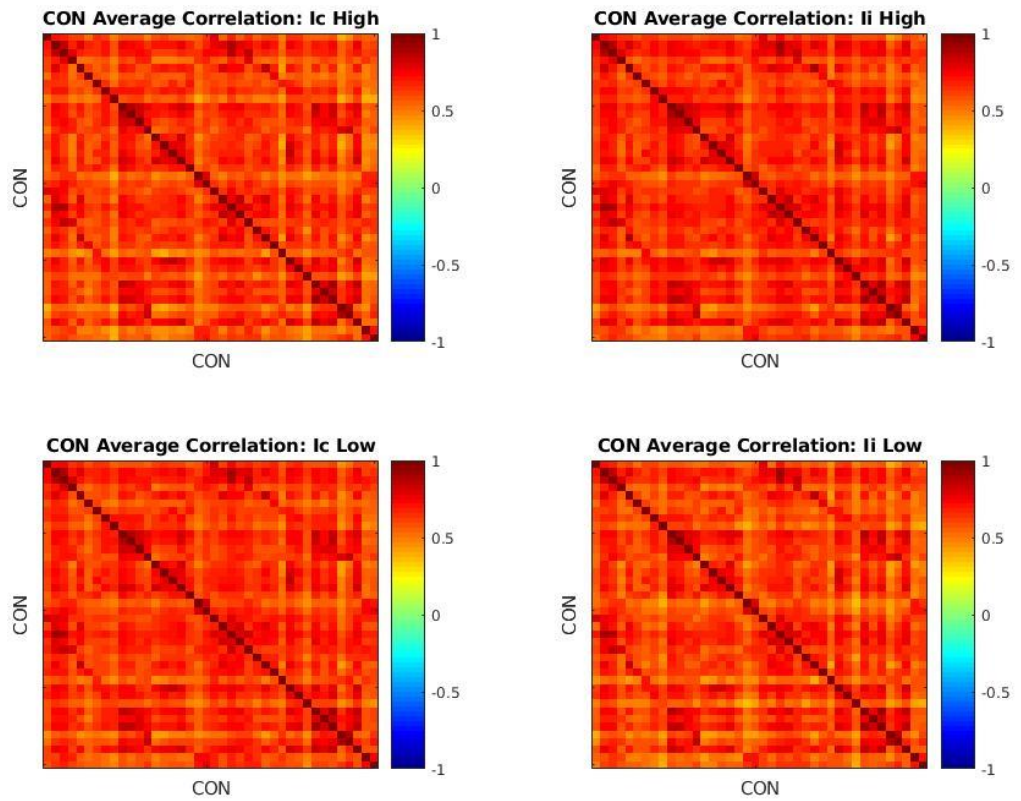


Figure B.2-Average correlations between CON nodes for Ic and Ii trials split by subsequent trial adjustment (defined by a median split) for subjects exhibiting a CSE.

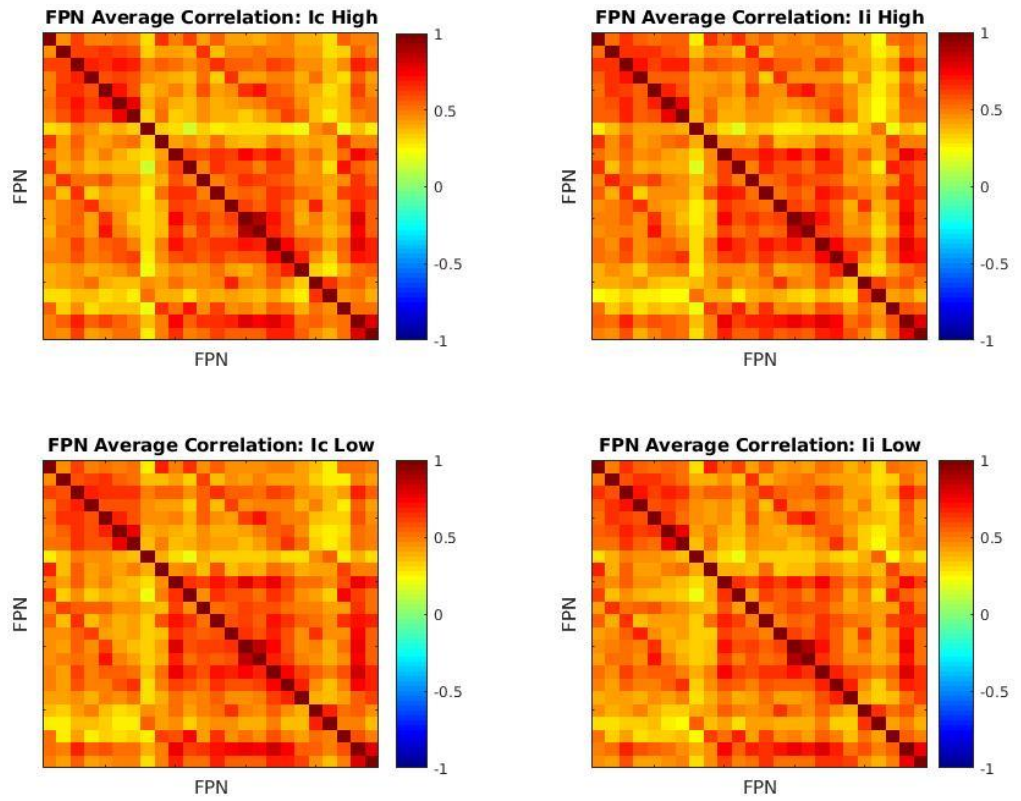


Figure B.3-Average correlations between FPN nodes for Ic and Ii trials split by subsequent trial adjustment (defined by a median split) for subjects exhibiting a CSE.

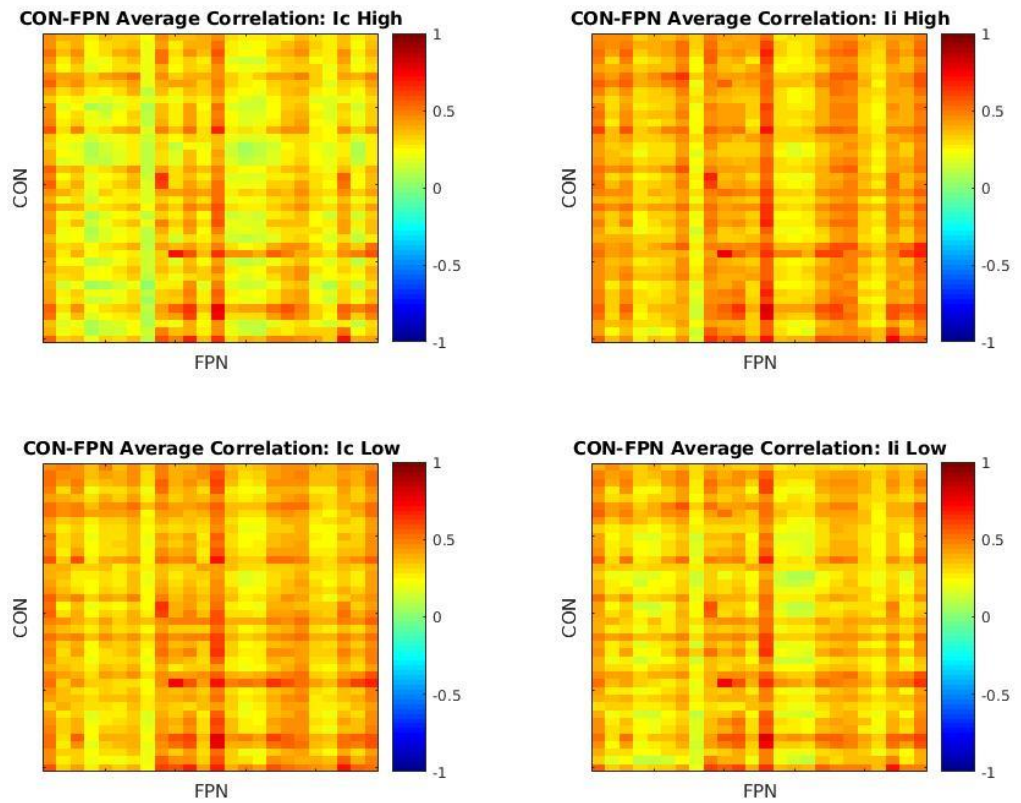


Figure B.4-Average correlations between CON and FPN nodes for Ic and Ii trials split by subsequent trial adjustment (defined by bottom and top quartiles) for subjects exhibiting a CSE.

