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Original Article

ORIGINAL ARTICLE

Functional Fractionation of the Cingulo-opercular Network: Alerting Insula and Updating Cingulate

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Abstract

The anterior insula (AI) and dorsal anterior cingulate cortex (dACC) are engaged in various cognitive and affective processes. An influential account posits that the AI and dACC's ubiquitous engagements reflect their role in the transient capture of attention by salient stimuli. Using fMRI here we tested this claim and functionally dissociated these regions. In the first experiment, we compared these regions' responses to emotion-laden and emotion-neutral salient "oddball" movie events. We found that while the AI only responded transiently to the onset and offset of neutral events, its response to affective events was sustained, challenging the transient attention capture account. By contrast, dACC remained transient regardless of event type. A second experiment distinguished the information encoded by these brain regions with the presentation of behaviorally salient events that require either maintaining the current task set or updating to a different one; the AI was found to signal the presence of the behaviorally relevant events, while the dACC was associated with switching of attention settings in response to the events. We conclude that AI and dACC are involved in signaling the presence of potentially or de facto behaviorally significant events and updating internal attention settings in response to these events, respectively.

Key words: anterior insula, attention, fMRI, salience network, stimulus-driven attention

Introduction

The anterior insula (AI) is one of the most ubiquitously activated regions of the brain and is engaged by a wide range of socioaffective and cognitive tasks (Menon and Uddin 2010; Nelson et al. 2010). In the socioaffective domain, this region has been associated with experiencing pain and disgust, empathy, body awareness, mood, and addictive behaviors (Phillips et al. 1997; Adolphs 2002; Craig 2002; Sanfey et al. 2003; Critchley et al. 2004; Hein and Singer 2008; Singer et al. 2009). In the cognitive domain, both elementary cognitive processes—such as the detection of salient sensory inputs—and more complex ones—such as decision making and attentional/executive control—also recruit this region (Downar et al. 2000; Dosenbach et al. 2006; Duncan 2010; Nelson et al. 2010; Tombu et al. 2011).

To account for this plethora of functions ascribed to the AI, several authors have suggested that it subserves a fundamental process, such as orienting attention toward a behaviorally relevant event or the implementation/maintenance of task sets (Dosenbach et al. 2006; Menon and Uddin 2010), and that it is such basic processes that underlies AI's activation in various cognitive and socioaffective processes. While it is debated whether this region plays a role in the sustained maintenance of task sets (Sridharan et al. 2008; Dubis et al. 2014), the AI's involvement in the transient capture of focal attention either by novel, salient stimuli (Downar et al. 2000; Menon and Uddin 2010) or by behaviorally relevant events (Dosenbach et al. 2006; Ploran et al. 2007; Nelson et al. 2010) is widely accepted. According to this attentional account of AI function, arousing socioaffective stimuli capture attention and strongly activate the AI because of their strong saliency and/or behavioral significance (Menon and Uddin 2010).

While the attentional salience account provides a parsimonious explanation for the extant data, there is yet little empirical work directly addressing this issue. Furthermore, even if the AI is specifically engaged in attentional capture, it is not clear what specific process the AI may be contributing to this cognitive process, as attention capture involves several distinct subprocesses, including detection and orienting of attention to a stimulus (Posner 1980; Escera et al. 1998). It is also unclear what is the contribution of the AI to attention relative to another brain region that frequently co-activates with the AI—the dorsal anterior cingulate cortex (dACC)—with which it forms a cingulo-opercular “salience” network (Seeley et al. 2007; Sridharan et al. 2008). While these 2 regions are indeed frequently functionally coupled with the presentations of salient events, we still do not know whether they each contribute distinct subprocesses to the detection of such events.

The overarching goal of the present study—carried out in 2 experiments—is to clarify the AI’s computational contribution to attention and affective processing, and to distinguish its role from that of the dACC. The first experiment contrasted the responses of AI and dACC to emotionally neutral and emotionally laden oddball events in order to assess the extent to which activity in these brain regions is driven by attentional or emotional characteristics of these events. We also probed other brain regions implicated in attentional processing of salient stimuli, namely, the inferior frontal junction (IFJ) and temporal–parietal junction (TPJ), to compare their response profiles to those of the AI and dACC. In a recent study, using 10-s long movie clips as oddball events presented randomly and unexpectedly while subjects were engaged in a visual goal-oriented task, we were able to dissociate between brain regions that responded continuously to the presence of oddball events (TPJ and IFJ) from those that responded only transiently to the oddball onset and offset (AI and dACC). While the set of oddballs used in this previous study were for the most part emotionally neutral, in the first experiment of the present study we have added an oddball set that is affectively laden in order to assess the AI and dACC’s response pattern under such conditions. The results of this first experiment—taken together with our previous study (Han and Marois 2014)—suggest that rather than conceiving the AI as exerting a strict role in transient attention or affective processing, it is best interpreted as continually signaling the presence of de facto or potentially behaviorally meaningful events, whereas the dACC responded solely to the transition between events.

Experiment 2 further dissociated the functions of the AI and dACC with an attentional cuing task that distinguished between simply signaling the presence of a behaviorally relevant event (in this case a visual cue) from signaling the appropriate task response to that event (either holding to the current task set or switching to another). The results indicate that while the AI only signals the presence of a behaviorally relevant event, the dACC codifies the switch between task events.

On the bases of the results of these 2 experiments, we conclude that the function of the AI consists in alerting the system for the presence of a de facto or potentially behaviorally relevant event, whereas the dACC is primarily involved in shifts of goal-oriented behavior in response to such an event.

Materials and Methods

Experiment 1

Participants

Fifteen adults (4 males, aged 23–33) participated for monetary compensation. All participants were right-handed with no history of neurological disorder. A power analysis of a published dataset obtained using a similar paradigm with the present study revealed that *N* of 6 should be sufficient (Han and Marois 2014), but to further guarantee that we have enough power, we chose to match sample sizes between the previous study (Han and Marois 2014) and the present ones (both Experiments 1 and 2). The Vanderbilt Institutional Review Board approved the experimental protocol and written informed consent was obtained from each participant.

Design and Procedure

The task was to search for targets (images of a dining room and a living room) in a rapid serial visual presentation (RSVP) of distractors (images of outdoor, indoor scenes, or buildings) presented at the center of the screen. A trial lasted 18 s and consisted of the presentation of 144 images, with each image lasting 125 ms and subtending 2° of visual angle. Each distractor image in the RSVP was randomly selected from a pool of 40 distractor images. Although a distractor image could appear more than once in the RSVP, no image was successively repeated. In each trial, participants detected and identified the targets in the RSVP by immediately pressing buttons assigned to each of the 2 targets with their right hands.

In a small subset of the trials (20 out of 135 total trials), the RSVP was replaced—unannounced to the subjects—by a salient, task-irrelevant 10 s-long movie clip (oddball). That created 4 trial types: Oddball-target (4 trials), Oddball-no target (16), Search-target (65), and Search no-target (50) trials. In the Oddball-target and Oddball-no target trials, the oddballs were presented 4 s after the trial onset. Half of the oddballs (Affective oddballs) consisted of emotion-laden movies depicting people suffering pain (4 movies), person expressing disgust (1), wounded human body parts (3), or repulsive insects (e.g., cockroach, spider) crawling over human body parts (2). These types of stimuli, when briefly presented, are known to robustly engage the AI (Wicker et al. 2003; Britton et al. 2006; Benuzzi et al. 2008; Singer et al. 2009; Gu et al. 2013). The other half (Standard oddballs) consisted of nonmeaningful, abstract animations (e.g., continuously transforming fractals, molecular polymerization, swirling waves, constantly rotating color patches in random direction, evolving line drawings of geometric shapes, dynamically transforming objects, moving flashlight in random direction, or continuously evolving colored geometric shapes). All the movies were downloaded from the World Wide Web and edited such that affective features/scenes are continuously shown throughout their 10-s long presentation. The standard movies were further edited to remove human/animal body parts or texts.

