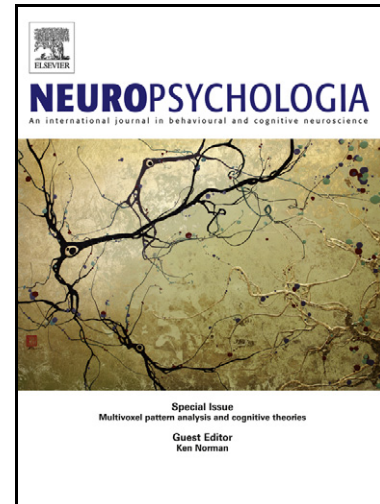


Prefrontal cortex contributions to controlled memory judgment: fMRI evidence from adolescents and young adults

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Running title: CONTROLLED RETRIEVAL AND DEVELOPMENT

Prefrontal cortex contributions to controlled memory judgment: fMRI evidence from adolescents  
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## Abstract

Cortical regions supporting cognitive control and memory judgment are structurally immature in adolescents. Here we studied adolescents (13-15 y.o.) and young adults (20-22 y.o.) using a recognition memory paradigm that modulates cognitive control demands through cues that probabilistically forecast memory probe status. Behaviorally, adolescence was associated with quicker responding in the presence of invalid cues compared to young adulthood. FMRI data demonstrated that while both groups increasingly activated posterior dorsolateral prefrontal (dlPFC), midline, and lateral parietal regions for invalidly compared to validly cued trials, this differential invalid cueing response ended sooner in adolescents, consistent with their generally quicker responding on cued trials. Critically, dlPFC also demonstrated reversed brain-behavior associations across the groups. Increased mean dlPFC activation during invalid cueing was linked to improved performance in young adults, whereas increases within adolescents were linked to impaired performance. Resting state connectivity analysis revealed greater connectivity between dlPFC and episodic retrieval linked regions in young adults relative to adolescents. These data demonstrate that the functional interpretation of dlPFC activation hinges on its physical maturation and suggest that the pattern of behavioral and neural response in adolescents reflects different functional integration of cognitive control and memory systems.

*Keywords: Adolescence, Cueing, Development, Memory, Recognition.*

## 1 Introduction

Although memory retrieval is critically dependent upon medial temporal lobe regions (Squire, 1992), recent functional imaging research demonstrates that a widespread collection of frontal and parietal areas are also engaged when observers render episodic memory judgments (Yonelinas, Otten, Shaw & Rugg, 2005; Dobbins, Rice, Wagner & Schacter, 2003; Wagner, Shannon, Kahn & Buckner, 2005; McDermott et al., 2000, Henson et al., 1999). This network includes frontopolar and posterior dorsolateral PFC, lateral parietal cortex, superior parietal cortex, and areas along the anterior and posterior midline cortex. Although the specific functional contribution of each region to episodic retrieval remains heavily debated (e.g., Vilberg & Rugg, 2008; Cabeza et al., 2008), these same regions are typically recruited during cognitive control tasks (Dosenbach et al., 2007; Vincent et al., 2008), and are often jointly described as belonging to a fronto-parietal cognitive control network critical for overriding automatic responding when it is contextually inappropriate. Recent findings suggest that the recruitment of regions within this network during recognition may also signify the need for cognitive control to overcome inappropriate mnemonic expectations. More specifically, O'Connor, Han and Dobbins (2010) used an explicit memory cueing procedure to instill trial-wise expectations in a recognition task by providing generally valid anticipatory cues ("Likely Old" or "Likely New") prior to each recognition memory probe. Their data demonstrated increased activation in prefrontal and parietal regions whenever recovered memory content violated cue induced memory expectations, suggesting that these regions were linked to violated expectations, and perhaps important for overriding the automatic responding accompanying the cue-induced expectations, or for integrating external cues and mnemonic information during recognition judgment.

Here we use a developmental functional imaging approach to further test this model of fronto-parietal engagement during episodic recognition. The key motivation for the study rests on the finding that structurally, prefrontal and parietal regions, along with their interconnections, reach maturity quite late (Olesen et al., 2003; Supekar, Musen, & Menon, 2009; Fair et al. 2009) with gray matter thinning and increased axonal myelination occurring throughout adolescence (Gogtay et al., 2004). This late maturation has been suggested to underlie the sometimes suboptimal performance of adolescents in tasks that require inhibitory control (Velanova, Wheeler, & Luna, 2009; Marsh et al., 2006; Rubia et al., 2006), feedback processing (Crone, et al., 2008), reward processing (Geier et al., 2010), risk taking (Eschel et al., 2007), and working memory (Geier et al., 2009; Crone et al., 2006). To date, however, virtually nothing is known about how the ongoing development of prefrontal regions might impact episodic memory judgments in adolescents (although see Ofen et al., 2007; Ghetti et al., 2010 for memory encoding research). This is important because memory judgments are often based upon noisy and reconstructed evidence, and because recovered memories can be vital in assessing the relative risks of decision alternatives. More generally, the comparison of populations with potentially different patterns of connectivity between prefrontal and other regions, may inform our functional interpretation of the role of prefrontal cortex during episodic memory judgments.

To our knowledge, only one neuroimaging study has examined recognition memory in adolescence (Paz-Alonso et al., 2008) and none have established whether adolescents efficiently use episodic memories to check or override cued expectations; a question with clear developmental and social significance. Indeed, one way to characterize impulsive decision making is as a tendency to respond on the basis of expectations with minimal evaluation of decision-relevant evidence. In the case of the explicit memory cueing procedure that we use

here, this would be marked by a tendency to respond quickly in line with the cued expectations before thoroughly considering recovered memory evidence and how that evidence confirms or conflicts with those expectations. In terms of concrete behavior, such a tendency would be primarily revealed during the invalidly cued trials, for example, when a studied test item follows a “Likely New” cue. Under this condition, impulsive responding would lead to an exceptionally low correct response rate in conjunction with a rapid reaction time. Current two-factor theories of decision making suggest that adolescents may demonstrate increased cue dependency relative to older individuals provided those cues are associated with rewarding outcomes. Within these frameworks it is suggested that the impulsive decision tendencies of adolescents reflect the differential developmental trajectories of brain networks supporting reward process versus those supporting cognitive control (Casey & Jones, 2010). Because the former peak during adolescence, whereas the latter are not fully mature until into the third decade, adolescents are thought to be prone to risky choices. Thus, our basic predictions when beginning the study were that relative to young adults, adolescents would demonstrate lower correct response rates under invalid cueing, that their responding would also be more rapid, and that they would not engage regions linked with cognitive control to the same extent as the young adults.

To examine the ability of adolescents to override expectations using memory content we contrasted mid-adolescents (13 to 15 y.o.) and young adults (20 to 22 y.o.) on a shortened version of the explicit mnemonic cueing task, choosing this adolescent age group because they were expected to demonstrate adult levels of recognition performance during standard, uncued recognition (Ghetti et al., 2010), ruling out basic difficulty interpretations of any dissociations potentially observed during the explicit mnemonic cueing task.

## **2 Materials and Methods**

## 2.1 Participants

Thirty-four individuals aged 13 to 22 years participated with informed consent obtained in accordance with the Institutional Review Board of the Washington University in St. Louis. Eighteen were adolescents aged 13-15 years (6 female, mean age, 14.39; SD, 0.78), and 16 were young adults aged 20-22 years (7 female, mean age, 21; SD, 0.73). One adolescent's data was excluded from the analysis because of equipment failure during scanning. Participants were right handed native English speakers with no history of neurological and psychiatric problems. Vision was normal or corrected to normal using magnet compatible glasses or contact lenses. Both adults and adolescents were paid \$25 per hour. Adolescents also received an iTunes gift card (\$25) as an incentive to avoid body motion during the scanning sessions.

## 2.2 Stimuli

For each participant, 280 words were randomly sampled from a pool of 390 words, with an average of 6.38 letters, 2.02 syllables, and Kucera-Francis corpus frequency of 9.45. From this, one list of 90 items (45 old and 45 new items) was used in one uncued study-test cycle and two lists of 95 items (45 old validly cued, 15 old invalidly cued, and 35 new validly cued items) were used in two subsequent cued study/test cycles.

## 2.3 Task and procedures

Before entering the scanner room, participants were administered the Vocabulary and Matrix Reasoning subtests of the Wechsler Abbreviated Scale of Intelligence (WASI) (The Psychological Corporation, 1999). Once completed, subjects entered the scanner and completed structural scanning followed by functional scans examining resting state (2 scans) and episodic recognition, respectively (3 scans). For the 2 resting state scans participants fixated a cross-hair

for 6 minutes with instructions to stay awake and remain still. For the episodic recognition experiment, 3 study-test cycles were administered with participants scanned only during test. The purpose of the first scanned recognition test was to examine baseline recognition skills without any preparatory cueing. During the study phase preceding the first recognition test scan participants indicated whether serially presented words had one or more syllables, having 2 seconds to respond for each of 45 words. A task prompt illustrating the correct key mappings was presented below each study item (“1 or 2 or more syllables”), and a fixation crosshair was presented for 500 ms before each item presentation. Immediately following study the studied items were intermixed with 45 new words and presented in a scanned baseline recognition test along with an additional 20 fixation trials of equal duration. The order of conditions was determined by a genetic algorithm that optimized the design efficiency for the contrasts of interest (Wager & Nichols, 2003). Stimulus onset asynchrony was 5 seconds and participants were required to respond within 3 seconds of memory probe onset using a four point response combining judgment (old or new) and confidence (high or low) (*high confident old*, *low confident old*, *low confident new*, and *high confident new*). A reminder prompt indicating the key mapping was presented below each test probe.