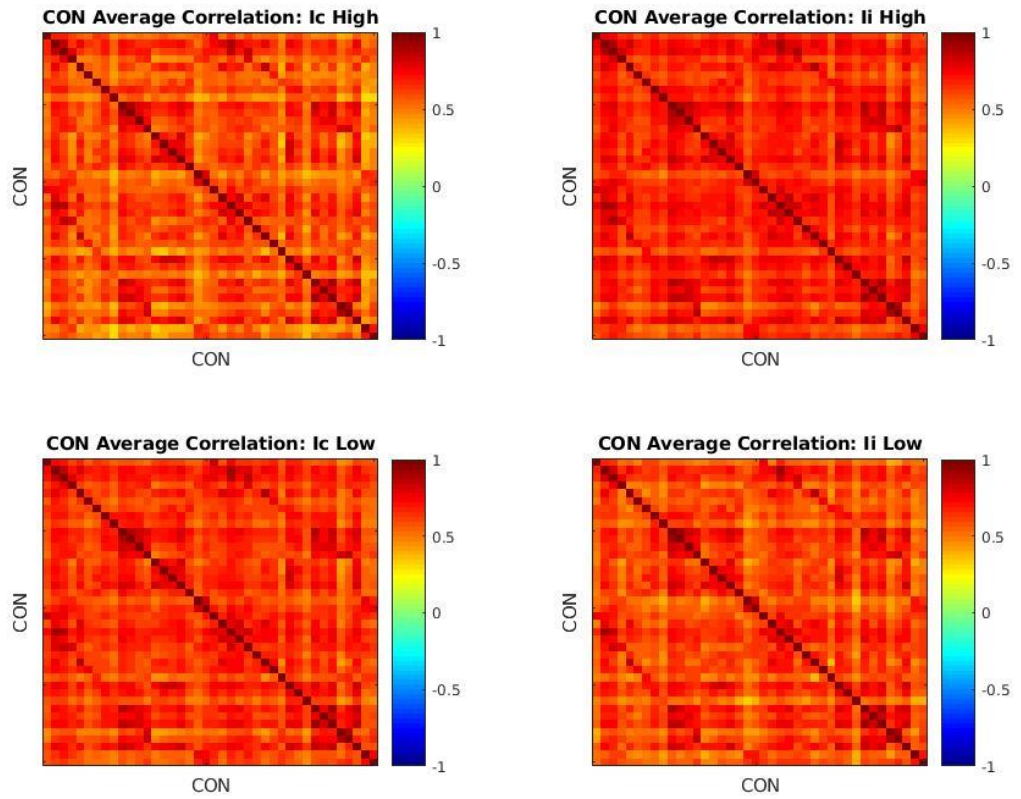


Figure B.5-Average correlations between CON nodes for Ic and Ii trials split by subsequent trial adjustment (defined by bottom and top quartiles) for subjects exhibiting a CSE.

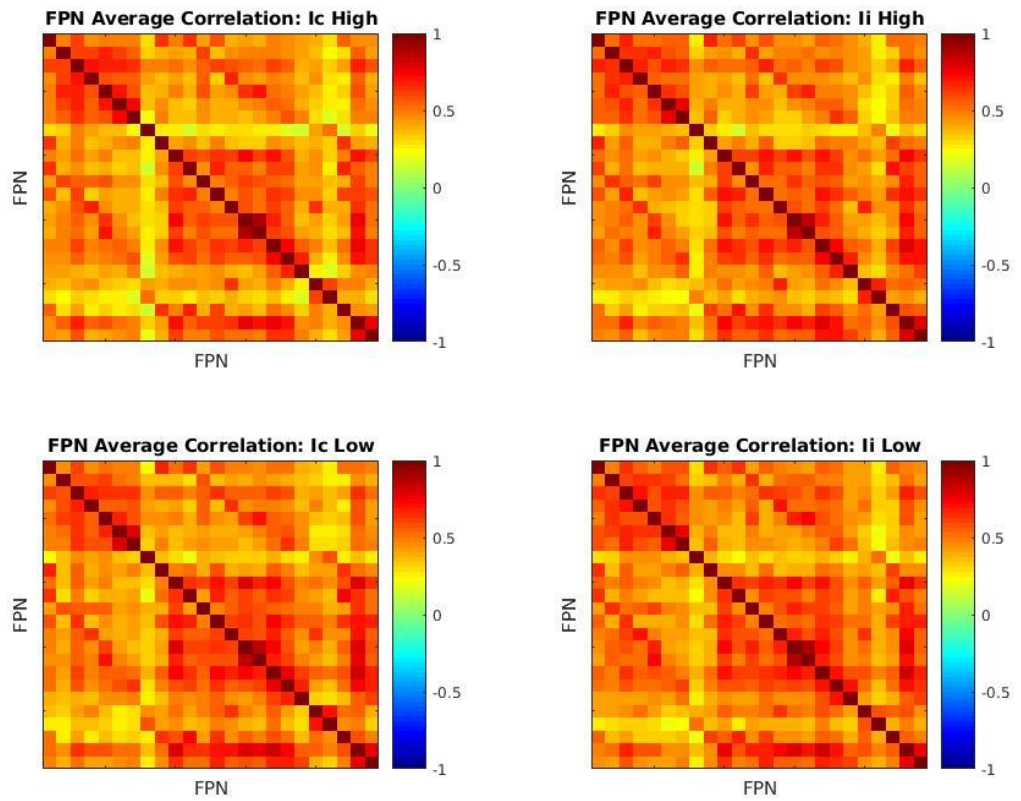


Figure B.6-Average correlations between FPN nodes for Ic and Ii trials split by subsequent trial adjustment (defined by bottom and top quartiles) for subjects exhibiting a CSE.

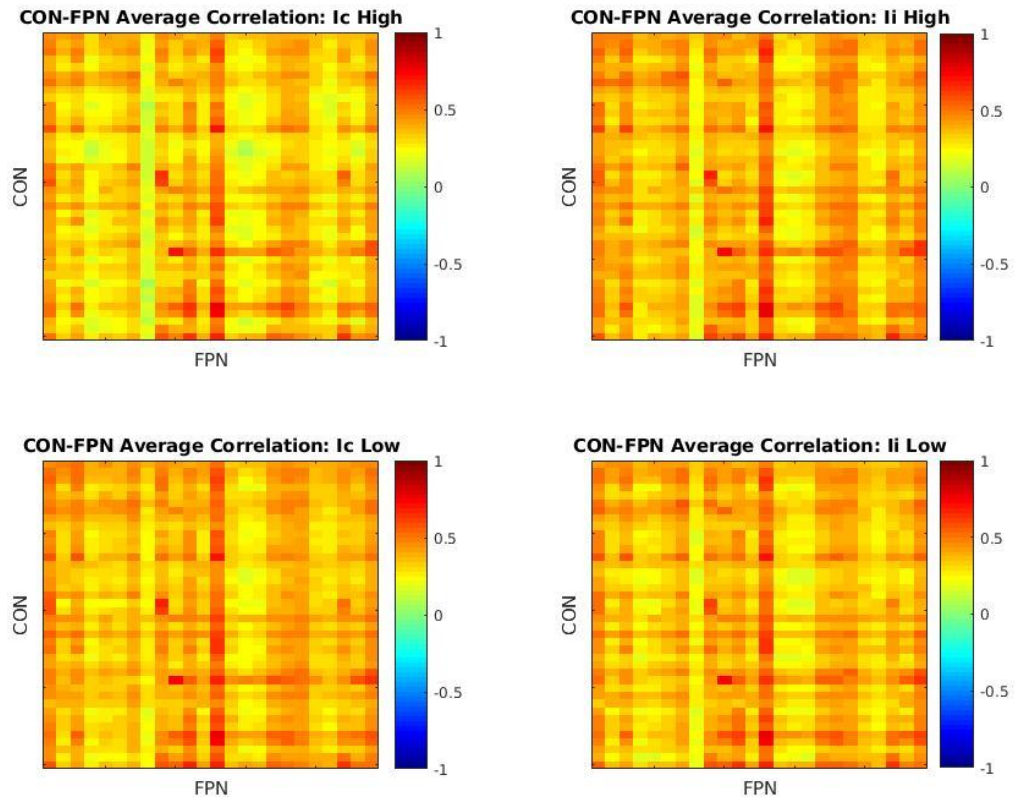


Figure B.7-Average correlations between CON and FPN nodes for Ic and Ii trials split by subsequent trial adjustment (defined by a median split) for subjects not exhibiting a CSE.