In the 4 oddball-target trials (2 each for affective and standard oddballs), a target followed the oddball offset either by a 125-ms (lag 2) or 1500-ms (lag 13) interval, during which distractors were presented. In the remaining oddball trials (16 trials), there was no target. Hence, while the majority of oddball trials did not contain a target, there were instances in which the oddball is followed by the target presentation, alleviating the development of an expectation by the subjects that oddball trials do not contain any target. Only the oddball trials that did not include a target were used for fMRI analyses to assess brain activity associated with oddball presentations without contamination by target presentations or motor responses.

The rest of the trials consisted of Search-target (65 trials) and Search no-target (50) trials that included no oddball. In the Search-target trials, a variable number of targets (1, 2, or 3) were imbedded in the RSVP of distractors. The second target (T2), when presented, followed the first target with a 4, 8, 10, or 12-s interval, while the third target (T3), when presented, was shown 15 s after the trial onset. The Search no-target trials did not include any target. The latter trials served to isolate the brain activity associated with goal-directed search without contamination by the target or motor responses.

fMRI Methods

All the imaging parameters and preprocessing steps were identical to those of a previous work (Han and Marois 2014). Specifically, anatomical 2D and 3D high-resolution T1-weighted images were acquired with conventional parameters on a 3T Philips scanner at the Vanderbilt Institute of Imaging Sciences. For the functional scan, thirty-three 3.5 mm axial slices (0.5 mm skip; 3.75 × 3.75 mm^2 in-plane) were taken parallel to the AC-PC line (TR, 2000 ms; TE, 35 ms; FA, 79°; FOV, 240 mm), for a total of 191 brain volumes per fMRI run. There were 9 functional runs, each of which included 15 trials. A blank interval of variable duration that follows an exponential distribution (9 trials × 4 s, 4 trials × 8 s, 2 trials × 12 s) was inserted between trials to facilitate deconvolution analysis of the BOLD responses (Serences 2004). Imaging data were analyzed using Brain Voyager QX 2.3 and custom softwares written in MATLAB. Data preprocessing included slice scan time correction, 3D motion correction, linear trend removal, and spatial smoothing with a 6-mm Gaussian kernel (FWHM). All functional data of each participant were aligned to the first functional run, which were then coregistered to each individual's anatomical T1-weighted image. Functional and anatomical data were transformed into standardized Talairach space (Talairach and Tournoux 1988). Regions of interest (ROIs) were defined as those responding to target presentations, as core areas of the saliency (AI and ACC) and stimulus-driven (IFJ and TPJ) attention areas are modulated by the detection of infrequent, behaviorally relevant stimuli and targets (Downar et al. 2002; Seeley et al. 2007; Corbetta et al. 2008; Asplund et al. 2010; Menon and Uddin 2010) see also (Han and Marois 2014). Specifically, to isolate such target-related activity, we constructed a group random effect SPM (q [FDR] <0.05), using a regressor for target presentation (Downar et al. 2002; Seeley et al. 2007; Corbetta et al. 2008; Asplund et al. 2010; Menon and Uddin 2010). The BOLD amplitude at the volumes of target presentation were contrasted with those during the intertrial interval (fixation period) activity (Target-defined ROIs, Table 1). For comparison, we also contrasted the Target activations with the Search activations, and this contrast yielded significant activation foci in the same regions. The results also did not differ depending on whether only correct trials or all the trials were included, so we only present the results of analysis using all the data here. Noteworthily, and unlike all the other core areas mentioned above, the TPJ was defined by negative beta weights (Asplund et al. 2010; Han and Marois 2014). Each ROI was drawn as the peak voxel and surrounding areas up to 1.33 cm^3 of the region (Dux et al. 2006).

Finally, to ascertain that the above ROIs are also implicated in processing of oddball stimuli, we constructed another SPM by running a contrast between the standard oddball activity and goal-directed search activity (Search no-target trials). This SPM revealed significant activational foci in the AI, IFJ, and TPJ that corresponded well with those defined with the target regressor (Table 1). Only the results from the target-defined ROIs were further analyzed and reported in this article.

Table 1 List of ROIs from Experiment 1. The ROIs were isolated either from an SPM isolating activity associated with target presentation, or from an SPM contrasting Standard oddball activity with goal-directed search activity (see Materials and Methods)

		Talairach coordinates		
ROI name	Mean t value	X	Y	Z
Target-defined ROIs (open contrast of target presentation)				
Left anterior insula (AI)	8.77	−28	22	0
Right anterior insula	7.42	29	19	0
dAnterior cingulate cortex (dACC)	7.18	−4	7	45
Left inferior frontal junction (IFJ)	5.92	−40	7	24
Right inferior frontal junction	4.92	44	9	21
Left temporoparietal junction (TPJ)	−4.77	−43	−68	27
Right temporoparietal junction	−6.79	47	−59	27
Standard oddballs versus Search trials ROIs				
Left anterior insula	5.24	−33	23	−5
Right anterior insula	3.65	27	26	−5
dAnterior cingulate cortex (dACC)	4.05	0	5	33
Left inferior frontal junction	5.20	−47	8	18
Right inferior frontal junction	6.80	45	12	18
Left temporoparietal junction	8.94	−41	−62	18
Right temporoparietal junction	10.91	48	−47	17

ROI analyses, including construction of activation timecourses and statistical assessment of those timecourses, were done in the same way as in our previous work (Han and Marois 2014). Specifically, event-related timecourses of the BOLD signal for each participant and trial type were estimated using a deconvolution analysis (using the 20 volumes immediately following the trial onsets). Then, the Beta estimates were averaged across participants, yielding group-averaged timecourses. As no hemispheric differences were found (P's > 0.2), timecourses of bilateral ROIs were collapsed to increase statistical power (Asplund et al. 2010). Then, the timecourse for Search activity (Search no-target trials) was subtracted from the timecourse for the trials containing oddballs (affective and standard oddballs) to isolate oddball-specific activity, as we have done in previous studies (Asplund et al. 2010; Han and Marois 2014), The subtraction of the search trial activation timecourse from the oddball timecourse served to isolate activity specifically associated with oddball processing, as it is possible that participants searched the oddball movies for upcoming targets. This subtraction procedure yielded similar results to those obtained with unsubtracted timecourse data.

Once the oddball timecourses were constructed, we statistically assessed whether those activations were transient or sustained. As in our previous study (Han and Marois 2014), the activity volumes associated with each oddball onset and offset, and the volume located in the middle between those 2 peak volumes, were determined. Specifically, the onset-related peak volume was defined as the volume with the greatest signal amplitude between the 3rd and 7th volumes immediately following the onset of the oddball (4–12 s from the oddball onset; (Dux et al. 2006), while the offset peak volume was defined as the volume with the greatest signal amplitude following the offset of the oddball (i.e., 14–22 s from the oddball onset). The