During the second and third study-test cycles we administered a shortened version of the Explicit Mnemonic Cueing task (Jaeger, Cox & Dobbins, 2012; O’Connor, Han, & Dobbins, 2010). During study, participants rated 60 words in the same manner as the first cycle. Immediately following each study list, a scanned recognition test was administered in which probabilistic cues (“Likely Old” or “Likely New”) preceded each recognition probe by 1.5 seconds. Following the cue’s appearance, both the cue and recognition probe were then presented for 3 seconds, followed by a 500 ms fixation period before the next trial (SOA 5



seconds). Participants were again required to respond while the probe was visible. During testing there were 45 trials in which the “Likely Old” cue preceded an old item (Figure 1). These cues never preceded new items and thus the “Likely Old” cue was perfectly predictive of upcoming item status. In contrast, the “Likely New” cue preceded 35 new probes (validly cued trials) and 15 old probes (invalidly cued trials) and hence was 75% predictive. Thus, it is only during baseline recognition (scan 1) and “Likely New” cue trials (scans 2 and 3) that there is considerable uncertainty prior to the appearance of the probe, either because no anticipatory cue was given (scan 1) or because the “Likely New” cue only probabilistically forecasts the memory probe (scans 2 and 3). A strictly deterministic “Likely Old” cue was used (instead of having both valid and invalid “Likely Old” cue trials) simply to shorten the time of the scans in order to avoid fatigue. Given that it was perfectly predictive, however, we do not consider this condition in the behavioral or functional imaging data because subjects could theoretically achieve perfect performance by simply relying on the cue without assessing memory. Prior to each cued recognition scan, participants were instructed that 80% of the cues were valid in order to emphasize perceived cue utility. Recognition judgments during the cued scans used the same four-point confidence rating scale as the first recognition scan.

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Insert Figure 1 about here

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## **2.4 fMRI acquisition and preprocessing**

Data were acquired using a 3T Siemens Trio whole-body MRI scanner (Siemens Medical Solutions, Erlanger, Germany) and a standard whole-head coil. The acquisition of functional

data was conducted using an interleaved ascending echo-planar pulse sequence (TR = 2500ms, TE = 27ms, 34 axial slices parallel to the anterior-commissure and posterior-commissure plane with isotropic 4mm voxels, and no inter-slice gap). For the uncued and cued runs, 226 and 236 volumes were acquired respectively. The first two volumes of each run were discarded to allow T1 stabilization. Foam pillows were utilized to minimize head motion. Preceding the active-task data acquisition, high-resolution T1-weighted and T2-weighted scans were acquired, and two resting-state functional connectivity sessions were conducted with participants fixating at a cross-hair for the period of 6 minutes in each. The resting-state data acquisition sequence was similar to the active task, with the exception of the TR (2200ms), the number of volumes acquired (164), and the number of axial slices per run (36). BOLD data were preprocessed using SPM5 (Wellcome Department of Imaging Neuroscience, London). Rigid body motion correction was conducted by aligning all volumes with the first collected volume, following correction for slice acquisition time using sinc interpolation. Functional data were spatially normalized to a canonical MNI echo-planar template using 12-parameter affine and cosine basis transformations, and resampled to 3mm isotropic voxels. Volumes were then spatially smoothed with a 6mm Gaussian kernel.

## 2.5 fMRI data analysis

Functional regions of interest (ROIs) were selected based on the comparison of invalid versus valid “Likely New” cue trials, collapsed across the age groups. This contrast is statistically unbiased with respect to group membership and hence was used to identify unbiased regions within the fronto-parietal network for further analysis. For this contrast, participants were treated as a random effect with volumes treated as a temporally correlated time series and modeled by convolving a canonical hemodynamic response function with a series of

delta functions marking the onset of each condition of interest, beginning with the onset of the memory probe. The modeled response duration was 3.5 seconds for the cued trials. Due to their low frequency, incorrect responses were grouped into one variable of no interest and not further considered. The parameter estimates of the best-fitting canonical hemodynamic response function for each condition were used in pairwise contrasts and stored as a separate image for each participant. These images were then tested against the null hypothesis of no difference between contrast conditions using one-tailed, repeated measures *t*-tests. Activations were considered significant and further analyzed when they consisted of 5 or more contiguous voxels and exceeded a  $\alpha$  threshold of 0.001, which is a typical threshold for memory research.

Time courses were extracted from identified ROIs using the averaged response across significant voxels within an 8 millimeter radius sphere centered on each cluster maximum using the MARSBAR toolbox for SPM5 (Brett et al., 2002) and a finite impulse response model. These data were subjected to offline statistical analysis of the first 6 time points constituting the first 12.5 seconds of post-stimulus response. The key purpose of the analysis was to determine whether adolescents and young adults demonstrated different responses as a function of whether the “Likely New” cue was confirmed or violated by the subsequently recovered memory content of the probes.

Resting state functional connectivity was examined by extracting the time course of one 8 mm diameter ROI in right posterior dlPFC using MARSBAR and entering it as a covariate of interest in conjunction with 18 sources of nonspecific variance (6 parameters resulting from the rigid body correction of head motion, and signals from the averaged whole brain, left lateral ventricle, left hemisphere white matter, and the 9 first derivatives of these covariates) in an SPM general linear model (see Fox et al., 2005). This identified regions that were significantly

functionally connected to posterior dlPFC in the participants. Following this, the age groups were contrasted to determine whether any regions demonstrated greater connectivity with posterior dlPFC for either adolescents or young adults. To avoid a potential confound of differential movement across groups, which is an aspect that has been shown to potentially corrupt resting state connectivity data in developmental group comparisons (Power et al., 2012), we used the realignment parameters from the SPMs of each subject to calculate a root mean square deviation (RMSD) index of scan-to-scan movement (Mazaika, Glover, & Reiss, 2011). This index was then entered as a covariate in the random effects resting state analysis that contrasted the two groups. Thus, the resting state data fMRI data employed two methods to correct for potential movement contamination. First, the movement parameters provided by SPM were entered at the first level model fit of each subject. Second, the RMSD movement measure was also entered as a covariate during the second level random effects model that contrasted the two groups. Finally, the RMSD movement measure was directly compared across the groups to determine whether a reliable difference in movement could be detected in this raw score.

### 3 Results

#### 3.1 Behavioral data

The groups demonstrated similar IQ levels as measured by the joint WASI score (FISQ-2) [ $t(31) = .25, p = .84$ ; adolescents,  $117.4 \pm 15.5$ ; adults,  $122.9 \pm 18.5$ ]. When analysis on each subtest was conducted separately, the vocabulary subtest did not show a group difference [ $t(31) = 1.21, p = .90$ ; adolescents,  $64.8 \pm 9.5$ ; adults,  $65.1 \pm 15.0$ ]. In contrast, the performance on the matrix reasoning subtest differed between groups [ $t(31) = 3.20, p < .005$ ; adolescents,  $54.8 \pm 8.5$ ; adults,  $60.4 \pm 9.5$ ] favoring the young adults (see WASI; The Psychological Corporation, 1999).

Recognition accuracy and reaction time (RT) data were analyzed using pairwise comparisons and ANCOVA methods. The latter was used to examine if observed RT differences during cueing remained when baseline performance was statistically equated (see Table 1 for means and standard deviations).

Beginning with accuracy, the groups did not differ in hit rates under the three possible cueing conditions (uncued, “Likely Old”, & “Likely New”) ( $t(31) = 1.81, p > .08$ ;  $t(31) = .19, p > .85$ ;  $t(31) = .60, p > .55$ ). They also did not differ in correct rejection rates under the two possible cueing conditions used for new materials (uncued & “Likely New”) ( $t(31) = -.08, p > .94$ ;  $t(31) = .67, p > .50$ ). Consistent with the null findings above, the groups also did not differ in recognition discrimination during uncued trials when accuracy was calculated using the signal detection measure,  $d'$  (adolescent = 2.06, young adult = 1.74;  $t(30) = .67, p > .51$ ).

Reaction time analysis was restricted to correct responding. During hits, RTs were similar for the groups during uncued trials ( $t(31) = -.13, p > .89$ ) and during validly cued “Likely Old” trials ( $t(31) = -1.48, p > .15$ ). However, the adolescent group was significantly faster when correctly responding to old recognition probes during invalidly cued “Likely New” trials ( $t(31) = -2.13, p = .04$ ). To further verify that this difference in reaction time could not be explained away by generally quicker responding on the part of the adolescents, ANCOVA was used with independent variables of Group (adolescent = 1, young adults = 0) and baseline reaction time during hits (Baseline), and a dependent variable consisting of the mean reaction time during invalidly cued hit trials. Thus, the model tests whether the groups remain different in their RTs to invalidly cued old materials, when baseline reaction time is statistically controlled. The reaction times during invalid “Likely New” trials continued to reliably differ across the groups ( $B_{\text{Group}} = -.171, SE_B = .063, p = .012$ ).