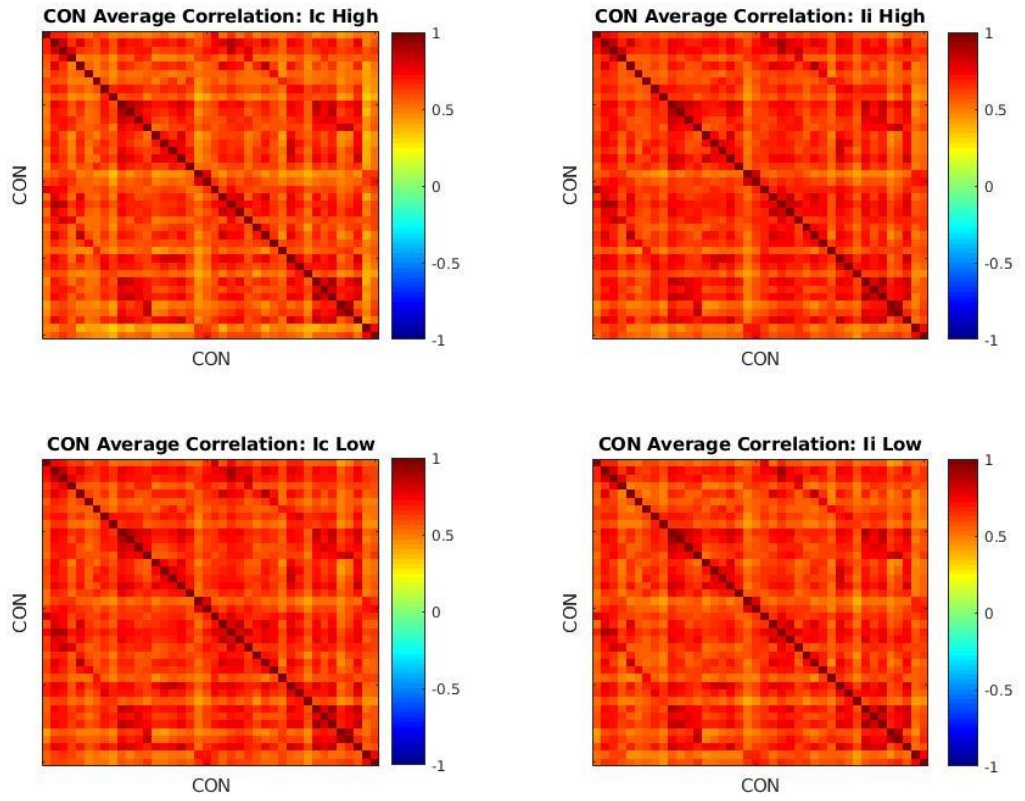


Figure B.8-Average correlations between CON nodes for Ic and Ii trials split by subsequent trial adjustment (defined by a median split) for subjects not exhibiting a CSE.

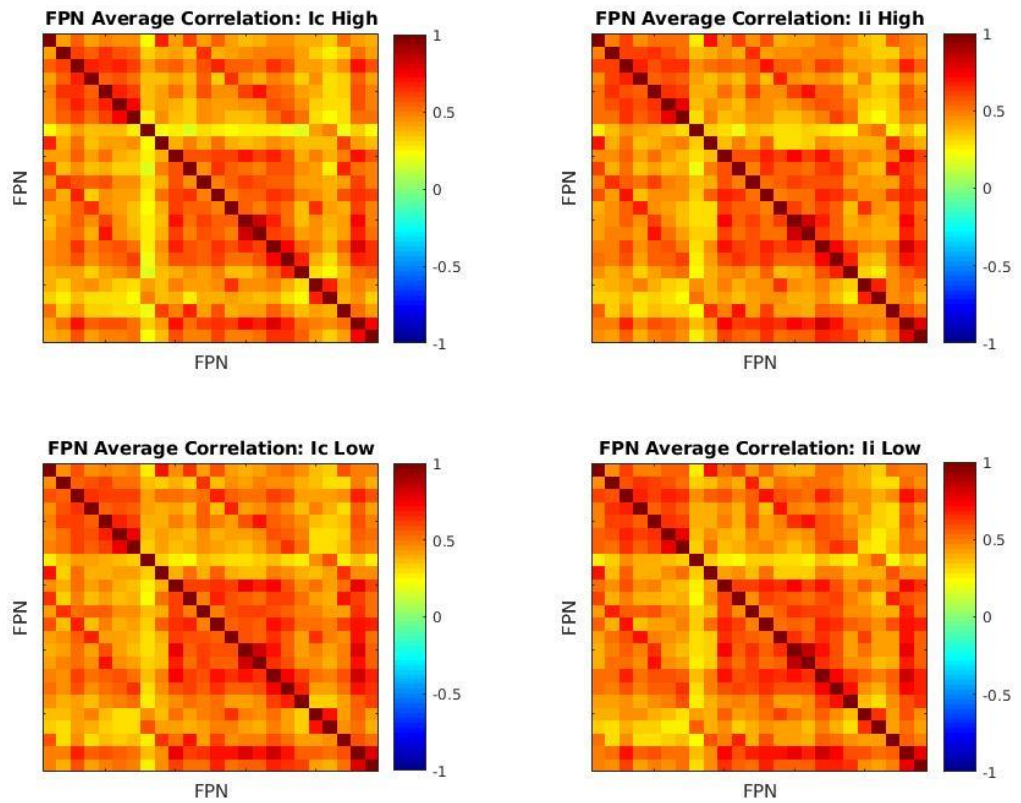


Figure B.9-Average correlations between FPN nodes for Ic and Ii trials split by subsequent trial adjustment (defined by a median split) for subjects not exhibiting a CSE.

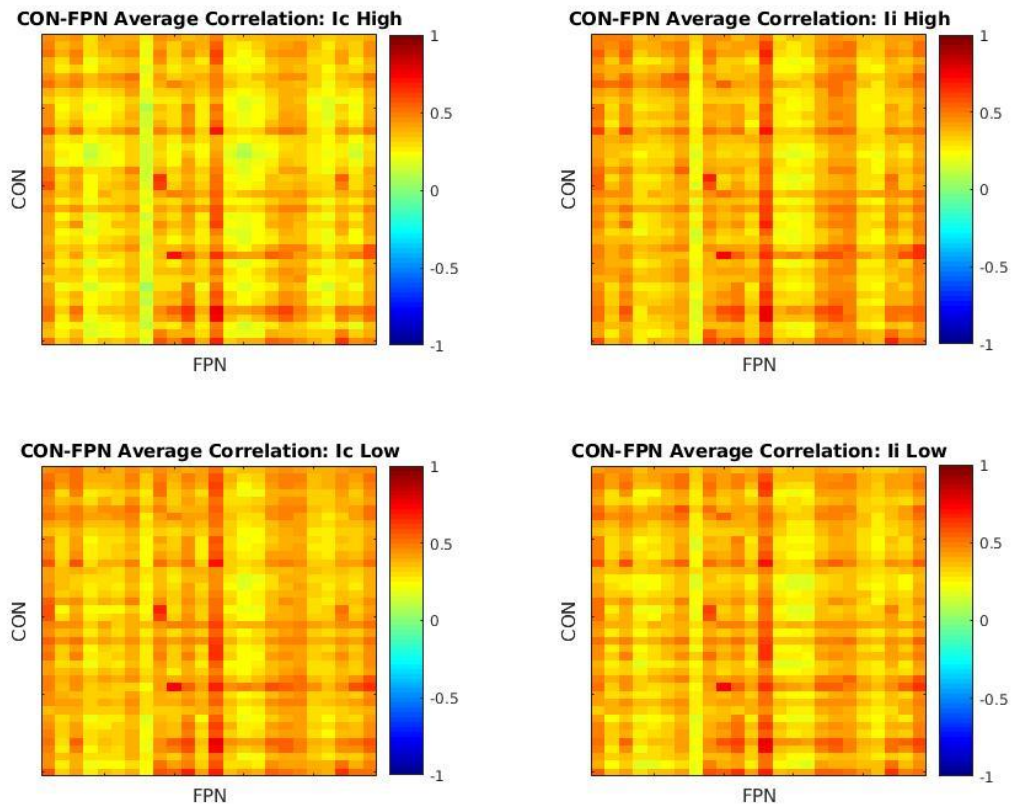


Figure B.10-Average correlations between CON and FPN nodes for Ic and Ii trials split by subsequent trial adjustment (defined by bottom and top quartiles) for subjects not exhibiting a CSE.

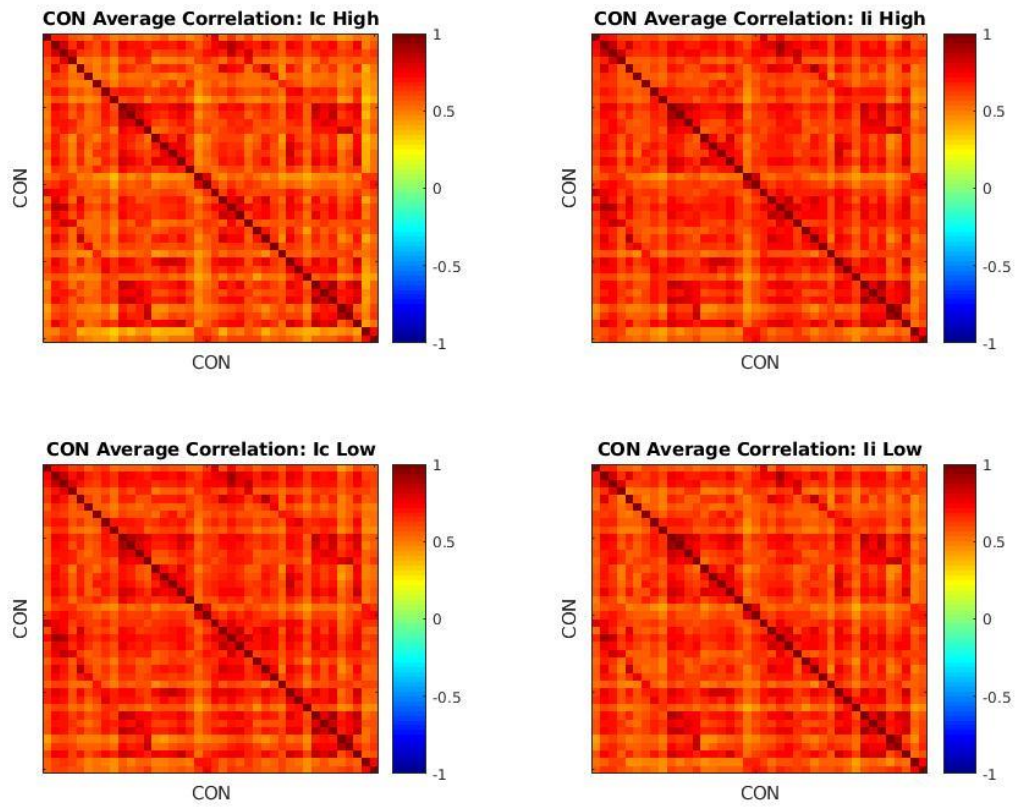


Figure B.11-Average correlations between CON nodes for Ic and Ii trials split by subsequent trial adjustment (defined by bottom and top quartiles) for subjects not exhibiting a CSE.