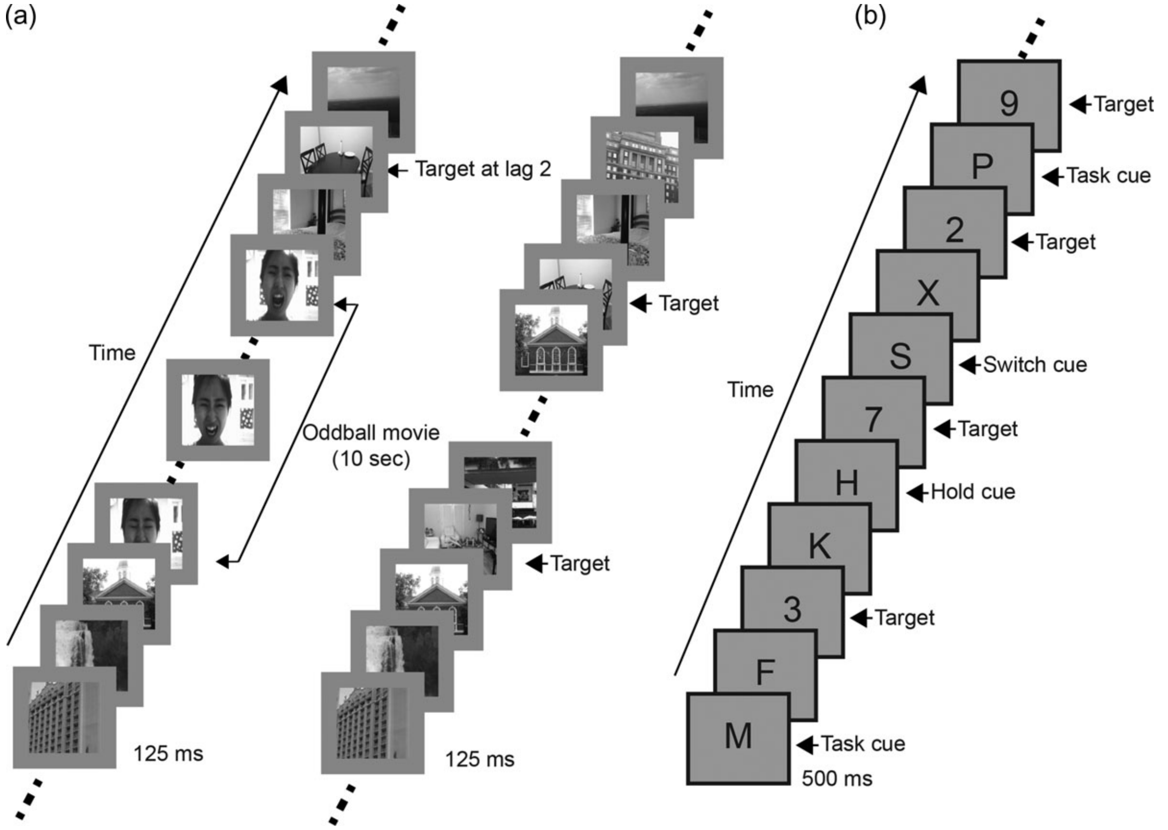

Figure 1. Task displays for Experiments 1 and 2. (*a*) Examples of an Affective Oddball trial (left) and Search-target trial (right) in Experiment 1. Participants were required to detect and identify target scenes in an RSVP of distractor scenes. The extended oddballs (Affective and Standard) occasionally interrupted the RSVP for 10 s, followed by the resumption of the RSVP. (*b*) Example of cue-target stimulus sequence in Magnitude/Parity task of Experiment 2. The "M" and "P" cues denote the magnitude and parity judgment tasks to be performed on the target numbers, respectively. In the face of an "H" cue, the task to be performed remains the same. In the face of an "S" cue, the task should be switched to the other. Other letters were distractors.

amplitudes of the onset and offset peak volumes were then compared with that of the volume corresponding to the middle point between those peaks, using paired *t*-tests. If the oddball response is transient, both the onset and offset activity should be significantly greater than the middle point activity, with the latter not being significantly different from baseline (zero). If the oddball response is sustained, there should not only be significant activation above baseline at the oddball onset and offset, but at the middle point volume as well.

Experiment 2

Participants

Fourteen adults (5 males, aged 25–33) participated for monetary compensation. Six participants among these had also participated in Experiment 1. The Vanderbilt Institutional Review Board approved the experimental protocol and written informed consent was obtained from each participant.

Design and Procedure

Subjects performed either a magnitude (M) or parity (P) judgment task on target digits embedded in a RSVP of letters, with specific cue letters instructing the subjects to either maintain the current task set or switch to the other task set. As shown in Figure 1*b*, at the beginning of an fMRI run, a task cue—either "P" or "M"—was presented, instructing participants to either judge the parity (odd or even digit) or magnitude (digit higher or lower than 5) of digits presented in an RSVP of alphanumeric characters. Participants responded to the target digits by pressing 1 of 2 finger responses from the right hand. The letters were all distractors except for the aforementioned "M" and "P" cues and the "H" and "S" cues, which instructed the participants to hold the current task set or to switch to the other task set (e.g., to now perform the P task instead of the M task on any subsequently presented targets), respectively. Participants were also instructed to make a response to the task cues (M, P, S and H) cues with their left index fingers to ensure that they paid attention to all cues. Other letters ("F," "K," "B," "G," "Q," "W," "X," and "Y") than the cue letters were distractors. Each stimulus (cue, target, and distractor) subtended 2° in height and was presented for 500 ms at fixation with no interstimulus interval. The 500-ms presentation of a cue or target was followed by a 3.5-s period of only distractor presentations to ensure that participants have enough time to make responses before the next cue or target stimulus presentation. The 500-ms cue/target presentation and the immediately following 3.5-s period constituted an event of interest. These events of interest were intermixed randomly under a constraint that no more than 2 Hold/Switch cue events appear in succession. That is, if 2 Hold/Switch cues appeared in succession (e.g., 2 Hold cues, 2 Switch cues, Hold followed by Switch, or Switch followed by Hold), the next event of interest would be a target. The 4-s long events of interest were separated from each other by intervals of variable duration that followed an exponential distribution (3 events × 8 s, 6 events × 6 s, 12 events × 4 s, 27 events × 2 s) to facilitate deconvolution of the hemodynamic responses.

The stimulus stream was presented continuously throughout each 382 s-long fMRI run. This generated a total of 48 events of interest per fMRI run, consisting of 8 Task cues (M and H), 12 Hold cues, 12 Switch cues, 14 targets, and 2 oddballs. Each participant performed 9 runs. Importantly, given that the purpose of the present study was to contrast brain activities between task set holding and switching, there were more Hold and Switch cues (96 trials each) than M and P cues (36 trials each). The relatively small number of M and P events rendered them sunuitable for subsequent multivariate pattern analyses.

In addition to the events of interest described above, this experiment also included 18 trials with Standard (nonaffective) 10-s long movie clips (Han and Marois 2014). We confirmed that these oddballs activated the standard ROIs and yielded transient onset/offset responses in AI and dACC and sustained responses in IFJ/TPJ as described in Han and Marois (2014) and in Experiment 1 of the present study, and thus are not further discussed here.

fMRI Methods

All the imaging parameters and preprocessing procedures were identical to those of Experiment 1. We probed the AI, dACC, TPJ, and IFJ ROIs group-defined by the open contrast of target presentation in Experiment 1 (see above and Table 1). For these ROI analyses, group-averaged event-related timecourses of the BOLD signal were constructed in the same way as Experiment 1, except that 8 volumes following the cue/target onset were used to construct activation timecourses. Then, peak amplitudes of BOLD responses for the Hold and Switch cues were compared via paired t-test. For result confirmation purposes, we also defined ROIs in each individual participant by isolating regions activated by the 18 oddball movies. The results from this ROI analysis were similar to the ones presented in the Results.

In addition to these univariate GLM analyses, we also performed an event-related multivariate pattern analysis (MVPA) of BOLD responses to examine whether a given brain region encoded task-related cue information (e.g., task implementation differences between H and S) even if that region did not exhibit differential BOLD response amplitude to the cues. MVPA has been extensively used to reveal how different cognitive operations or mental states are represented within a given brain region (Kamitani and Tong 2005; Haynes and Rees 2006; Norman et al. 2006). We performed MVPA as in previous studies (Esterman et al. 2009; Tamber-Rosenau et al. 2011, 2013) using OSU SVM toolbox (adaptation of libsvm: http://www.csie.ntu.edu.tw/~cjlin/libsvm/) for MATLAB and custom MATLAB software. The identical preprocessing procedure was applied to the functional data except that no spatial smoothing was performed. Then, the signal in each voxel was z-transformed relative to the entire timecourse within each run. To prevent mean difference in BOLD amplitude across the cue types from biasing MVPA results, the mean activity of all the voxels for each type of event was subtracted from each voxel for that type (Esterman et al. 2009; Tamber-Rosenau et al. 2011, 2013).

Independently for each ROI, participant, and TR, all but one run of data was used to train a linear support vector machine that was then tested on the held-out run; this process was iterated until all runs had served as the test data once. Within an ROI, an individual participant's decoding accuracy for each TR was concatenated to form an event-related (er-) MVPA. This is to verify that significant decoding at the peak volume is not driven by any artifact or noise and that the er-MVPAs conform to the typical hemodynamic response pattern. Then, these participant-specific er-MVPAs were averaged across participants, yielding group-averaged er-MVPA timecourses. Given the typical pattern of hemodynamic responses, decoding accuracy should peak at 4–6 s after the event onset.