Turning to RT during correct rejections, there were no reliable differences across the groups for the two possible cueing conditions (uncued, & “Likely New”) ( $t(31) = .50, p > .61$ ;  $t(31) = -1.25, p > .21$ ).

Overall, the behavioral data demonstrate one clear difference across the groups; namely, that the adolescents responded more quickly when correctly identifying studied materials in the presence of invalid anticipatory cues (“Likely New”). This pattern of findings suggests that the groups might differ considerably during the “Likely New” cue trials which served as the focus of the fMRI analysis below.

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Insert Table 1 about here

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### **3.2 fMRI analyses**

#### **3.2.1 *Invalid versus Valid “Likely New” Cue Response***

In the fMRI analysis we focus on the “Likely New” cue trials. During these trials participants encounter either new materials, in which case the cued expectation is valid, or old materials, in which case the cued expectation is invalid. During the latter it is assumed that participants must use cognitive control in order to override the incorrectly cued expectation, and more specifically that they must use the recovery of episodic information to exert control. As noted above in the methods, in order to shorten the tests, “Likely Old” cues were always followed by old items. Because these cues are 100% valid participants need not actually evaluate the memory evidence following the cue in order to achieve an accurate outcome and thus activation during these trials is difficult to interpret and not directly examined below. Thus,

our primary goal in restricting analysis to the “Likely New” cue trials was to examine whether there were reliable group differences in the use of memory evidence when it either confirmed (new items) or violated (old items) the expectation instilled by the cue which is identical across the two types of subsequent recognition probes. Below we refer to these as valid and invalid trials for ease of exposition.

In order to obtain unbiased prefrontal and parietal ROIs for group comparison, we compared invalid to valid trials collapsed across the two groups. Increased activation during invalid memory cueing was observed primarily in regions within the ostensible fronto-parietal control network, including anterior/frontopolar PFC (~BA 10), posterior dlPFC (~BA 9/46), superior medial PFC (~BA 8), and lateral parietal areas (~BA 40) among others (Figure 2; Table 2). These regions closely match those observed in O’Connor et al. (2010) that used the full version of the explicit memory cueing task (in which both “Likely New” and “Likely Old” cues were probabilistic and could be invalid). This is only the second report to demonstrate that this network of regions is engaged when episodic memory evidence violates subject’s expectations on a trial-by-trial basis. ROIs were defined using an 8 mm radius sphere centered on each regional maxima capturing the significant voxels within that area. The response within this area was extracted, averaged across significant voxels within the sphere, and then used to compare the groups. Even though an initial threshold of  $p < 0.001$  was used to generate the SPM, we increased the threshold to  $p < 0.00001$  to separate the Medial Frontal Cortex cluster from the right posterior dlPFC cluster in order to obtain a separate ROI for each of these regions.

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Insert Table 2 about here

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Insert Figure 2 about here

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### **3.2.2 Time course analysis**

To determine if the groups differed during invalid versus valid cueing during the “Likely New” cues, we contrasted the time course for the two cueing outcomes across the groups using mixed ANOVAs with factors of Group, Cue Outcome (valid and invalid), and Time Point (TRs 1 through 6). Of the seven regions considered, four yielded significant 3-way interactions, namely, left parietal cortex [ $F(5,155) = 2.69, p = .023$ ], left frontopolar PFC [ $F(5,155) = 2.37, p = .042$ ], medial prefrontal cortex [ $F(5,155) = 2.37, p = .041$ ], and right dlPFC [ $F(5,155) = 2.26, p = .051$ ]. The interaction resulted because the differential response to invalidly versus validly cued items was prolonged in time for the young adults compared to the adolescents (Figure 3). That is, whereas the adults tended to display a sustained difference in activation under the invalid versus valid trials, this differential response collapsed more quickly for the adolescents. Figure 3 also demonstrates that there were no gross morphological differences in the raw time courses of the adolescents and young adults. Aside from these four regions, the remainder of regions also tended to show a sustained differential response for the young adults compared to the adolescents. To more easily appreciate this widespread pattern, Figure 4 shows the difference time course (invalid “Likely New” time course minus valid “Likely New” time course) for all seven regions and the two groups of subjects. It is clear that the pattern is general. Whereas the differential response is similar for the adolescents and young adults during the first three time points of the trial, the young adults maintain a differential response much further into the epoch. Indeed, as the 95% confidence intervals show, the fourth and fifth time points (7.5 & 10 seconds



post stimulus onset) differ across the groups in 13 of the 14 comparisons in Figure 4. Overall, these findings correspond with the behavioral data, which indicated more prominent response slowing during invalidly cued trials for young adults compared to adolescents which would be anticipated to yield sustained differential effects in regions supporting cognitive control.

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Insert Figures 3 and 4 about here

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One potential concern given the current shortened explicit memory cueing design is that the differences observed across the groups might not reflect differences in cognitive control mechanisms, but instead simply reflect differences in recognition memory ability. That is, while the contrast compares invalid and valid outcomes, it also compares old and new items. Under this interpretation, the differences in Figures 3 and 4 would reflect young adults recovering more (or higher quality) recognition content than adolescents. Even though this is inconsistent with the lack of between group accuracy differences in the present data, and with the observation of invalid cueing effects in the same regions for both old and new items in a prior experiment (O'Connor et al., 2010), we nonetheless investigated this interpretation further by using the same ROIs to examine hits and correct rejections during the initial baseline recognition scan, in which cues were absent. If the response is linked to the exertion of cognitive control following violated expectations instead of recognition mechanisms, then there should be minimal differences for the groups during scans in which items were not preceded by anticipatory cues. The shaded panel in Figure 4 demonstrates the differential response to hits and correct rejections (hits minus corrections) for the two groups during the initial baseline recognition scan. There is no indication that the groups were different in their responses during the late periods of the trials,

unlike their clear differentiation during the cued trials. This null effect of stimulus type was observed in all of the ROIs in Figure 3, although it is only illustrated for right frontopolar PFC, dlPFC, and lateral parietal region for clarity. These findings suggest that group differences arose during cued trials because the groups differ in the processing engaged when memory content violates versus confirms cued expectations, not because they differ in basic recognition memory retrieval responses.

### **3.2.3 Brain behavior correlations**

In light of the group differences found in reaction time and in the time courses of dorsolateral prefrontal activations during invalid cueing, we further examined whether engagement of posterior dorsolateral PFC during performance was linked to similar behavioral outcomes within the adolescent and young adults groups on an individual by individual basis. Aside from the evidence above, we focused on dlPFC because it is known to be structurally immature in adolescents (Gogtay, et al. 2004) and theoretically linked with effective cognitive control in the prior literature on young adults (Weissman, Warner, & Woldorff, 2004). In particular, we were interested in whether engagement of the region during invalidly cued old trials was indicative of effective resolution of violated mnemonic expectations; in short, whether activation of these regions was linked to overriding the invalid “Likely New” cue and instead correctly responding “old” based on internal memory evidence (viz., effective cognitive control). To address this question, we averaged the six time-points of the response during invalidly cued hit trials (“Likely New” cue followed by old item) and correlated these average activation values with the hit rates for the invalidly cued trials of each individual within each group (see Figure 5). For young adults, activation and hit rates during invalidly cued trials were positively correlated in right posterior dlPFC ( $r = .58$ ,  $p = .018$ ). In the homologous left hemisphere region the

correlation approached significance ( $r = .49$ ,  $p = .054$ ) (Figure 5). Thus, engagement of posterior dlPFC regions in young adults was associated with successful resolution of the invalidly cued trials, a pattern consistent with prior findings examining cognitive control in non-episodic memory tasks in young adults (MacDonald, Cohen, Stenger, & Carter, 2000). Although this relationship was positive in the remaining areas of the fronto-parietal network (except right posterior parietal cortex), none of the correlations were reliable.

Strikingly, in contrast to the young adults, the same analysis conducted on the adolescents demonstrated robust negative correlations between posterior dlPFC activation and hit rates during invalid cueing in both hemispheres (right,  $r = -.75$ ,  $p = .0003$ ; left,  $r = -.72$ ,  $p = .0006$ ), with the difference in correlation values across the two developmental groups clearly significant (right,  $z = 4.25$ ,  $p < .001$ ; left,  $z = 3.75$ ,  $p < .001$ ). This negative relationship in the adolescents was also observed in all remaining fronto-parietal ROIs and these values were significantly different than those of young adults in the superior medial PFC ( $z = 2.22$ ,  $p < .026$ ), frontopolar PFC (right,  $z = 2.98$ ,  $p < .005$ ; left,  $z = 2.94$ ,  $p < .005$ ), and left parietal ( $z = 3.01$ ,  $p < .005$ ) cortices. Thus, engagement of the same regions linked to individual improvements in performance during invalid cueing in young adults, were linked to performance decrements in adolescents. When adolescents increasingly engaged regions within this broad network, they tended to respond with the invalid expectation instilled by the “Likely New” cue, and not on the basis of their internal memory evidence, hence, hit rates declined. To our knowledge, this is the first documented evidence of a fully reversed brain-behavior correlation across developmental groups and it is noteworthy given that the groups here only differ by approximately 5 or 6 years of age.