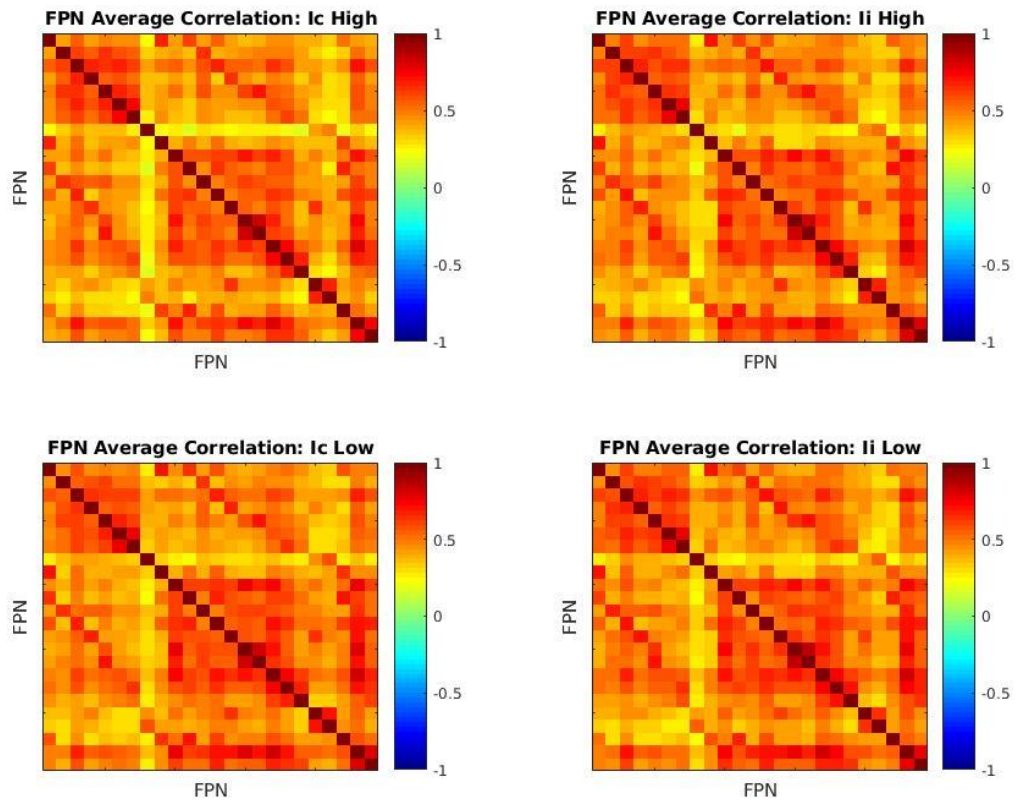


Figure B.12-Average correlations between FPN nodes for Ic and Ii trials split by subsequent trial adjustment (defined by bottom and top quartiles) for subjects not exhibiting a CSE.

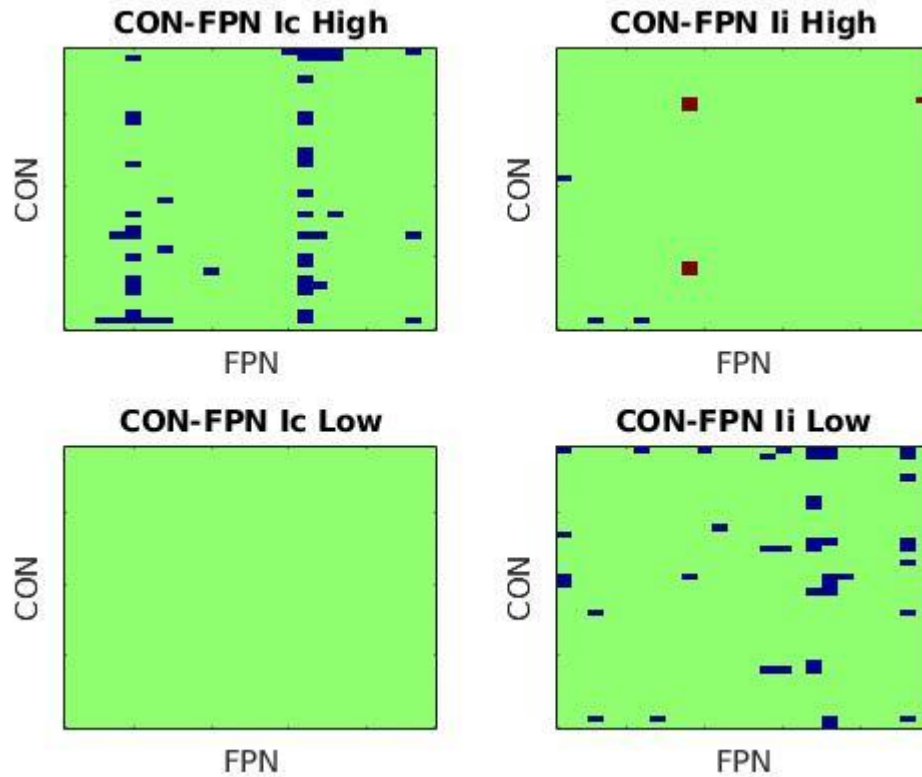


Figure B.13-CON-FPN connectivity differences between CSE subjects and those lacking a CSE by trial type and adjustment level (defined by median split) with p values below the .05 uncorrected threshold. Blue marks negative group differences and red marks positive group differences.

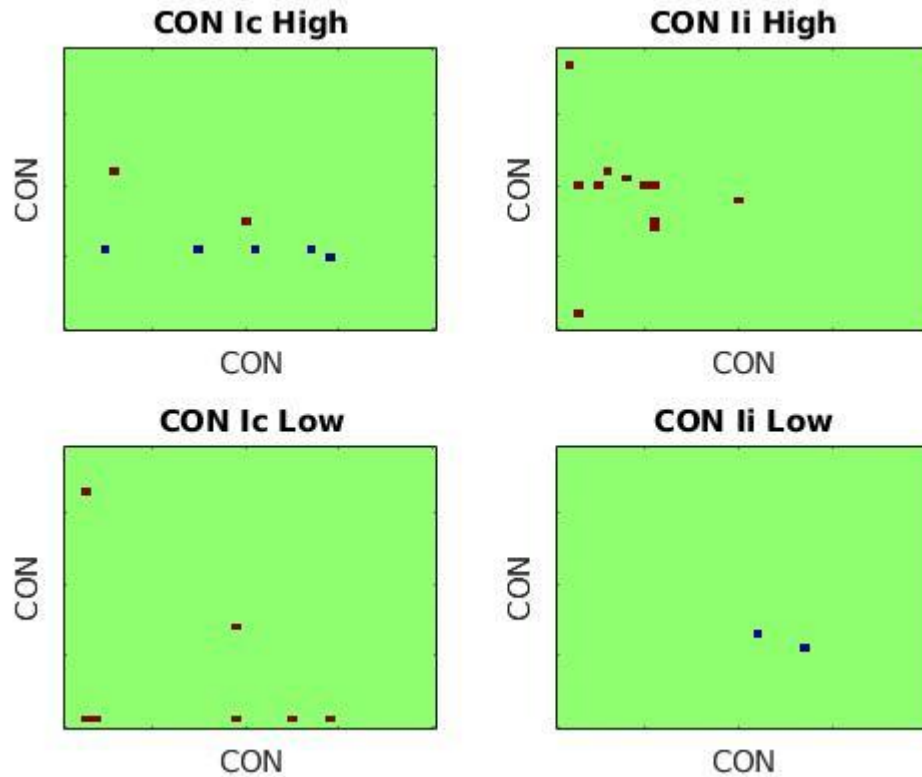


Figure B.14-CON connectivity differences between CSE subjects and those lacking a CSE by trial type and adjustment level (defined by median split) with p values below the .05 uncorrected threshold. Blue marks negative group differences and red marks positive group differences.