To assess whether the multivoxel pattern of activation in a given ROI encodes different cue information, the peak decoding accuracy for each cue type was compared with an empirically determined threshold (Esterman et al. 2009; Tamber-Rosenau et al. 2011, 2013). Specifically, a permutation test was run in which the cue type labels were randomized and the testing procedure was repeated 1000 times. This permutation test produced a probability distribution, whose mean was about 0.5. Then, the 95th percentile of this distribution (about 52%) was taken as the threshold for above-chance classification.

Results

Experiment 1

In a recent study, we demonstrated that the AI and dACC only responded transiently to the onsets and offsets of 10 s-long oddball movie clips depicting emotionally neutral and nonarousing events (Han and Marois 2014). In the first experiment of the present study, we examined whether these brain regions would still show only transient responses even when the oddball movie clips are emotionally laden. If the AI/dACC only shows transient responses to these “affective” oddballs, this result would support the claim that the primary role of these brain regions is related to the transient capture of attention. By contrast, if the AI/dACC shows sustained responses to the affective oddballs, this would suggest that their function is broader than attention capture per se and must include the sustained signaling of highly arousing stimuli. The goal of this fMRI experiment was to distinguish between these alternatives.

The behavioral results of Experiment 1 revealed that overall target accuracy for trials without oddball was about 71%, indicating that the main task was attentionally demanding (Han and Marois 2014). Consistent with our previous work, when the target followed the offset of a standard oddball at a short interval (125 ms), target performance was significantly worse than when the interval between the target and oddball was long (38.9% vs. 66.7%, Wilcoxon signed-rank test, $P < 0.05$). For the emotional oddball trials, the performance difference did not reach significance (55% vs. 66%, $P > 0.50$), likely owing to the fact that there was only a single trial for each oddball type and each oddball-target interval per subject. To confirm that emotional oddballs presentations disrupt task performance we ran a similar behavioral experiment ($N = 20$) in which we doubled the number of trials with oddballs. Although target detection accuracy was not significantly affected at short lag relative to long lag for both Standard (75% vs. 83%, $P = 0.27$) and Affective oddballs (85% vs. 92.5%, $P = 0.19$), there were significant costs in reaction time (RT) with both oddball types (1101 vs. 889 ms, $P < 0.05$ for Standard, and 1130 vs. 923 ms, $P < 0.05$ for Affective oddballs), most likely owing to a speed accuracy trade-off. These results suggest that both standard and emotional oddball presentations capture attention and interfere with target detection performance of a goal-oriented task.

The hemodynamic responses of the AI and dACC to the Affective and Standard oddballs are shown in Figure 2 (see Table 1 for Talairach coordinates of the AI and other ROIs). The AI showed a double-peaked response to the Standard oddballs, consistent with our previous findings (Han and Marois 2014);

the amplitudes of activity at the onset and offset volumes were greater than that at the middle point ($t[14] = 5.11$, $P < 1.6 \times 10^{-4}$, $t[14] = 2.93$, $P < 0.05$, respectively), and the middle point activity was not significantly different from baseline, $P > 0.43$ (one-sample t-test comparing the middle point signal amplitude with zero). By contrast, the Affective oddballs elicited a sustained response; there was significant activity at the middle point, $t(14) = 2.51$, $P < 0.05$, which was not different from those at the onset and offset volumes, P's > 0.29. In line with this, the middle point activity for the Affective oddballs was also greater than that for the Standard oddballs, $t(14) = 3.86$, $P < 0.005$. We verified that this pattern was not an artifact of subtracting Search trial activity from Oddball trial activity; the unsubtracted timecouse also showed the same pattern of results (the insets of Fig. 2). Thus, unlike the Standard oddballs, which only transiently engaged the AI at oddball onsets and offsets, the Affective oddballs generated sustained AI activation throughout their presentation. The dACC also showed a transient response to the Standard oddballs, with no sustained activation, P's < 0.005 (Fig. 2; see also (Han and Marois 2014)). However, unlike the AI, it only showed a transient response to the offset of the affective oddball, $P < 0.05$, with neither onset-related nor sustained activity, P's > 0.68. While the absence of sustained activity and a strong response to oddball offsets is consistent across the 2 oddball types, it is unclear why the dACC failed to respond to the onset of Affective oddballs. However, given that an onset response is observed in unsubtracted timecourses (Fig. 2), it would be premature to make strong conclusions about the dACC's response to the onset of affective oddballs without further data.

We also probed the response of the core regions of the stimulus-driven attention network—the IFJ and TPJ (Corbetta and Shulman 2002; Corbetta et al. 2008; Asplund et al. 2010)—to Standard and Affective oddball presentations. The IFJ and TPJ showed sustained responses to both types of oddballs (Fig. 3), P's < 0.005. While there were no peak onset differences between oddball types for either ROIs, P's > 0.55, both the IFJ and TPJ showed greater peak offset activity with the Affective oddballs, P's < 0.005. Sustained activities of the IFJ and TPJ to both the Standard and Affective oddballs are consistent with our prior results employing a similar standard oddball paradigm (Han and Marois 2014). We hypothesized that the TPJ activity might reflect this region's involvement in oddball event interpretation (Han and Marois 2014), whether these events depict human agency or not. The greater TPJ activity for Affective oddballs may reflect its sensitivity to human faces or other body parts included in several of the Affective oddballs (Frith and Frith 2006; Hampton et al. 2008). As for the IFJ, its engagement may reflect an interpretive function or, more likely, an attentional function (Bishop et al. 2004; Dolcos and