Although the two groups evinced similar overall IQs as estimated by the composite WASI scores, the adolescent group nonetheless scored reliably lower on the matrix reasoning subtest. Given this, we further analyzed the dlPFC brain-behavior correlations to see if the matrix reasoning scores mediated the relationship between mean activation and performance during invalid cueing. However, entry of the matrix reasoning score into regressions of dlPFC activation onto invalid hit rates did not lessen the negative relationships observed for adolescents. Robust standardized regression coefficients remained for both the right ( $\text{Beta} = -.87$ ,  $\text{SE}_{\text{Beta}} = .21$ ,  $p = .001$ ) and left dlPFC ( $\text{Beta} = -.71$ ,  $\text{SE}_{\text{Beta}} = .20$ ,  $p = .003$ ) predictors of invalid cueing hit rates. Similarly, matrix reasoning scores did not lessen the observed positive relationships between left ( $\text{Beta} = .51$ ,  $\text{SE}_{\text{Beta}} = .24$ ,  $p = .054$ ) and right dlPFC ( $\text{Beta} = .57$ ,  $\text{SE}_{\text{Beta}} = .23$ ,  $p = .024$ ) for young adults. Thus, the qualitative reversal in brain-behavior relationships observed for the two developmental groups is not a function of a general difference in non-verbal reasoning ability, at least as measured by this behavioral test.

It is also important to note that the reversed brain-behavior relationship across the groups cannot be explained as an artifact of a potentially differently shaped hrf across the two groups. First, as noted above and shown in Figure 4, there does not seem to be gross difference in the shapes of the time courses for the two groups during invalid cueing. Second, the brain-behavior analysis used the mean response in dlPFC spanning 15 seconds. Thus, even if the shape of the hrf were different across the groups, one would expect the same direction of correlation if the region signaled the same function or process in the two groups. In other words, any positive relationship between neural activity and BOLD signal, captured within this 15 second epoch, would yield the same sign of brain-behavior correlation in the two groups if the region supported

the same process. Thus, the fact that the sign is reversed strongly suggests the mean activation signals qualitatively different information in the two groups.

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Insert Figure 5 about here

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### **3.2.4 *Resting state functional connectivity***

As noted in the introduction, recent developmental research has suggested a possible shift in resting state functional connectivity patterns, with the increasing formation of long range networks during development (Fair et al., 2009). Given the strong double dissociation of activation and performance in right posterior dlPFC and the linkage of dlPFC to effective cognitive control in prior work (Morishima, Okuda & Sakai, 2010; Savine & Braver, 2010), we examined whether patterns of connectivity with this seed region differed across the adolescents and young adults at rest, which would suggest structural connectivity differences in the two groups. To examine this, time series were extracted from the right dlPFC ROI and entered as a variable into a resting state connectivity analysis. Also, the scan-to-scan index of total head motion, RMSD, was entered as a covariate to track potential movement differences between the groups (Mazaika, Glover, & Reiss, 2011). Figure 6a shows a similar global pattern of functional connectivity with right posterior dlPFC across the two groups. However, when the groups were directly compared, young adults demonstrated greater connectivity between right posterior dlPFC and posterior cingulate, anterior cingulate, right hippocampal regions and left inferior and right superior frontal gyri (.001, 5 voxels; Figure 6b; table 3).

The reversed contrast (greater connectivity in the adolescents versus adults) yielded only three small (5 voxels each) differences indicating greater connectivity in the adolescents in the left temporal-parietal junction, in a posterior area of the right dorsal parietal cortex, and a white matter region above right anterior insula. Because of the sparseness of the map, small spatial extent of the clusters, and the location of one cluster within white matter, these regions are not considered further.

A t-test comparing the two groups on the RMSD movement measure did not suggest any reliable difference in movement tendencies across the groups ( $t(31)=0.55$ ,  $p > .58$ ). This lack of movement differences is consistent with prior work showing that adolescents in this upper age range do not appear to move appreciably more than young adults (Power et al., 2012). Thus, it appears that the two groups in the current study were equally able to comply with the instruction to lie as still as possible during the resting state scans and that the connectivity differences observed across the groups are not driven by movement artifact.

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Insert Table 3 about here

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Insert Figure 6 about here

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#### 4 Discussion

The current experiment yielded four important differences between adolescents and young adults during a recognition task in which memory expectations were manipulated using

external cueing. First, adolescence was associated with quicker reaction times during the joint processing of cues and memory content when cues were invalid. This finding did not reflect a generally quicker responding for adolescents as reaction times for the groups were similar during uncued recognition trials, and because the ANCOVA procedure yielded a significant group difference even when baseline reaction times were present in the model. Also, this reaction time difference cannot be characterized as a speed/accuracy tradeoff on the part of the adolescents because the two groups did not differ on any measure of accuracy. To our knowledge this is the first demonstration of a behavioral developmental difference in the use of recognition memory to override invalid memory expectations.

Second, and consistent with these reaction time findings, young adults also demonstrated a prolonged differential neural response distinguishing invalid and valid memory cueing trials (Figures 3 and 4). This prolonged response occurred in bilateral posterior dorsolateral PFC, midline premotor regions, posterior cingulate and bilateral lateral parietal areas among others. Activation in all of these regions have all been associated with tasks examining cognitive control (Dosenbach et al., 2007) and their maturation and interconnectivity is likely incomplete in the adolescent group.

Third, in posterior dorsolateral PFC regions previously associated with cognitive control, there was a double dissociation of the adolescents and young adults in terms of the relationship between mean activation and performance during the invalidly cued trials. Young adults were more likely to correctly override the invalid cues and identify items as studied, as activation in left and right posterior dorsolateral PFC increased. The pattern in adolescents was qualitatively and significantly reversed. In these participants, increased activation was associated with the

production of the cued, incorrect response; namely, as activation increased, these participants were more likely to incorrectly report that the item was “New”.

Finally, when the right dorsolateral PFC region was used as a seed in a resting state connectivity analysis on these same participants, it demonstrated greater functional connectivity with right hippocampus, posterior and anterior cingulate and two PFC regions in the young adults compared to the adolescents. All of these regions of increased connectivity in the young adults have been linked to either semantic retrieval, episodic memory retrieval, or cognitive control (Dobbins & Han, 2006; Maguire, Frackowiak, & Frith, 1997; Wagner, Shannon, Kahn, & Buckner, 2005). The right hippocampal region finding is particularly interesting given the reversed brain-behavior pattern of the adolescents in which increasing recruitment of posterior dlPFC led to reductions in the effective use of memory content to override a cue induced expectation. Additionally, the posterior cingulate serves as a major output pathway of the hippocampus (Duvernoy, 1998), further suggesting diminished connectivity between episodic memory relevant structures and the right posterior dlPFC in adolescents compared to young adults.

Below we consider three different interpretations of these findings beginning with the initial hypothesis that adolescents would demonstrate impulsive responding during the Explicit Memory Cueing task.

#### *Impulsive responding on the part of adolescents?*

On the whole, the data do not support the impulsivity hypothesis. Although the adolescents responded rapidly during invalid cueing and demonstrated reduced differential invalid versus valid activation in regions associated with cognitive control, the remaining findings do not fit with the characterization of their performance as impulsive. First, the



accuracy of report during invalid cueing was actually numerically higher for adolescents than young adults indicating that they were not more adversely affected than the adults by the instilling of invalid memory expectations. Second, the dlPFC brain-behavior correlation observed within the adolescent group is qualitatively at odds with the impulsivity hypothesis. If a lessened invalid cueing response in dlPFC reflected rapid and impulsive responding without fully evaluating conflicting memory evidence, then presumably increased activation during invalid cueing would reflect more careful consideration of the evidence and the exertion of cognitive control. However, the brain-behavior correlation was negative in the adolescents, that is, increased activation reflected poorer performance under invalid cueing.

*Superior neural ‘efficiency’ on the part of adolescents?*

Applied the current data, a neural efficiency account would contend that the adolescents are better able to resolve the conflict generated during invalidly cued trials, perhaps through mechanisms such as the more rapid transfer of information from memory to decision systems. Thus, they might display less differential activation to invalid versus valid cues and respond more quickly on the invalid trials with slightly superior accuracy. This pattern would be consistent with a group that was able to more efficiently resolve the apparent inconsistency that follows a “Likely New” cue when an old item is encountered. The efficiency interpretation however runs into two problems. First, it is largely a redescription of the data patterns since there is no independent marker or measure of efficient information processing available. Moreover, the efficiency account runs into problems when the direction of the actual brain-behavior correlations is considered. For adolescents, the observed brain-behavior relationship makes sense in that increased activation during invalid cueing (presumably reflecting less efficient conflict resolution) is associated with poorer accuracy. However, when applied to the

young adults the account falters because this population demonstrates better accuracy as activation increases, leading to the implausible conclusion that for young adults inefficiency is beneficial. In other words, one cannot take the group level effects shown in Figure 3 as indicative of greater efficiency on the part of adolescents and simultaneously explain why greater activation during invalid cueing for young adults improves performance. Furthermore, the efficiency model does not readily incorporate the resting state connectivity findings in that it is unclear why a less efficient sub-population (young adults) should demonstrate greater functional connectivity with regions linked to semantic and episodic memory retrieval. If anything, one might have predicted the reverse under an efficiency framework.