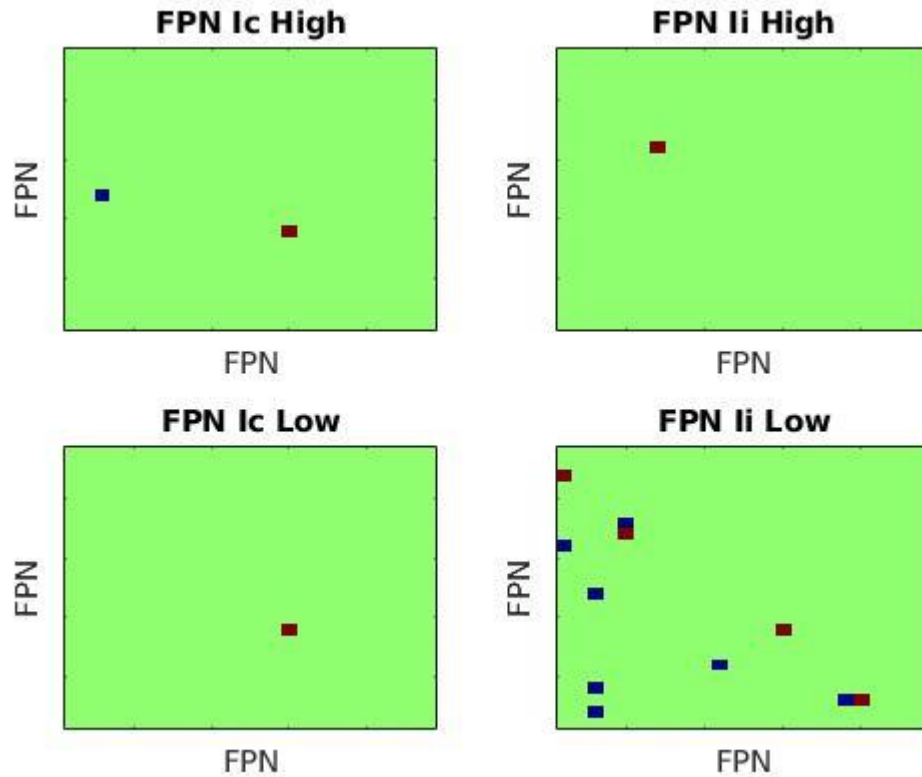


Figure B.15-FPN connectivity differences between CSE subjects and those lacking a CSE by trial type and adjustment level (defined by median split) with p values below the .05 uncorrected threshold. Blue marks negative group differences and red marks positive group differences.

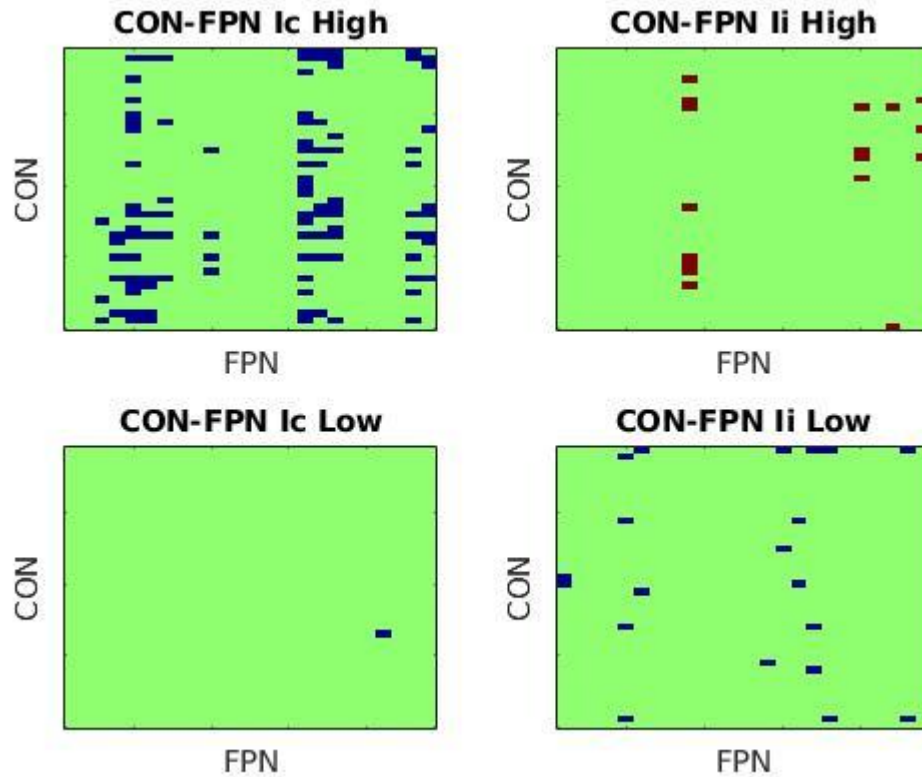


Figure B.16-CON-FPN connectivity differences between CSE subjects and those lacking a CSE by trial type and adjustment level (defined by bottom and top quartiles) with p values below the .05 uncorrected threshold. Blue marks negative group differences and red marks positive group differences.

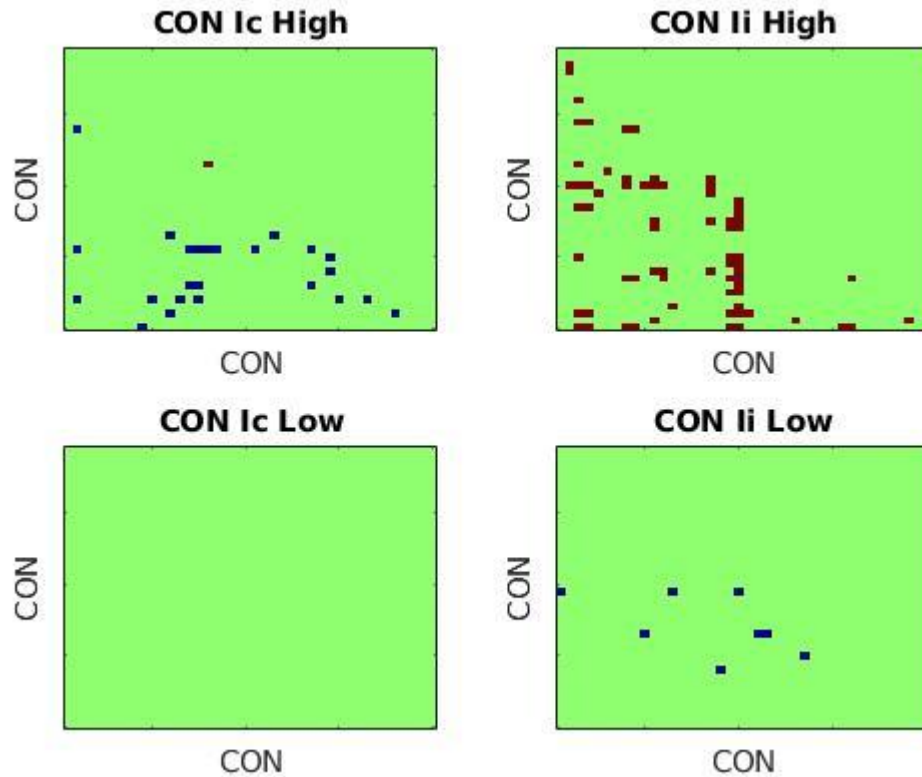


Figure B.17-CON connectivity differences between CSE subjects and those lacking a CSE by trial type and adjustment level (defined by bottom and top quartiles) with p values below the .05 uncorrected threshold. Blue marks negative group differences and red marks positive group differences.

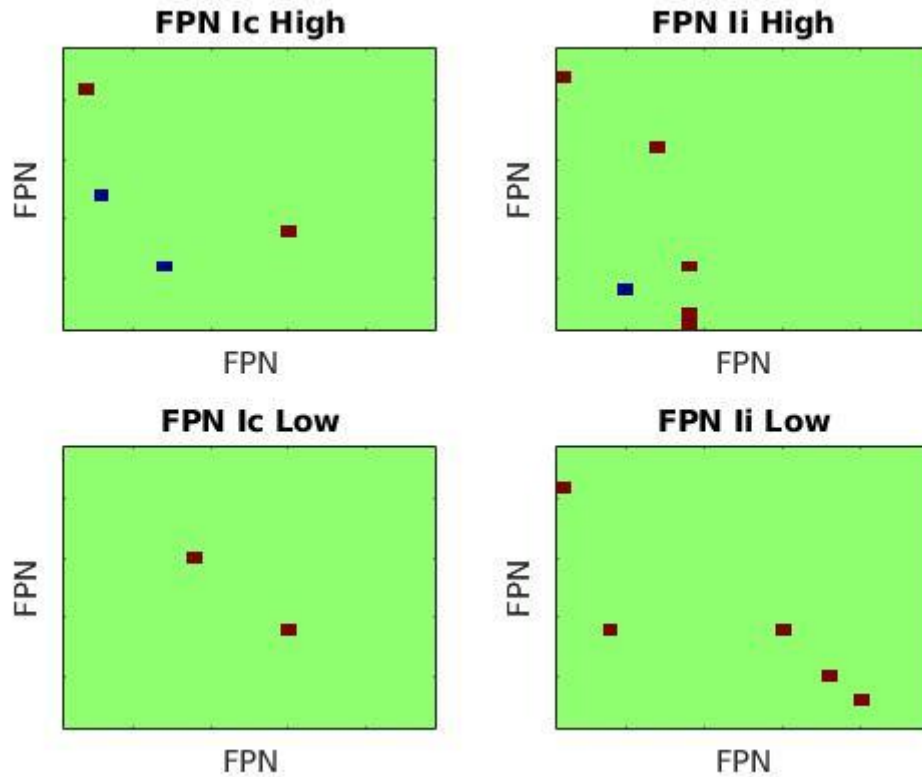


Figure B.18-FPN connectivity differences between CSE subjects and those lacking a CSE by trial type and adjustment level (defined by bottom and top quartiles) with p values below the .05 uncorrected threshold. Blue marks negative group differences and red marks positive group differences.