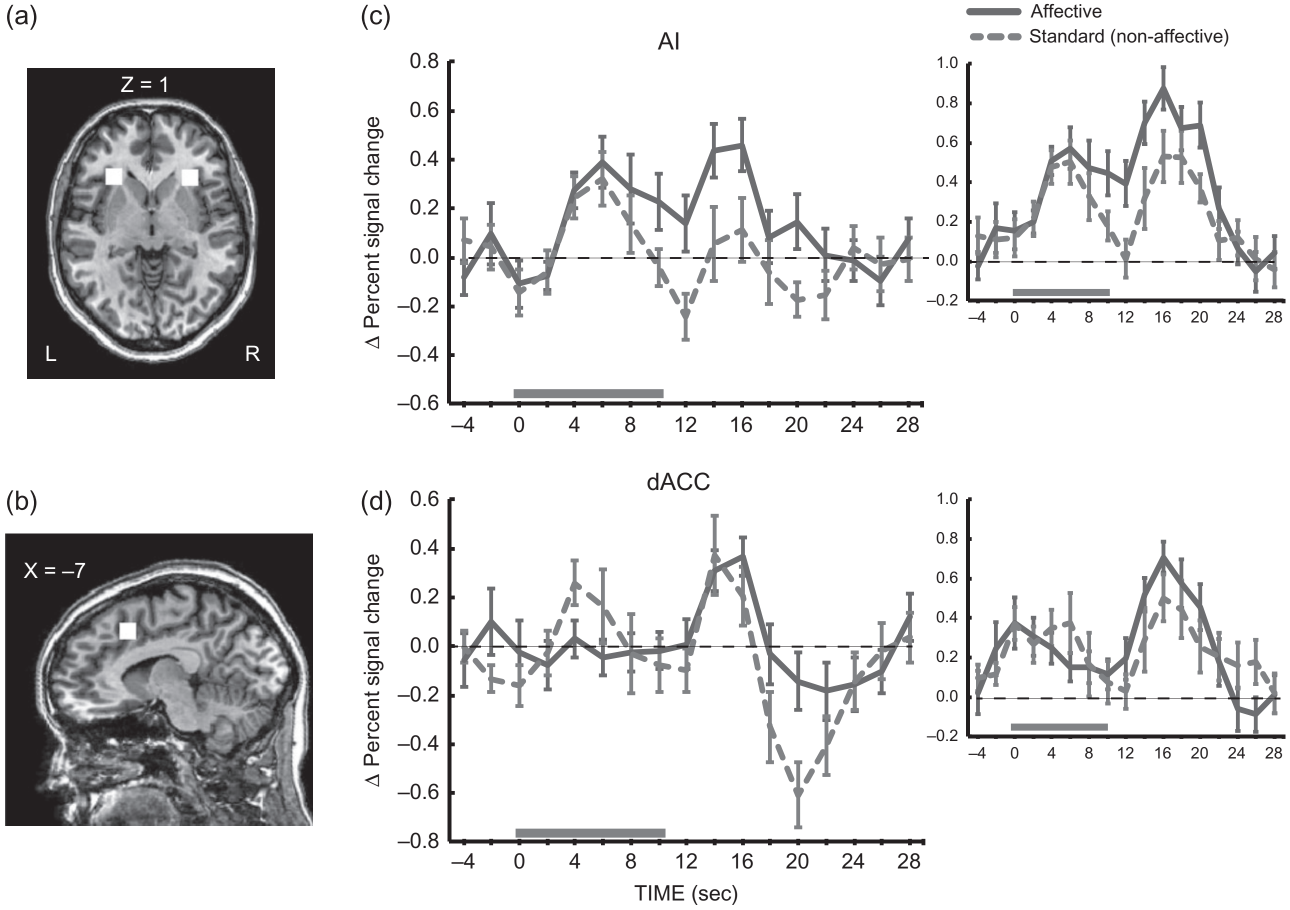

Figure 2. BOLD responses of AI and dACC to the Affective and Standard oddballs. (*a*, *b*) Anatomical locations of the AI and dACC, respectively. (*c*) Activation timecourse of the AI. (*d*) Activation timecourse of the dACC. The oddball onset is at time point zero. Gray horizontal lines on the plots indicate 10-s long oddball presentations. Dotted lines represent baseline activity (zero). The insets in the AI and dACC timecourse plots show unsubtracted timecourses. Error bars represent standard errors of the mean.

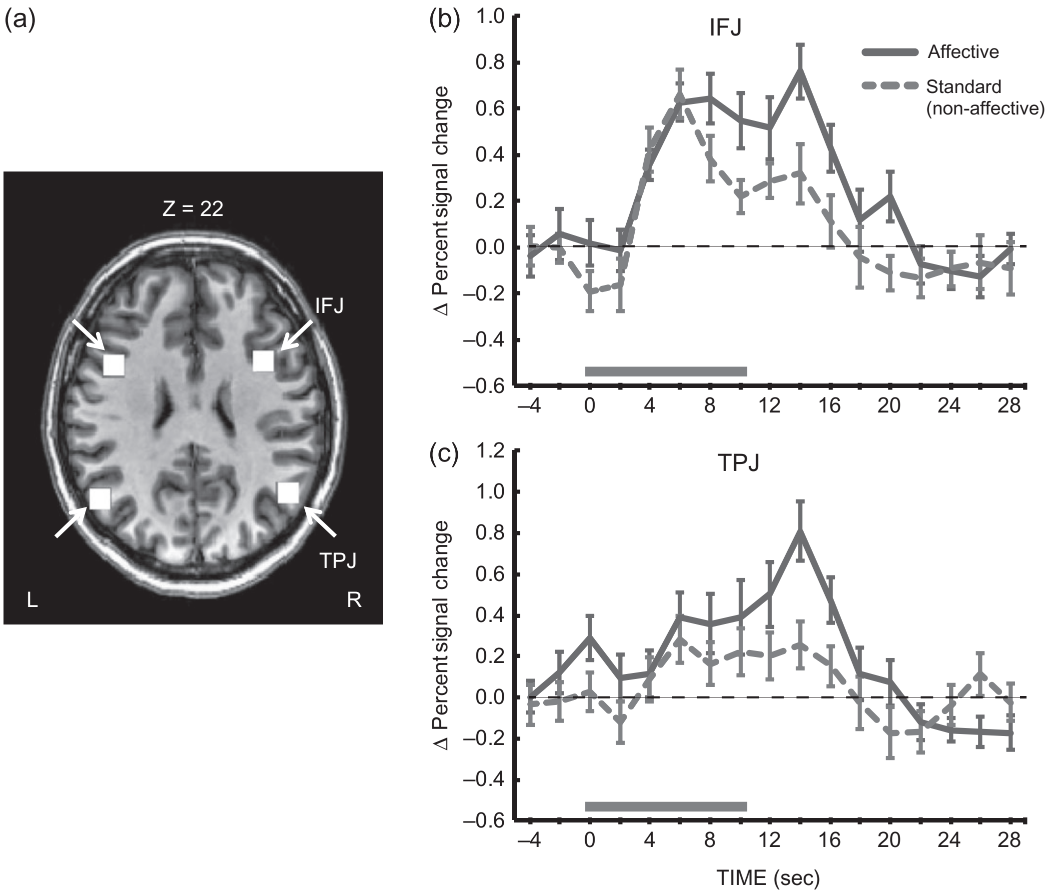

Figure 3. Activities of regions in stimulus-driven attention network to the Affective and Standard oddballs. (*a*) Anatomical locations of the IFJ, TPJ. (*b*) Activation timecourse of the IFJ. (*c*) Activation timecourse of the TPJ. The oddball onset is at time point zero. Gray horizontal lines on the plots indicate 10-s long oddball presentations. Error bars represent standard errors of the mean.

McCarthy 2006; Asplund et al. 2010; Han and Marois 2014), which may be amped up with the arousing Affective oddballs. Finally, the cause of the greater offset activity for Affective oddballs in both areas is currently unclear, though it could simply reflect a hemodynamic carry-over of the sustained activity differences.

Finally, we also examined the responses of the putamen and thalamus to oddball presentations as growing evidence suggests that these 2 brain regions are subcortical components of a broader cortico-striatal-thalamo-cortical salience network (Peters et al. 2016). The bilateral putamen and thalamus ROIs were defined as the center of their respective Talairach coordinates (transformed from the MNI coordinates taken from the Harvard-Oxford atlas) and surrounding area up to 1.33 cm^3. When probed, these regions showed a single-peaked, sustained response to the Affective oddballs, P's < 0.005, but only a transient response to the onset of standard oddballs (Fig. 4). These results suggest that the response profiles of the striatal and thalamic regions share more functional similarities to those of the AI than the dACC.

Saliency Account

The sustained activity to the Affective oddballs in AI (and to a lesser extent in the Putamen/Thalamus) is inconsistent with a strict transient capture of attention account of AI function, though it could still be compatible with the saliency hypothesis. According to that framework, the AI activates in a sustained manner with the affective oddballs because they are more salient than the standard oddballs (Downar et al. 2003; Menon and Uddin 2010; Nelson et al. 2010). We recently showed, however, that the AI (and dACC) is equally engaged by high- and low-salience stimuli, whereas other frontoparietal attention regions (IFJ and TPJ) showed far greater activity to the high-salience ones (Han and Marois 2014). Specifically, the AI showed equivalent activation to the presentations of 10 distinct novel oddballs and the repeated presentations of the same oddball 10 times (see Fig. 5, adapted from (Han and Marois 2014)). While saliency has been variably defined (Downar et al. 2000; Itti and Koch 2001; Seeley et al. 2007), it is generally agreed that novelty is one of the critical factors (Downar et al. 2000). Hence, the finding that high- and low-salience oddballs showed equivalent AI activity is inconsistent with a strict "saliency" account of AI function. Rather, our results generally favor a broader account of AI and dACC function, namely the capture of attention by behaviorally significant events (Menon and Uddin 2010; Nelson et al. 2010; Dubis et al. 2014).