*Age-related compensation on the part of young adults?*

This account assumes a developmentally novel form of cognitive control on the part of the young adults enabled by a) the late physical maturation of the fronto-parietal cognitive control network, and b) increased functional connectivity of this network with regions supporting episodic and semantic memory retrieval. Under the model the group difference in the responses to invalid versus valid trials does not reflect impulsivity or greater efficiency on the part of the adolescents, but instead the fact that the young adults are using additional or greater amounts of memory information to bias choices when cued expectations are violated by initial unexpected familiarity signals. Critically, this model is ‘compensatory’ because the cued accuracy of young adults is not superior to that of adolescents. In fact, it is slightly numerically lower both in terms of the invalidly cued hit rates and the validly cued correct rejection rates (Table 1). Additionally, although the groups did not differ in baseline accuracy when  $d'$  was considered, the baseline hit rate did trend lower for the young adults compared to the adolescents ( $p = .079$ , two-sided). Thus, the data suggest that through slowing during invalid trials and the consideration of

additional information, the young adults are able to bring their performance up to that of the adolescents.

This model accommodates the reversed brain behavior associations by assuming that the response of dlPFC is heavily dependent upon the functional network within which it is embedded. In the case of young adults, the region has greater functional connectivity with distal areas linked to semantic and episodic retrieval and hence its activation during invalid cueing is assumed to reflect not only processes linked to conflict detection (e.g., from anterior cingulate) but potentially the contribution of memory retrieval information from regions such as the posterior cingulate and right hippocampus. In this light, the net activation of the region may track the accumulation of evidence from memory linked regions and hence overall demonstrate a positive association with hit rates during invalid cueing in the young adults. In contrast, because of the reduced connectivity, the activation of adolescents would be assumed to be less reflective of memory retrieval because the dlPFC is largely isolated from these areas in terms of functional connectivity. In the absence of such information the response could be characterized as reflecting basic conflict or ‘difficulty’ (without memory signaling) and this accords with the strong negative correlation between activation and success in the adolescent group. Thus, under this framework, the response of the right dlPFC is critically dependent upon its functional connectivity with distal regions supporting memory, and this connectivity increases considerably even across the short developmental span considered here. It is perhaps important to note that the differences in connectivity indicated by the resting state analysis were quite prominent as shown in Figure 7. Indeed, the average effects size for the group comparisons was 1.43 (Cohen’s *d*) across the six regions, and the minimum effect size in the set was 1.23 for the right anterior cingulate region.

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Insert Figure 7 about here

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Although the thought that individuals aged 20 to 22 would need to compensate for any sort of memory decline seems shocking, there are several factors that support the plausibility of this interpretation. First, age-related memory declines are routinely demonstrated during the third decade, leading several researchers to suggest that age-related declines (and presumably compensatory mechanisms) may be fully underway in populations previously thought to be immune from such concerns. For example, the behavioral data of Park et al. (2001) suggest that the amount of episodic memory decline that is evident from 20 to 30 years of age is comparable to the declines routinely seen across later decades of life. When one considers that life spans exceeding the third decade are largely absent in our evolutionary history, the hypothesis that compensatory mechanisms that evolved in order to mitigate declining core discrimination skills, such as recognition, begin operating soon after adolescence seems reasonable. Put another way, individuals that were able to compensate for declining recognition accuracy by judiciously biasing judgments using environmental cues would be at an advantage relative to those who could not. While compensation through adaptive biasing of judgments would be advantageous to the current elderly population, it is arguably the case that the adaptive pressures shaping modern cognition must have been applied to individuals much younger than today's seniors who were unlikely to have survived as little as 1000 years ago and who are generally no longer fertile. Under this evolutionary perspective, the age-related possibly compensatory mechanisms often studied in individuals in their 60s and beyond, should be well underway in individuals in their 20s.

Of course at this point the age-related compensation explanation offered above is only speculative. Further evidence for such an early onset of compensatory mechanisms would require clearer demonstration that baseline abilities in the absence of cues were in fact lower for the young adults than the adolescents, and that through the provision of external cues, the young adults were able to minimize or eliminate this performance difference. Additionally, evidence for this pattern across domains such as recognition and perception would be desirable.

*Cognitive control during recognition judgment.*

Putative links between cognitive control and episodic recognition have likely often been obscured because activations during memory paradigms are most naturally interpreted in light of whether or not retrieval was successful. Although regions within a putative fronto-parietal control network are frequently engaged during recognition memory (e.g., Vilberg & Rugg, 2008), it is unclear why regions traditionally associated with the exertion of cognitive control should also be increasingly recruited for the correct detection of old materials (hits) versus the correct detection of new materials (correct rejections). Indeed, it is important to keep in mind that the “hit” and “correct rejection” terminology for correct responses during recognition is entirely arbitrary and does not convey anything meaningful about the relative amount of deliberative control needed to identify new versus old items in this simple discrimination task. However, as noted in the introduction, recent work using the Explicit Memory Cueing task suggested that engagement of regions within this network during recognition was likely a marker of violated expectations and/or the exertion of cognitive control (O'Connor, Han, & Dobbins, 2010). From this perspective, memory judgments that are rare or unexpected give rise to the need for cognitive control of a particularly important form, namely, using internal memory

evidence (regardless of whether it signals oldness or newness) to overcome biased or automatic response tendencies.

The current developmental functional imaging results are consistent with this interpretation in that increasing engagement of this network when developmentally mature was linked to successful exertion of cognitive control. That is, young adults who increasingly recruited dlPFC were increasingly able to provide the correct recognition response despite invalid cueing. In contrast, activation of dlPFC when it is presumably developmentally immature appeared to correspond simply to trial difficulty and hence demonstrated a reverse relationship between activation and task success (Figure 5). This should not be taken to mean that the activation was deleterious to performance, but instead that the region's BOLD response primarily carried information linked to the degree of difficulty each adolescent was having with the discrimination under invalid cueing. Since the uncued behavioral recognition data revealed admirable recognition skills in adolescents, it is clear that their qualitatively different pattern of activation during the cued trials does not reflect a core episodic retrieval deficit or a general inattentiveness during the tasks. Instead, the differences between the adolescents and young adults seem to be linked to the way that cued expectations and recovered memory content combine to influence performance, and this in turn may critically depend on developmental differences in functional connectivity suggested by the resting state connectivity analysis. Although adolescence is a period sometimes marked by impulsive behavior (Casey & Jones, 2010), and recent functional imaging work has focused on basic inhibitory control and impulsive reward responding in adolescence (Velanova, Wheeler, & Luna, 2009; Cohen, et al., 2010), it appears that the current Explicit Memory Cueing task does not tap the same kinds of basic inhibitory or reward discounting processes engendered in these paradigms, and thus the kinds of

control required in these tasks may not well match that captured here in which the observers must use episodic memory to override cue instilled expectations.

The adolescent period studied here remains a developmental period that is extremely understudied in terms of basic memory functioning and we are aware of only one report (Paz-Alonso et al., 2008) examining episodic retrieval in mid-adolescence. Using the Deese/Roediger-McDermott (DRM) false memory paradigm administered to three age groups (8-y.o., 12-y.o., and 21 to 22 y.o.), these researchers demonstrated that age significantly predicted the differential recruitment of dorsolateral PFC and parietal regions during false alarms to semantically related lures compared to the correct rejection of lures that were unrelated to the DRM study lists. This led to the conclusion that only young adults engaged prefrontal regions linked to controlled aspects of memory retrieval. However, in this developmental study there were no clear correlations between individual behavior and activation, and basic recognition accuracy appeared to noticeably differ across the age groups. Critically, the current data also demonstrate a key pragmatic benefit of working with this developmental period. Despite the fact that these adolescents have documented structural and functional connectivity patterns that differ from adults, they are quite capable of high levels of performance and task compliance. Thus they serve as a potentially optimal group to study the effects of changes in functional and structural connectivity on cognitive processes without having to worry about the potential confound of gross differences in behavioral task proficiency.

## 5 Conclusion

In conclusion, the current study yielded reliable dissociations of adolescents and young adults in behavioral, event-related functional MRI, and resting-state functional connectivity MRI data. Furthermore, it appears to be the first developmental imaging study to demonstrate a fully

reversed brain-behavior relationship across adolescents and young adults, a finding that is remarkable given that the groups are only separated by about 5 to 6 years of age. These findings would not have been apparent had the groups been compared using standard recognition memory procedures. Instead, the differences emerged when the manner in which participants use external cues to inform their memory attributions was scrutinized. Although the work was motivated by the hypothesis that adolescents might be overly cue-dependent and impulsive during responding, the findings were more compatible with a compensatory account in which young adults elevate their performance to that of adolescents through more thorough joint consideration of external cues and internal evidence; a skill which is critical during invalid cueing and which may benefit from increased structural connectivity between dlPFC and regions linked with episodic retrieval.