APPENDIX C: PARAMETRIC MODULATION MAPS

CON Based Parametric Modulation cI Trials



X = -58

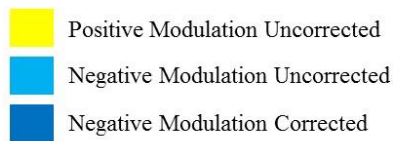
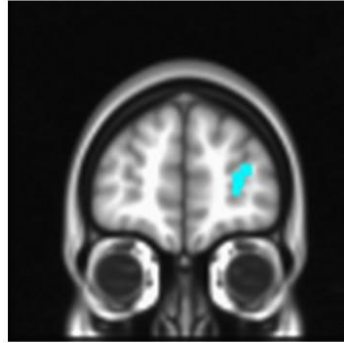


Figure C.1-Previous trial CON residual activity based parametric modulation in the FPN on cI trials (Corrected is defined as $q=.05$ and uncorrected as $p=.05$).

CON Based Parametric Modulation iC Trials



Y = 52

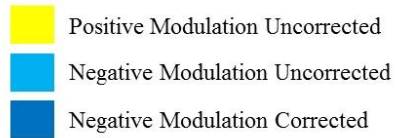


Figure C.2-Previous trial CON residual activity based parametric modulation in the FPN on iC trials (Corrected is defined as $q=.05$ and uncorrected as $p=.05$).

CON Based Parametric Modulation iC Low Adjustment Trials

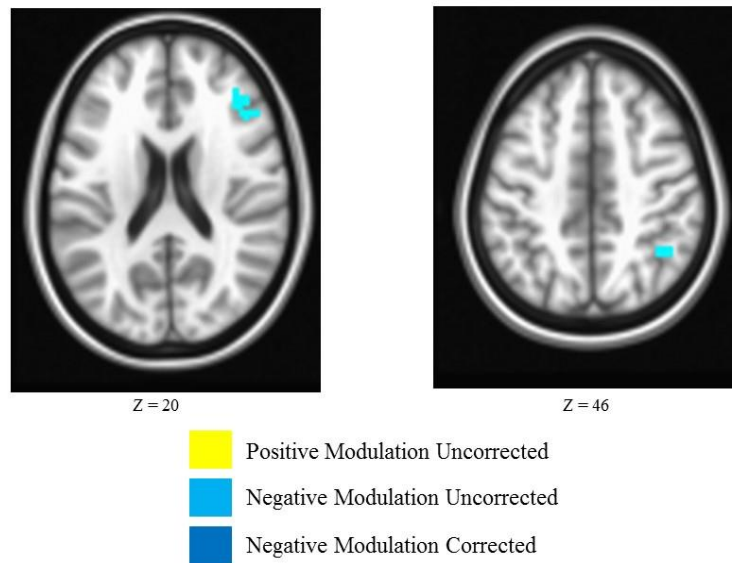


Figure C.3-Previous trial CON residual activity based parametric modulation in the FPN on iC low adjustment trials (Corrected is defined as $q=.05$ and uncorrected as $p=.05$).

CON Based Parametric Modulation iI Trials

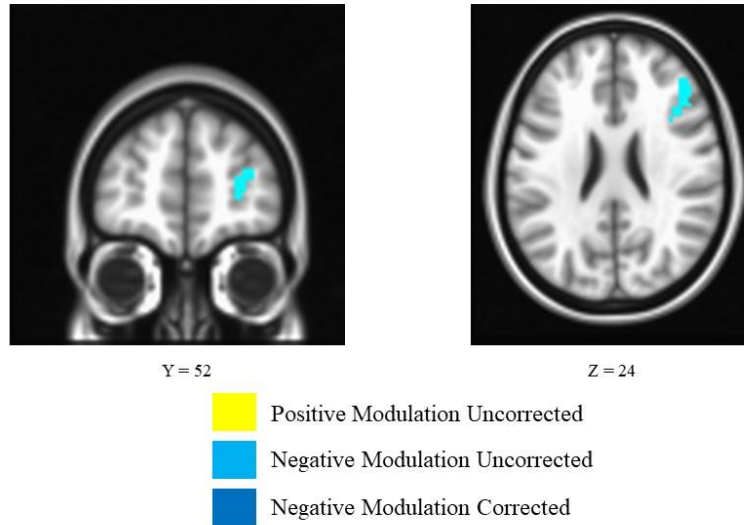


Figure C.4-Previous trial CON residual activity based parametric modulation in the FPN on iI trials (Corrected is defined as $q=.05$ and uncorrected as $p=.05$).

CON Based Parametric Modulation in High Adjustment Trials

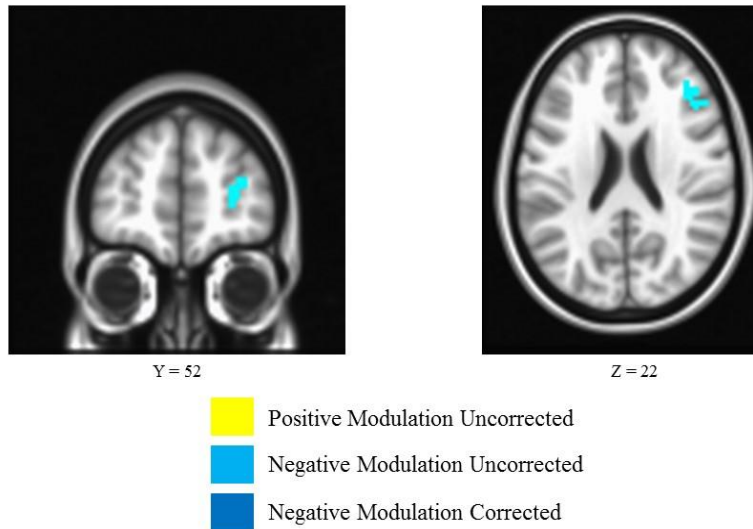


Figure C.5-Previous trial CON residual activity based parametric modulation in the FPN on high adjustment trials (Corrected is defined as $q=.05$ and uncorrected as $p=.05$).

ACC Based Parametric Modulation cC Trials

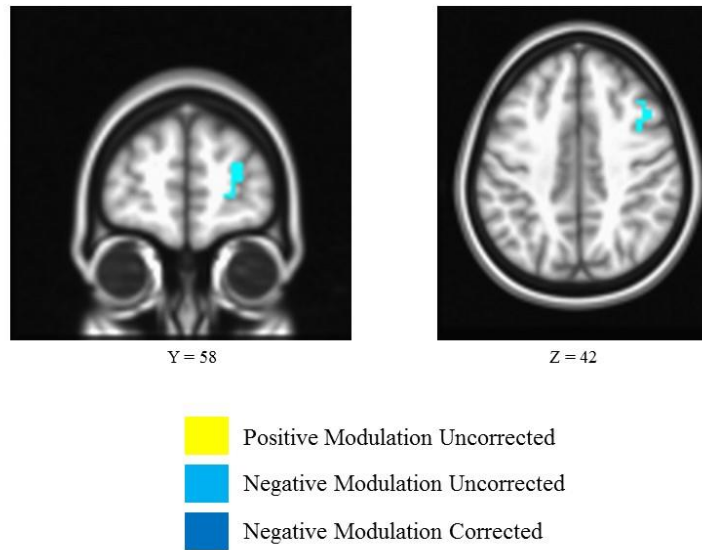
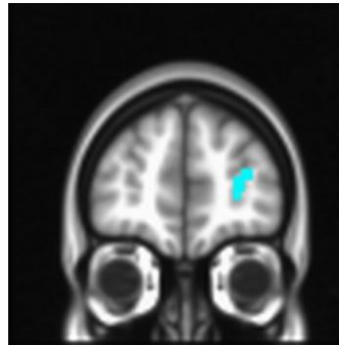


Figure C.6-Previous trial right ACC residual activity based parametric modulation in the FPN on cC trials (Corrected is defined as $q=.05$ and uncorrected as $p=.05$).