Experiment 2

Experiment 1 showed a dissociation of responses in AI and dACC to Standard and Affective oddballs: while the AI responded continuously to Affective oddball movie clips but only transiently to Standard oddball onsets and offsets, the

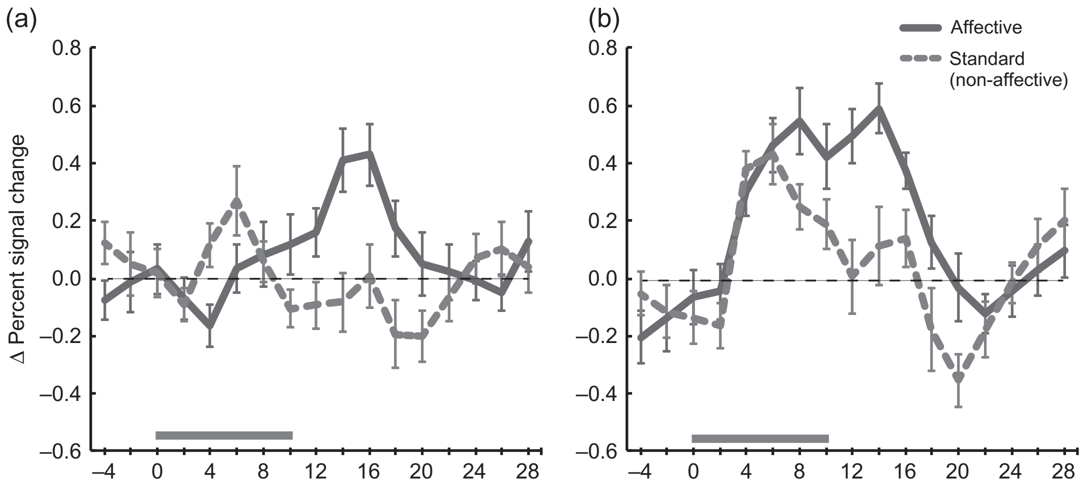

Figure 4. Activities of the putamen and thalamus to the affective and standard oddballs. (*a*) Putamen (Talairach coordinates: right/left, 21/−21, 5/4, 0/0) activity. (*b*) Thalamus (Talairach coordinates: right/left, 13/−11, −24/−24, 9/8) activity. Gray horizontal lines on the plots indicate 10-s long oddball presentations. Error bars represent standard errors of the mean.

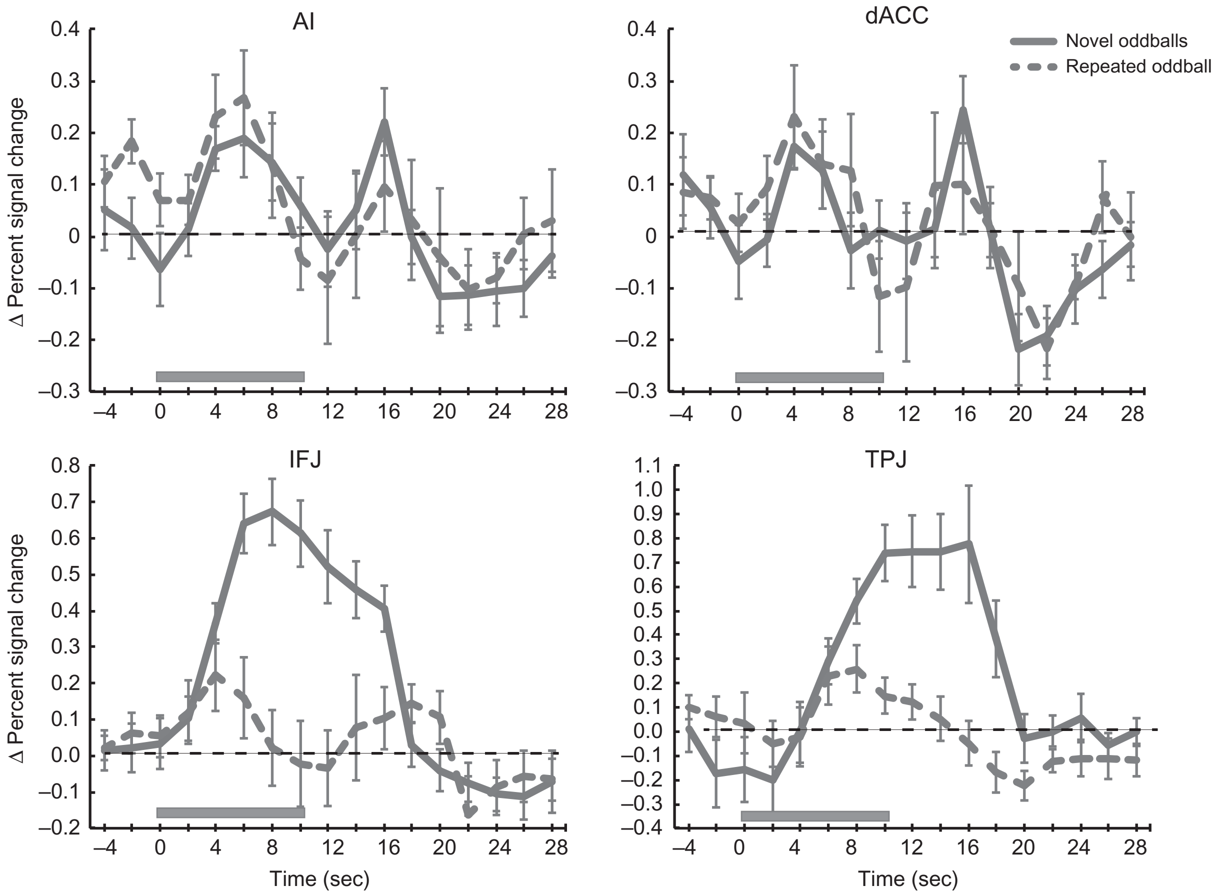

Figure 5. Activities of regions in salience network and stimulus-driven attention network to the Novel (high-salience) and Repeated (low-salience) oddballs. Adapted from Han and Marois (2014). Functional fractionation of the stimulus-driven attention network. Journal of Neuroscience, 34(20), 6958–6969. AI, anterior insula; dACC, dorsal anterior cingulate cortex; IFJ, inferior frontal junction; TPJ, temporal parietal junction. Error bars represent standard errors of the mean.

dACC only responded transiently to both oddball types. We further showed above that a strict saliency account of AI and dACC function fails to fully explain our data here and from a previous study (Han and Marois 2014). These are consistent, however, with claims that these brain regions are involved in the capture of attention by behaviorally significant events (Menon and Uddin 2010; Nelson et al. 2010; Dubis et al. 2014). In that framework, events that are wholly unanticipated (such as standard oddballs) or that depict threatening situations (affective oddballs) summon attention for further processing due to their de facto or potential behavioral significance. It is unclear, however, what specific computations may be carried out by the AI and dACC in the capture of attention by behaviorally relevant events. Specifically, we do not know whether these brain regions are involved in the detection of a behaviorally relevant event (e.g., onset and offset of oddball) and/or in updating or switching of attentional settings towards (or away from) that event, as both of these processes are associated with the capture of attention (Posner 1980; Escera et al. 1998). The goal of Experiment 2 is to dissociate the roles of the AI and dACC in behavioral event detection and attention switching.

To address this issue, we adapted a well-established RSVP paradigm for dissociating behavioral event detection and attention set switching (Yantis et al. 2002; Chiu and Yantis 2009; Esterman et al. 2009; Tamber-Rosenau et al. 2011). Specifically, participants searched for digits imbedded in a rapid serial visual presentation of letters to determine their magnitude or parity, responding to each digit with an appropriate button press. Task cues—letters “M” and “P”—were occasionally presented during the RSVP to instruct participants to perform the magnitude or parity judgment task, respectively. Other types of cues, letters “H” and “S,” required participants to hold the current task or switch to the other task, respectively. The key events for this study are the H and S cue presentations. This is because while both cues require detection of a behaviorally relevant event, the S cue additionally includes a switching operation that is not present in the H cue. Thus, brain regions that are involved in attention set switching should show greater activity than those that are involved in detection.

The behavioral results from the fMRI study revealed that the overall accuracy of cue responses was 95.2 % without significant differences across cue types, *P*’s > 0.18 (pairwise *t*-test), suggesting that subjects generally paid attention to the cues. The proportion of correct target responses was significantly lower than that of cue response (82. 4%, $P < 0.0001$), and did not differ significantly whether it was preceded by a Hold or Switch cue (*P*’s = 0.6647). RT data revealed that RTs for the cues (mean = 938 ms) were similar across cue types, while target RTs (1303 ms) were longer than those for the cues, *P*’s < 0.0001, revealing the greater response discrimination demands for target presentations.