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Table 1. Behavioral performance.

			Cue		
			No Cue	“Likely New”	“Likely Old”
Adults	Response proportions	Hits	.734 (.123)	.595 (.213)	.851(.063)
		CRs	.869 (.096)	.869 (.082)	-
	Confidence	Hits	1.729 (.256)	1.658 (.287)	1.730 (.235)
		CRs	1.637 (.247)	1.732 (.191)	-
	Reaction times	Hits	1.397 (.212)	1.542 (.231)	1.355 (.175)
		CRs	1.470 (.216)	1.459 (.215)	-
Adolescents	Response proportions	Hits	.807 (.105)	.633 (.152)	.856 (.095)
		CRs	.866 (.096)	.890 (.097)	-
	Confidence	Hits	1.813 (.159)	1.808 (.197)	1.824 (.165)
		CRs	1.766 (.254)	1.771 (.216)	-
	Reaction times	Hits	1.386 (.263)	1.364 (.247)	1.240 (.260)
		CRs	1.517 (.305)	1.357 (.251)	-

Note. Mean response proportions, confidence, and reaction times for hits and correct rejections for both age groups. Standard deviations values are in parentheses. CRs, correct rejections.

Table 2. Contrasts for clusters from Hit Invalid > Correct Rejections Valid ( $p < 0.001$  uncorrected) for all participants.

	BA	MNI coordinates			voxels	Z score
		<i>x</i>	<i>y</i>	<i>z</i>		
L Frontopolar	10	-36	51	0	72	4.55
R Frontopolar	10	42	57	0	74	5.56
L dlPFC	9	-51	21	36	302	4.64
R dlPFC*	9	51	24	39	30	5.06
L Parietal	40	-45	-57	42	609	5.71
R Parietal	40	45	-54	54	529	5.42
Superior Medial PFC*	6/8	6	39	42	185	5.83

Note. L, Left; R, Right; \*  $p < 0.00001$ , uncorrected.



Table 3. Contrast for resting state maps from adult > adolescents ( $p < 0.001$  uncorrected). Seed region on right dorsolateral PFC (MNI coordinates,  $x = 51, y = 24, z = 39$ ).

	BA	MNI coordinates			voxels	Z score
		$x$	$y$	$z$		
Posterior Cingulate	24	6	-24	39	48	4.19
Anterior Cingulate	24	6	30	15	11	3.82
R Anterior Cingulate	10/11	15	42	-3	7	3.38
R Hippocampus	-	24	-33	-3	7	3.58
L Inferior Frontal Gyrus	44	-51	21	-3	17	3.85
R Superior Frontal Gyrus	8	24	48	42	7	3.57

Note. L, Left; R, Right.

#### Footnotes

1. One adolescent was removed from this analysis because of a perfect correct rejection rate rendering  $d'$  incalculable. This reduced the degrees of freedom of the t-test to 30.

## Figure captions

Figure 1. Partial explicit mnemonic cueing design. “Likely Old” cues were perfectly predictive in this reduced design and hence not considered in the functional imaging analysis. In contrast, “Likely New” cues probabilistically forecast memory probe status with 75% validity leading to the need for joint consideration of cue and memory content during responding.

Figure 2. The unbiased contrast of invalidly cued hits (“Likely New” cue followed by old item) and validly cued correct rejections (“Likely New” cue followed by new item) used to define regions of interest across both developmental groups ( $p < 0.001$ , 5 contiguous voxels).

Figure 3. Raw time courses for four regions demonstrating significant 3-way interactions between Group, Cue Outcome and Time Point. The plots demonstrate that the interactions result from a prolonged differential response in the young adults compared to the adolescents. . Dashed lines indicate the response to new items following the “Likely New” cue (valid trials) whereas solid lines indicate the response for old items following the “Likely New” (invalid trials). Data are from correct responses only.

Figure 4. Difference time courses (i.e., invalidly cued hits minus validly cued correct rejections) demonstrated for unbiased ROIs for adolescents and young adults

Figure 5. Correlations between mean hit rate during invalid cueing and mean BOLD response during the same (averaged across time points 1 through 6) in left and right dlPFC ROIs. Adolescents and young adults demonstrated a reversed association such that increasing activation was associated with effective cognitive control in the latter and impaired cognitive control in the former.

Figure 6. Resting state connectivity maps for young adults and adolescents. Panel a demonstrates regions demonstrating significant connectivity with a right dlPFC seed region in both groups. Panel c illustrates regions with significantly greater connectivity in young adults than adolescents.

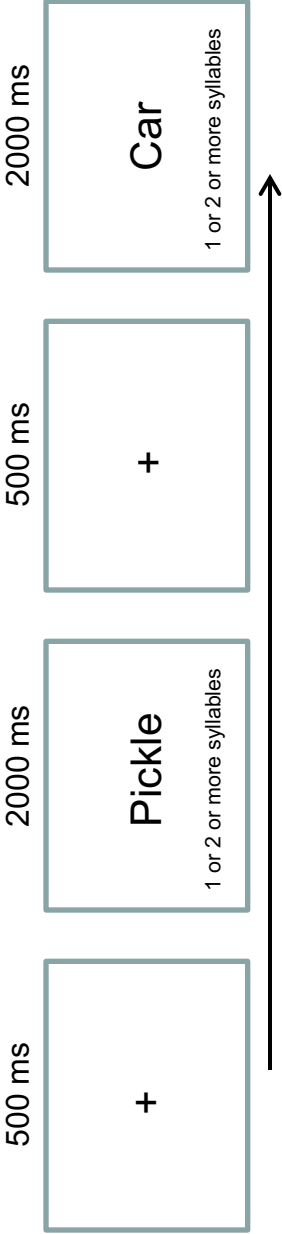
Figure 7. Boxplot demonstrating mean connectivity between six regions and right dorsolateral PFC for adolescents and young adults. Box indicates 1 standard error of the mean, box plus whiskers indicates 2 standard errors of the mean. vlPFC = ventrolateral prefrontal cortex, SFG = superior frontal gyrus, hipp = hippocampus, post cing = posterior cingulated, anter cing = anterior cingulated, R-anter cing = right anterior cingulated.

#### Highlights:

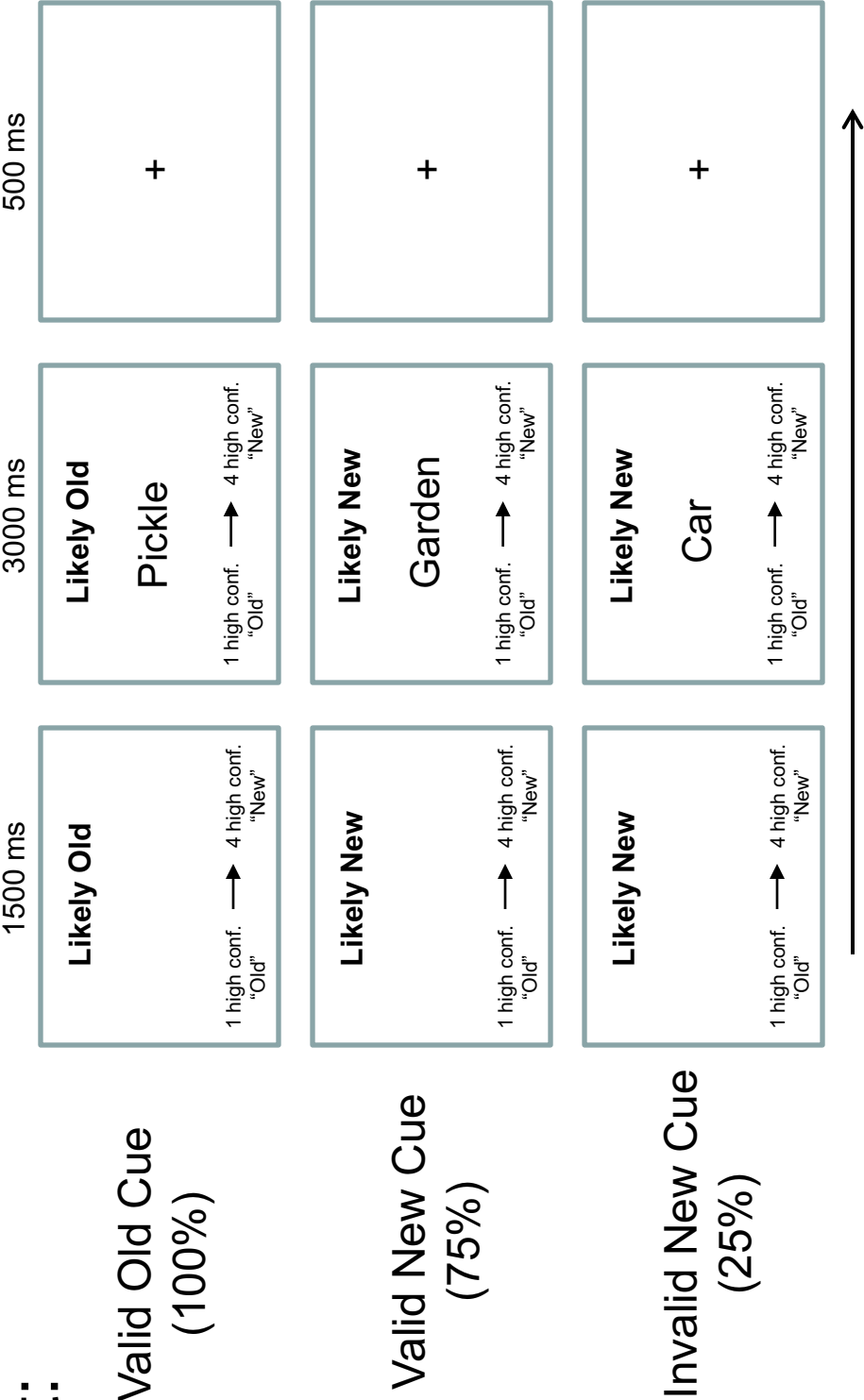
- Dorsolateral PFC engagement impairs controlled memory judgment in adolescence.
- Reduced connectivity between dorsolateral PFC and memory regions in adolescence.
- Neural signature of confirmatory biases in early adolescence.
- Reversed brain-behavior relationships across young adulthood and adolescence.