ACC Based Parametric Modulation cI Trials



Y = 52

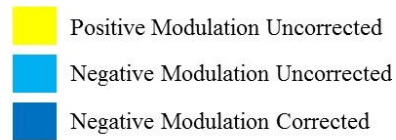


Figure C.7-Previous trial right ACC residual activity based parametric modulation in the FPN on cI trials (Corrected is defined as $q=.05$ and uncorrected as $p=.05$).

ACC Based Parametric Modulation iC Trials

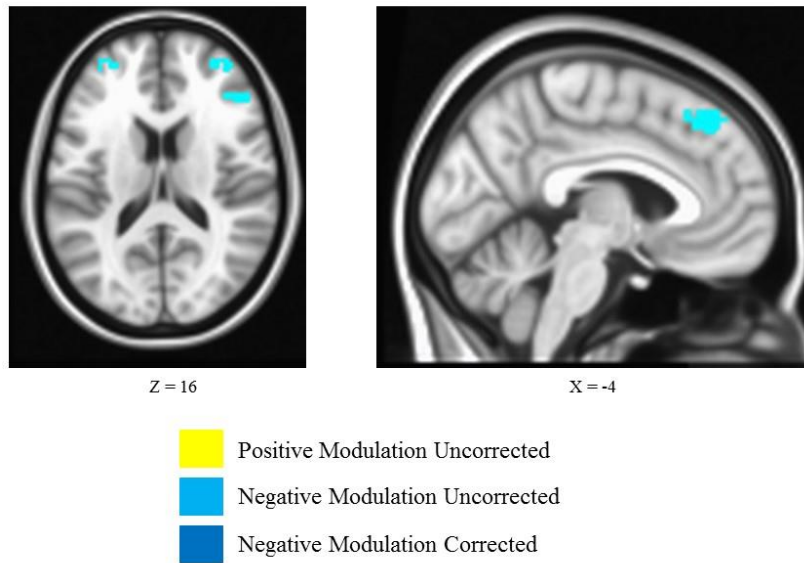


Figure C.8-Previous trial right ACC residual activity based parametric modulation in the FPN on iC trials (Corrected is defined as $q=.05$ and uncorrected as $p=.05$).

ACC Based Parametric Modulation iC Low Adjustment Trials

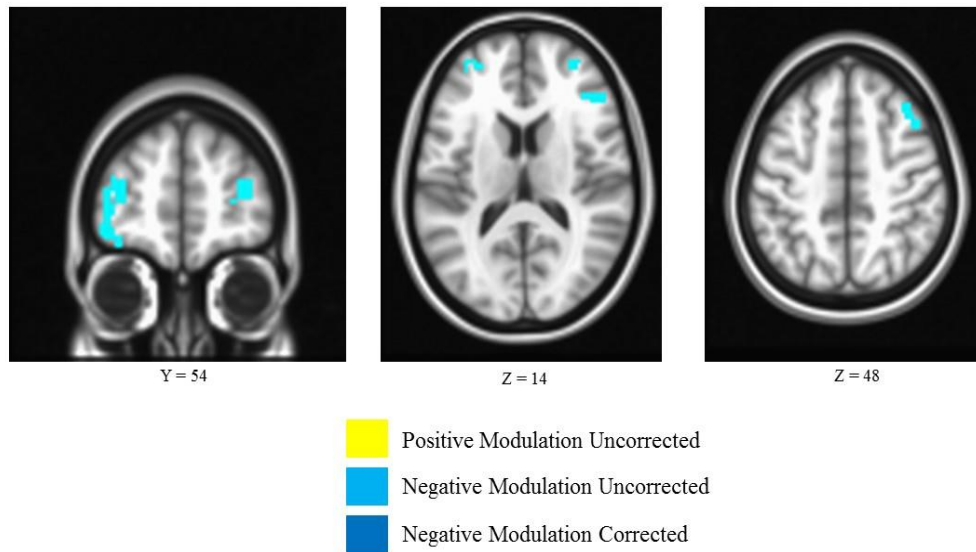


Figure C.9-Previous trial right ACC residual activity based parametric modulation in the FPN on iI low adjustment trials (Corrected is defined as $q=.05$ and uncorrected as $p=.05$).

ACC Based Parametric Modulation iI Trials

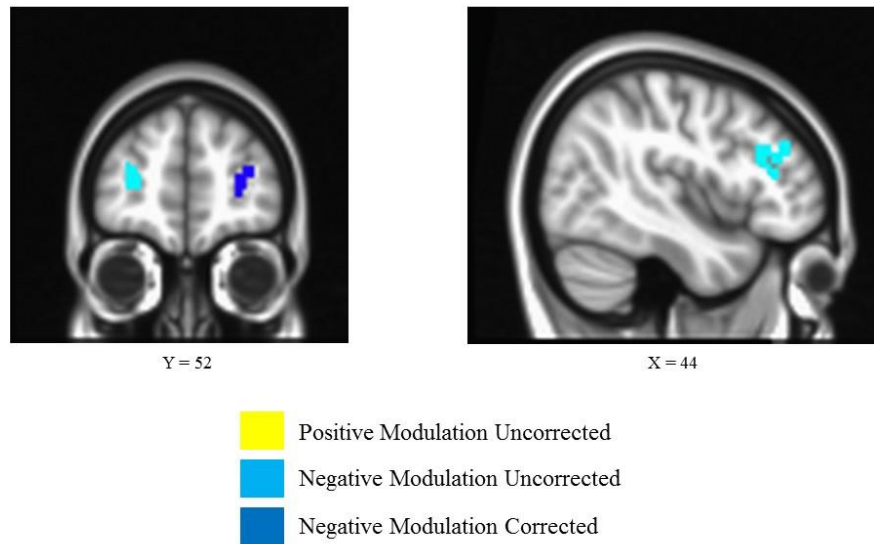


Figure C.10-Previous trial right ACC residual activity based parametric modulation in the FPN on iI trials (Corrected is defined as $q=.05$ and uncorrected as $p=.05$).

ACC Based Parametric Modulation in High Adjustment Trials

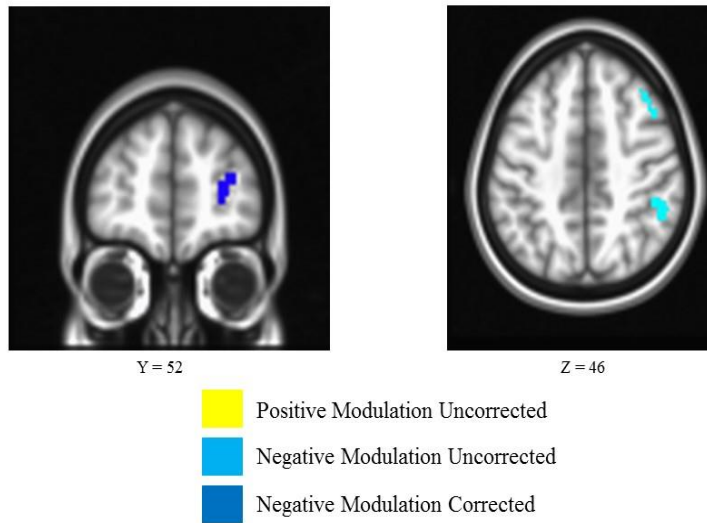
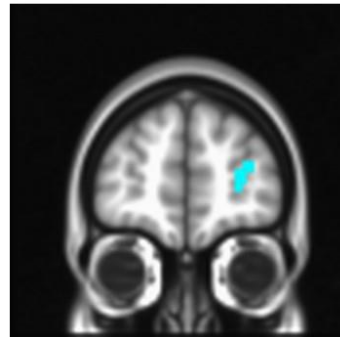


Figure C.11-Previous trial right ACC residual activity based parametric modulation in the FPN on high adjustment trials (Corrected is defined as $q=.05$ and uncorrected as $p=.05$).

ACC Based Parametric Modulation in Low Adjustment Trials



Y = 52

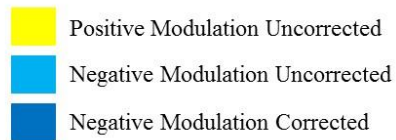


Figure C.12-Previous trial right ACC residual activity based parametric modulation in the FPN on low adjustment trials (Corrected is defined as $q=.05$ and uncorrected as $p=.05$).