Univariate fMRI Results

Probing of brain regions defined in Experiment 1 revealed that the AI showed no difference in activities to the Hold and Switch cues, $P > 0.25$ (Fig. 6). By contrast, the dACC showed significantly greater activity to the Switch cue than to the Hold cue, $t(13) = 3.93$, $P < 0.006$, and this Switch–Hold cue activity difference was larger in dACC than AI, $P < 0.001$. Turning to the core stimulus-driven attention network, neither the IFJ nor TPJ showed differential activities to the Hold and Switch cues, $P > 0.35$ and $P > 0.43$, respectively. Further, the TPJ region tended to deactivate during the presentation of the task-related stimuli, as is often observed in previous studies (Todd et al. 2005; Shulman et al. 2007; Corbetta et al. 2008; Asplund et al. 2010). Lastly, the putamen and thalamus also yielded similar results to the AI, IFJ and TPJs, *P*’s > 0.10.

To assess whether there were any additional “switch” brain regions that were not identified by the ROI analyses, we carried out a whole-brain voxel-based random effect analysis, contrasting activity to the Switch cue with activity to the Hold cue (Fig. 7). This SPM analysis (q[FDR] <0.05) revealed a significant activation focus in dACC (Talairach coordinates: −4, 6, 45), which corresponded well to the region defined using the target regressor (Talairach coordinates: 0, 11, 45). Another significant activational focus was found in the medial superior parietal lobule (mSPL). This latter finding is consistent with previous evidence of switching-related activity in mSPL (Yantis et al. 2002; Chiu and Yantis 2009; Esterman et al. 2009; Tamber-Rosenau et al. 2011), thereby providing validation to the present methodological approach.

Together, these ROI and whole-brain results suggest that only the dACC (and mSPL), but not the AI, is involved in switching, at least when such switching does not involve spatial shifts of attention. (Yantis et al. 2002; Chiu and Yantis 2009; Esterman et al. 2009; Tamber-Rosenau et al. 2011).

Multivariate Results

The univariate analyses showed that AI activity (as well as IFJ, TPJ, and subcortical activity) was not preferentially engaged by behavioral cues that required attention switches compared with cues that required maintaining the current attention set. Further, these results suggest a dissociation of function between the 2 core elements of the “salience” network—the AI and dACC—with the AI (and presumably dACC) involved in behavioral event detection, but only the dACC involved in attention set switching. However, it is possible that the AI is encoding the task rules (Switching vs Holding) rather than, or in addition to, the detection of a behaviorally relevant event per se, a pattern that would not be detectable with univariate analyses. To assess this issue, we turned to multivariate pattern analysis (MVPA) to examine whether switching and holding rules could be decoded from activation patterns in these regions (Kamitani and Tong 2005; Norman et al. 2006) (see Materials and Methods).

As shown in Figure 8, and not surprisingly given the univariate results, MVPA of the dACC revealed that this brain region discriminates between switching and holding rules (peak decoding accuracy of event-related MVPA timecourse at volume at 6 s after cue onset: $t[13] = 3.38$, $P < 0.005$). By contrast, the classifier did not distinguish between switching and holding cues from the AI activation pattern (peak decoding accuracy was not different from chance, $P > 0.68$). Consistent with these findings, decoding accuracy was significantly better in dACC than AI, $P < 0.005$. Thus, while the MVPA findings provide further support for a role of dACC in attention switching, that is not the case for the AI; there is no evidence that it encodes task rules. Given that the AI was not preferentially activated for attentional switching and did not encode task rules, we conclude that it only detects the presence of behaviorally relevant cues.

Remarkably, the switching and holding rules could be successfully decoded from the IFJ activation pattern even though these 2 rule conditions yielded indistinguishable BOLD responses with the univariate analysis, as peak decoding accuracy was significantly higher than chance, $t(13) = 2.28$, $P < 0.05$, and was also significantly greater than the AI decoding accuracy, $P < 0.05$. These results suggest that while dACC primarily instantiates attentional switching, the IFJ encodes the task rules for switching and holding of attentional sets (Woldorff et al. 2004). This latter finding would be consistent with the hypothesis that the IFJ encodes task rules (Brass and von Cramon 2002; Bunge et al. 2003) or, more generally, the arbitrary input/output mapping of information pathways to subserve adaptive behavior, of which attention switching may be just one incarnation.

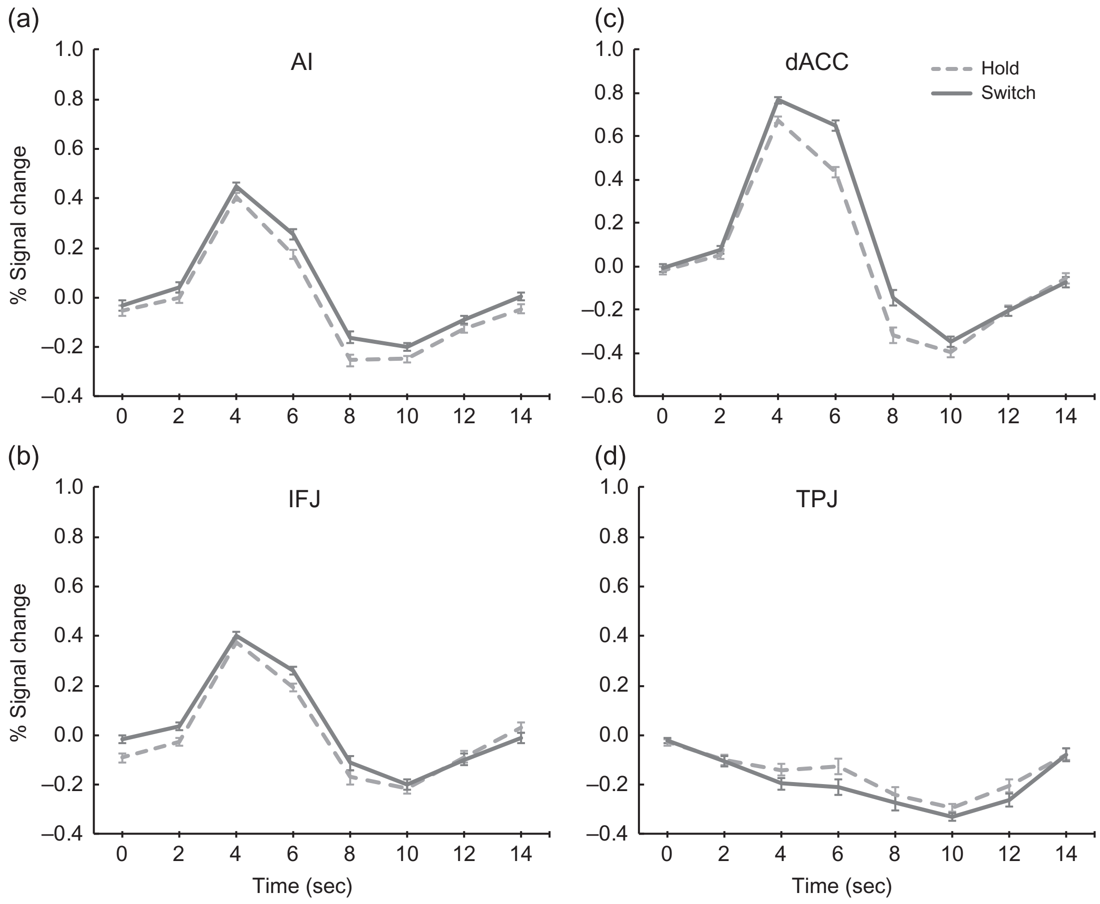

Figure 6. Timecourses of activation to the Hold and Switch cues in Experiment 2. (*a*) AI activity. (*b*) IFJ activity. (*c*) dACC activity. (*d*) TPJ activity. The cue onset is at time point zero. Error bars represent standard errors of the mean.