Figure 1 Partial Explicit Mnemonic Cueing Design – Cued Scans 2 & 3

Study:



Test:



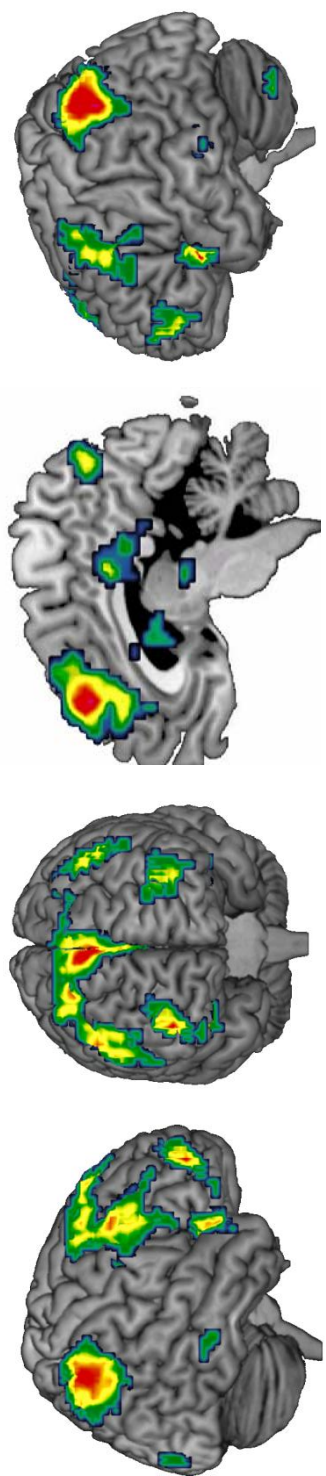


Figure 2

Figure 3

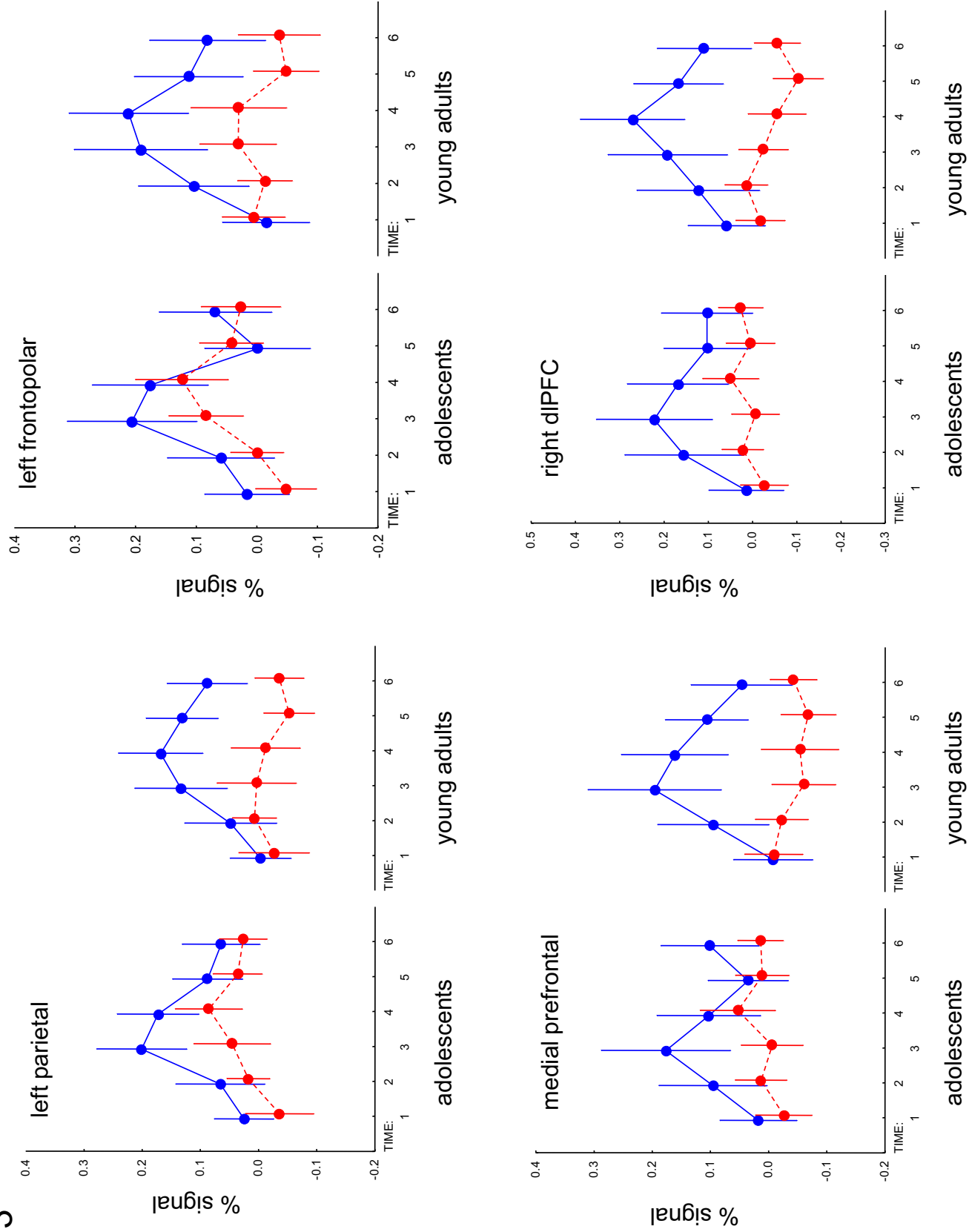