CON Based Parametric Modulation Differences for iC Trials

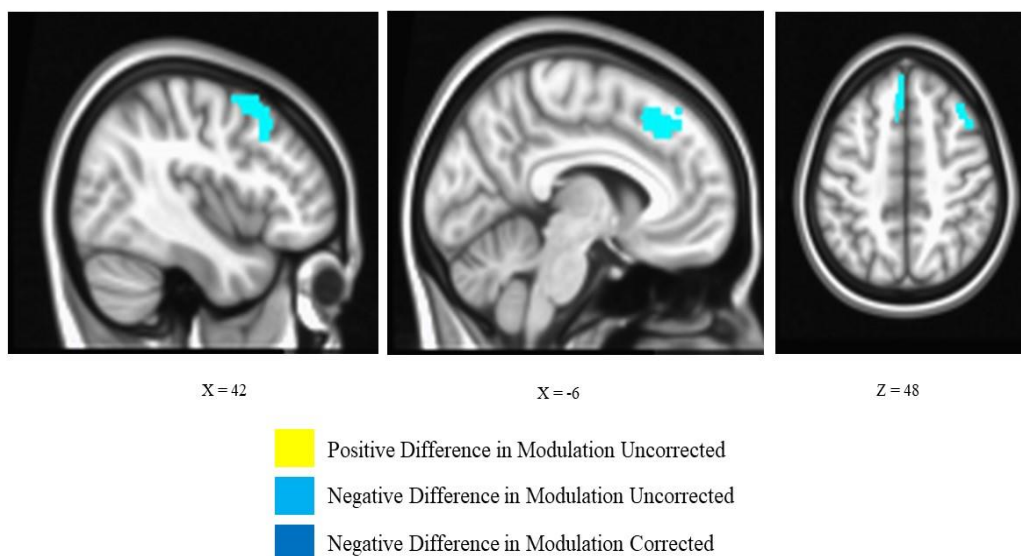


Figure C.13-Difference in modulation between subjects with and without a CSE on previous trial right CON residual activity based parametric modulation in the FPN on iC trials (Corrected is defined as $q=.05$ and uncorrected as $p=.05$).

ACC Based Parametric Modulation Differences for iC Trials

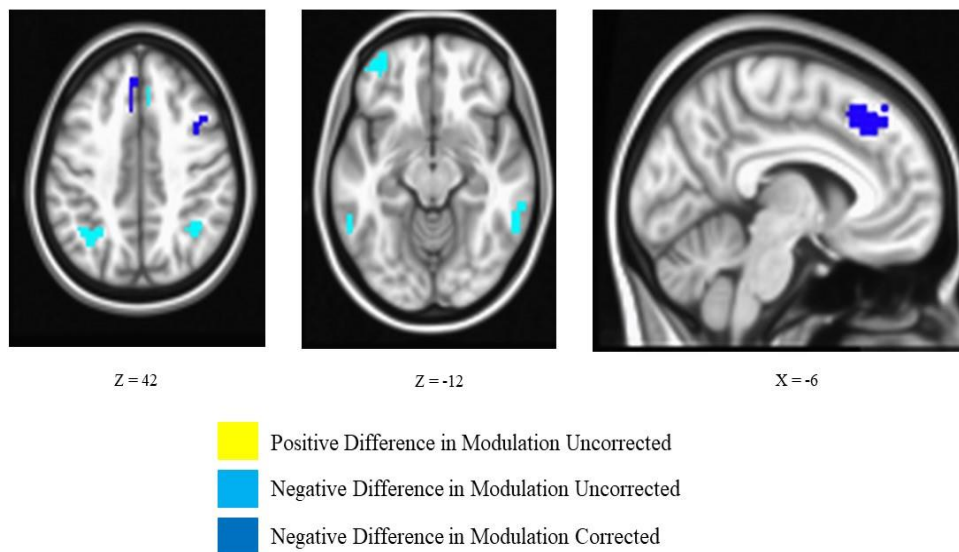


Figure C.14-Difference in modulation between subjects with and without a CSE on previous trial right ACC residual activity based parametric modulation in the FPN on iC trials (Corrected is defined as $q=.05$ and uncorrected as $p=.05$).

APPENDIX D: TASK DEPICTION AND NETWORK REGIONS

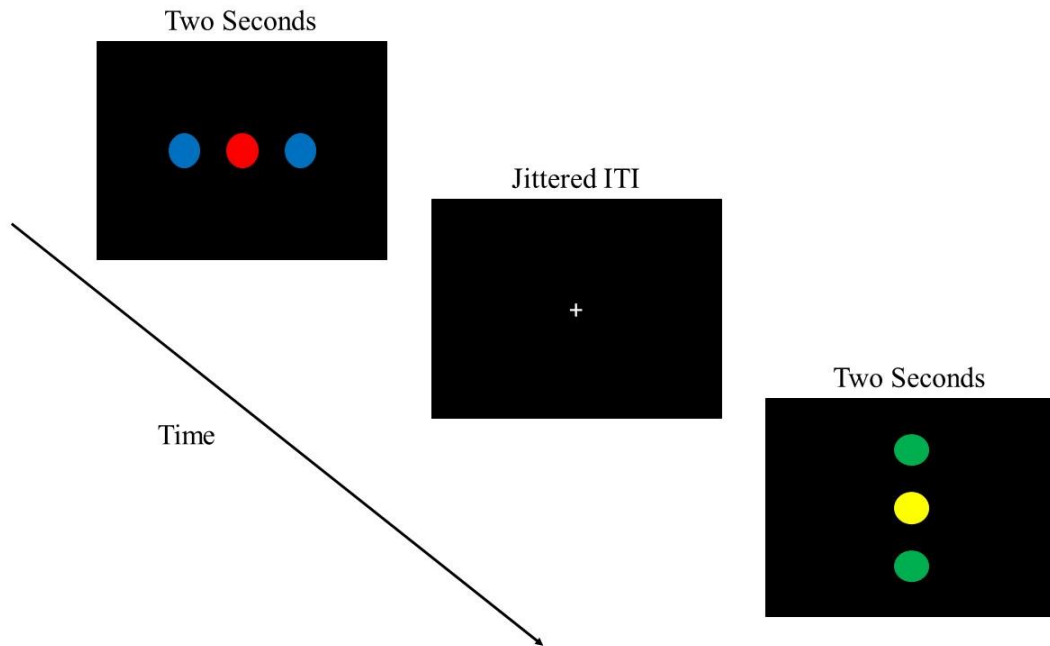


Figure D.1-Depiction of the Kim and Cho inspired confound minimized CSE inducing task used in this study.

Table D.1-CON Region Locations

CON Index	Region Location
1	Left Mid-Cingulate-Posterior
2	Left Mid-Cingulate-Anterior/SMA
3	Left Caudal Dorsal Anterior Cingulate
4	Left Rostral Dorsal Anterior Cingulate
5	Left SMA
6	Left Precentral Gyrus
7	Left Inferior Parietal Lobule
8	Left Ventral Posterior Insula
9	Left Ventral Anterior Insula
10	Left Dorsal Mid to Anterior Insula
11	Left Dorsal Posterior Insula
12	Left Dorsal Anterior Insula
13	Left Dorsal Anterior Insula & Left Inferior Frontal Gyrus
14	Left Rolandic Operculum
15	Left Ventral SupraMarginal Gyrus
16	Left Dorsal SupraMarginal Gyrus
17	Left Rolandic Operculum/Insula
18	Left Inferior Frontal Gyrus Opercularis
19	Left Anterior PFC/Frontal pole
20	Left Middle Frontal Gyrus
21	Right Mid-cingulate-Posterior
22	Right Ventral SMA
23	Right Ventral Mid-cingulate
24	Right Dorsal Mid-cingulate
25	Right Dorsal Anterior Cingulate
26	Right Rostral Dorsal SMA
27	Right Caudal Dorsal SMA
28	Right Precentral Gyrus
29	Right Posterior Supramarginal Gyrus
30	Right Anterior Supramarginal Gyrus
31	Right Ventral Posterior Insula
32	Right Ventral Anterior Insula
33	Right Dorsal Mid to Anterior Insula
34	Right Dorsal Anterior Insula-A
35	Right Dorsal Posterior Insula
36	Right Dorsal Anterior Insula-B
37	Right Dorsal Anterior Insula & Inferior Frontal Gyrus
38	Right Rolandic Operculum
39	Right Superior Frontal Gyrus
40	Right Anterior PFC

Table D.2-FPN Region Locations

FPN Index	Region Location
1	Left DLPFC
2	Left Middle Temporal Gyrus
3	Left Superior Medial Frontal Gyrus
4	Left Anterior PFC & OFC
5	Left Inferior Parietal Lobule
6	Left Caudal Middle Frontal Gyrus
7	Left Rostral Middle Frontal Gyrus
8	Left Anterior PFC
9	Left Lateral Anterior PFC
10	Right Ventral Inferior Parietal Lobule
11	Right Lateral Anterior PFC
12	Right Middle Temporal Gyrus
13	Right Medial Frontal Gyrus
14	Right Inferior Frontal Gyrus
15	Right Anterior Dorsal Inferior Parietal Lobule
16	Right Posterior Dorsal Inferior Parietal Lobule
17	Right Middle Frontal Gyrus
18	Right DLPFC
19	Right Posterior Inferior Frontal Gyrus
20	Right Anterior Ventral PFC
21	Right Anterior Dorsal PFC
22	Right Superior Frontal Gyrus
23	Right Dorsal Middle Frontal Gyrus
24	Right Middle Frontal Gyrus & Precentral Gyrus

Note: In regards to labels like “Right Anterior Dorsal Inferior Parietal Lobule” it refers to the anterior and dorsal portion of the inferior parietal lobule.

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