Figure 4

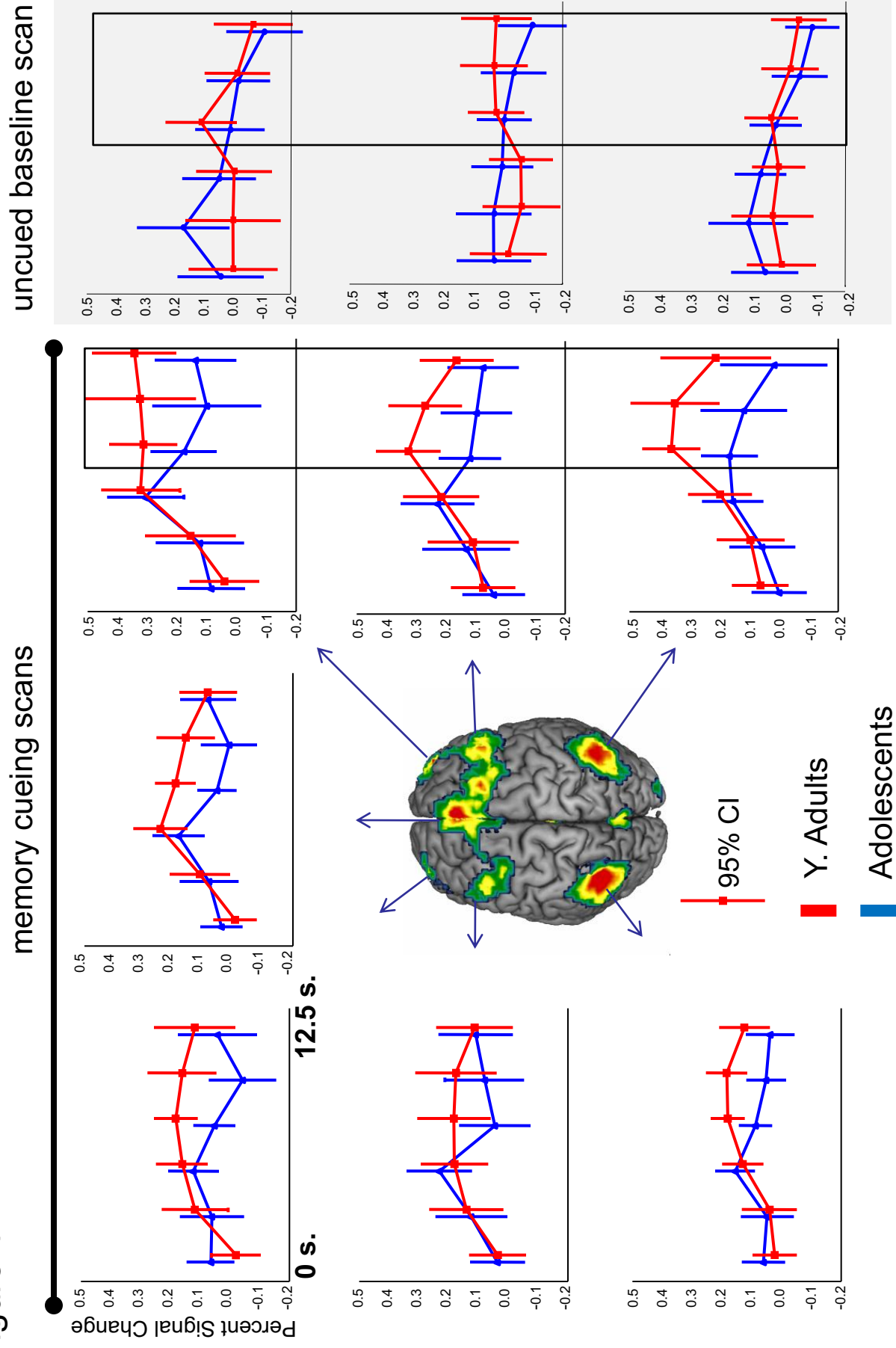


Figure 5.

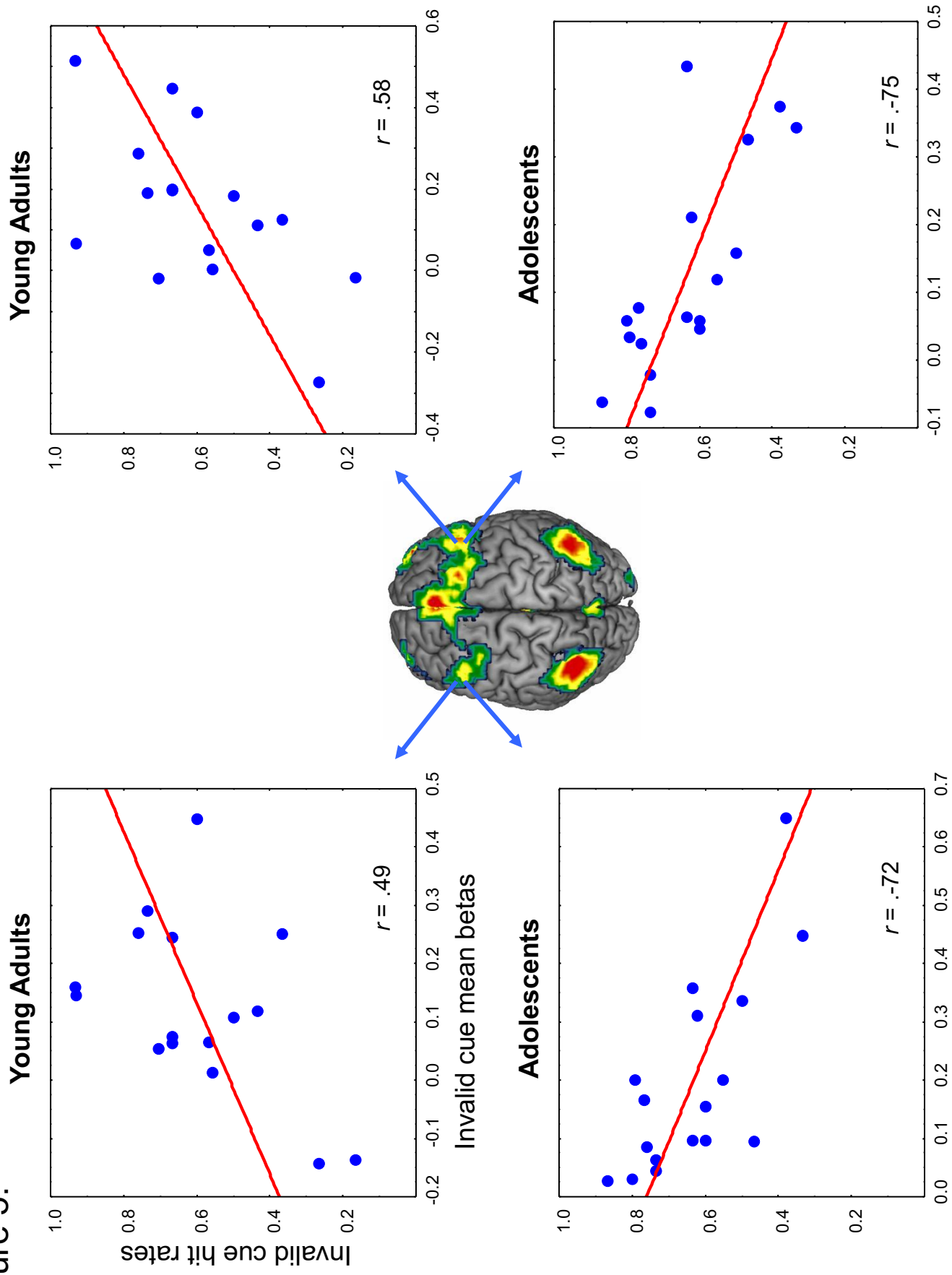




Figure 6.

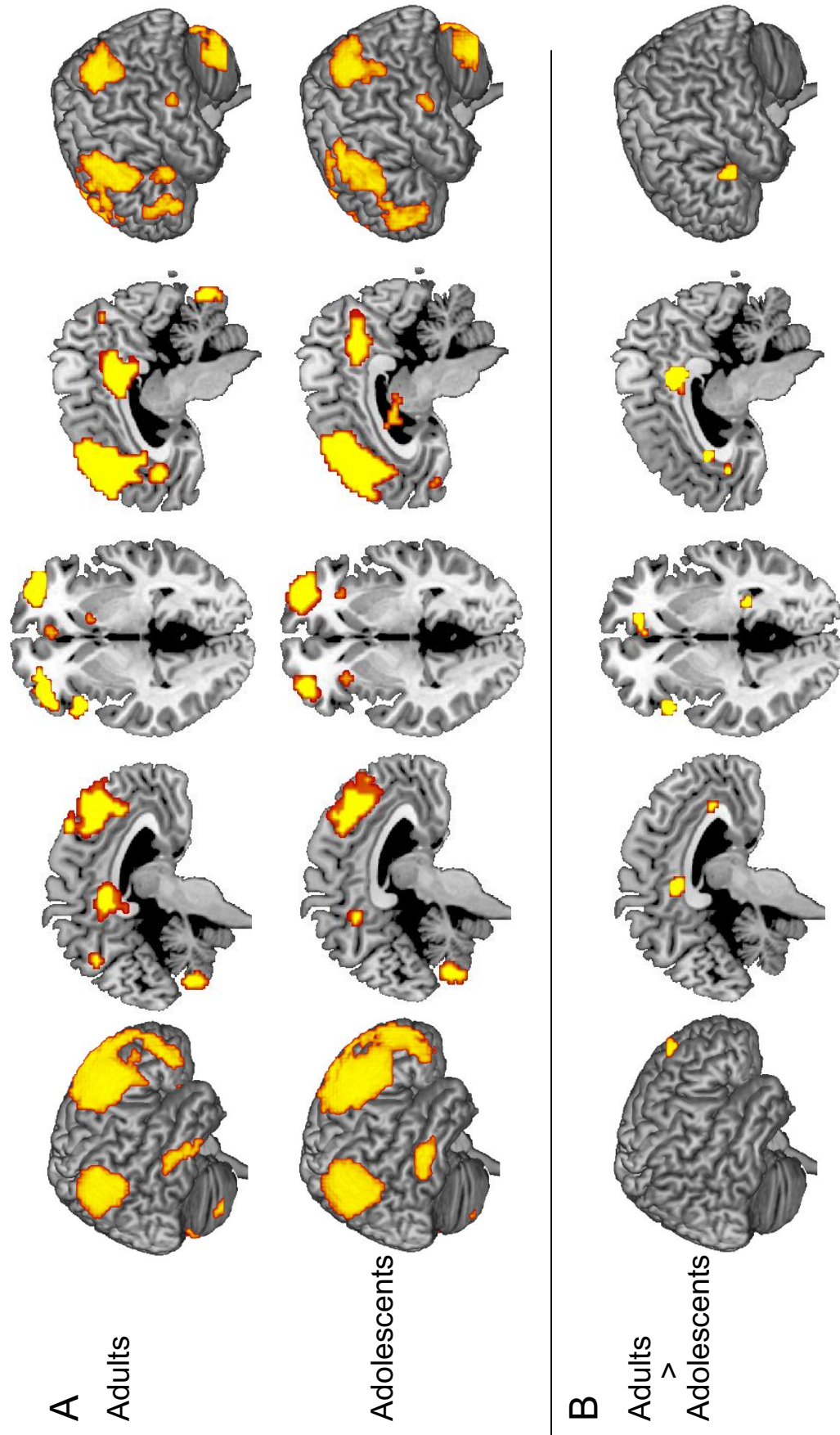


Figure 7.