Interestingly, the activation pattern in the TPJ, which is a region deactivated during the task (Fig. 5*d*; see also (Todd et al. 2005; Shulman et al. 2007; Asplund et al. 2010), nevertheless discriminated the switching rule from the hold rules; its peak classification performance was better than chance, $t(13) = 2.26$, $P < 0.05$. This decoding result may fit well with the proposition that the TPJ is involved in evaluating/analyzing the meaning of behaviorally relevant stimuli (Doricchi et al. 2010; Geng and Mangun 2011; Chan et al. 2015; Vossel et al. 2015). Along this vein, a recent study (Lee and McCarthy 2016) demonstrated that the activation pattern in the TPJ correlated across tasks with cognitive demands as varied as biological motion, theory of mind, and attention reorienting. This result implies that the TPJ may subserve a common computation across these various tasks. Given the stimulus decoding demands placed by each of them, it may very well be that this core process corresponds to stimulus/event evaluation, which may involve comparing the event to the contents of stored information in memory (Lee et al. 2016).

Finally, the univariate GLM and multivariate pattern analyses revealed that the putamen and thalamus activities did not differ across cue type. This is a reminiscent of the finding in Experiment 1 in which these regions had a similar response profile to the AI. Taken together, these results suggest that when a behaviorally significant event occurs, the cortico-striatal-thalamo-cortical loop comprising the AI, putamen, and thalamus are primarily involved in detection of the event rather than switching attention to the detected event.

Discussion

The main findings of the 2 present experiments are clear. First, the AI showed a sustained response to the presentation of emotion-laden oddball stimuli, whereas the dACC showed only a transient response to those stimuli. Second, in the face of behaviorally relevant stimuli in Experiment 2, the AI was involved in simply detecting those stimuli, whereas the dACC was recruited with shifting of goal-directed behavior following the presentation of the stimuli. These findings, together with those of Han and Marois (2014), not only shed new light on the roles of the 2 core components of the cingulo-opercular network, they also functionally dissociate these 2 brain regions from one another.

Previous Accounts of AI function

In Experiment 1, the AI showed robust, transient responses at the onset and offset of temporally extended standard oddballs, consistent with its role in the transient capture of attention (Menon and Uddin 2010; Nelson et al. 2010; Han and Marois 2014). Experiment 2 is also consistent with such transient attention account, though more in event detection than in

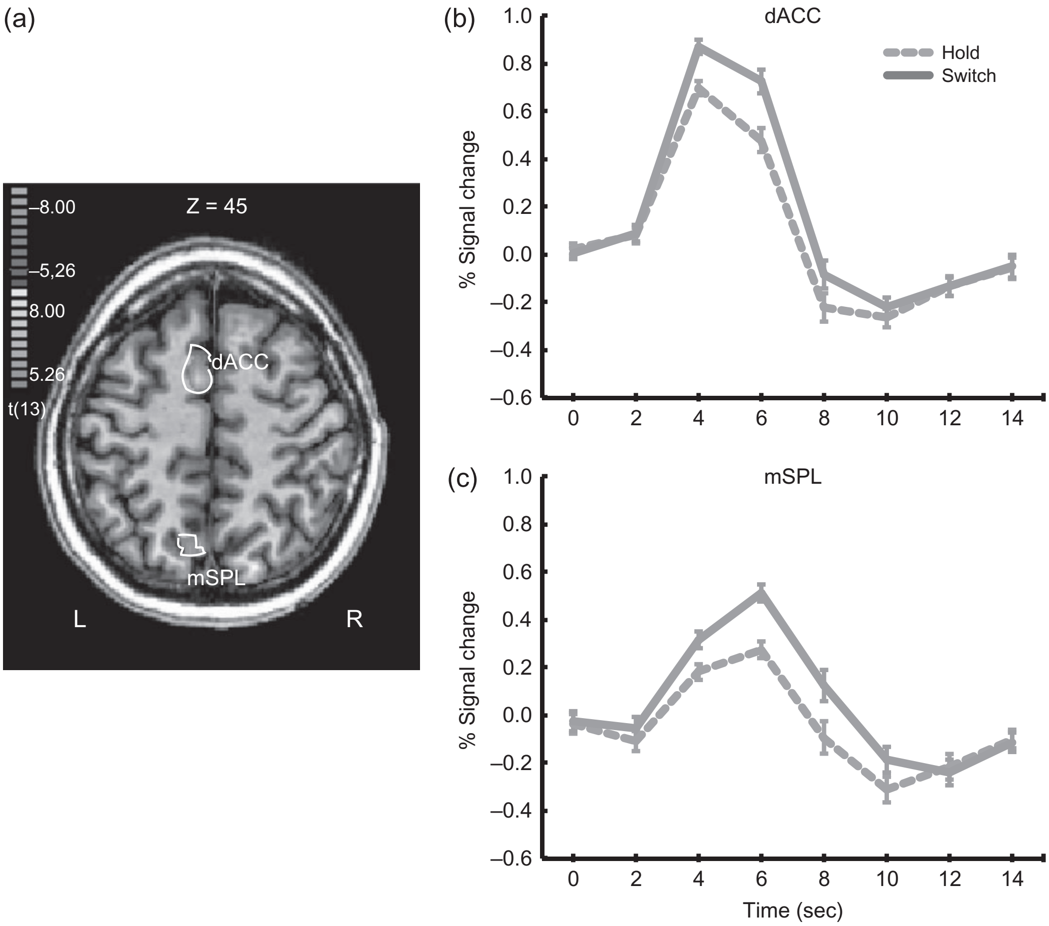

Figure 7. SPM of Switch versus Hold activity and activation timecourses of the activational foci (q(FDR) <0.05). (*a*) Anatomical locations of the ACC (Talairach coordinates: –4, 6, 45) and mSPL (Talairach coordinates: –9, –63, 45). (*b*) Activation timecourse of the dACC. (c) Activation timecourse of the mSPL. Error bars represent standard errors of the mean. The timecourses are only shown for highlighting the shapes of the hemodynamic response; no statistical tests were carried out on them.

attention switching per se. However, the response of the AI to affectively ladened oddballs in Experiment 1 is inconsistent with models of AI function that ascribe purely transient signaling functions to this brain region (Sridharan et al. 2008; Menon and Uddin 2010); unlike dACC, which showed only a transient response regardless of oddball types, the AI showed sustained activity throughout the presentation of the affective oddballs.

If not the transient capture of attention, then what might account for the AI's sustained response to affective oddballs? Given that the oddballs were task-irrelevant, this sustained activation cannot be easily explained by its role in the maintenance of task sets (Dosenbach et al. 2006; Nelson et al. 2010). It is also unlikely that the affective stimuli elicited sustained AI activity because they were more salient than the standard oddballs. While salience is not explicitly defined in this salience/attention framework (Seeley et al. 2007; Menon and Uddin 2010), in computational terms a salient stimulus is one that stands out from its contextual environment (Koch and Ullman 1985; Itti and Koch 2001), with stimulus novelty being one crucial factor (Downar et al. 2000). Yet, our recent work has shown that manipulating the saliency of standard oddballs by varying their novelty did not differentially affect the AI's response, even though it led to increased activation of the dorsal parietofrontal attention areas (Han and Marois 2014), regions well known to encode stimulus saliency (Gottlieb et al. 1998; Geng and Mangun 2009; Bogler et al. 2011; Santangelo and Macaluso 2013). Yet another alternative explanation for sustained AI activity with the affective oddballs may be that they evoked general arousal. However, a previous study found that it was the dorsal lateral prefrontal cortex, not the AI, whose activity was correlated with psychophysiological measures of arousal (Critchley et al. 2001). A strict affective account of AI function also fails to fully capture its response pattern, for it cannot easily explain the transient onset and offset responses to standard oddballs. Finally, recent meta-analyses suggest that different regions of the AI may mediate cognitive and affective processing (Deen et al. 2011; Touroutoglou et al. 2012), with the dorsal portion being primarily devoted to cognitive functions and the ventral sector predominantly involved in affective processing. However, the coordinates of our AI straddle these areas, and when we probed the dorsal and ventral sectors, both yielded comparable response patterns to those shown above. Thus, our results do not appear to fit under such regional specialization account of the AI.

An Alerting Response Function of the AI

As an alternative to strict affective or saliency/attention accounts and dual affective/cognitive models of AI function, we suggest a more parsimonious explanation of both the AI's transient and sustained response with Standard (neutral) and Affective oddballs. According to this account, the AI serves to

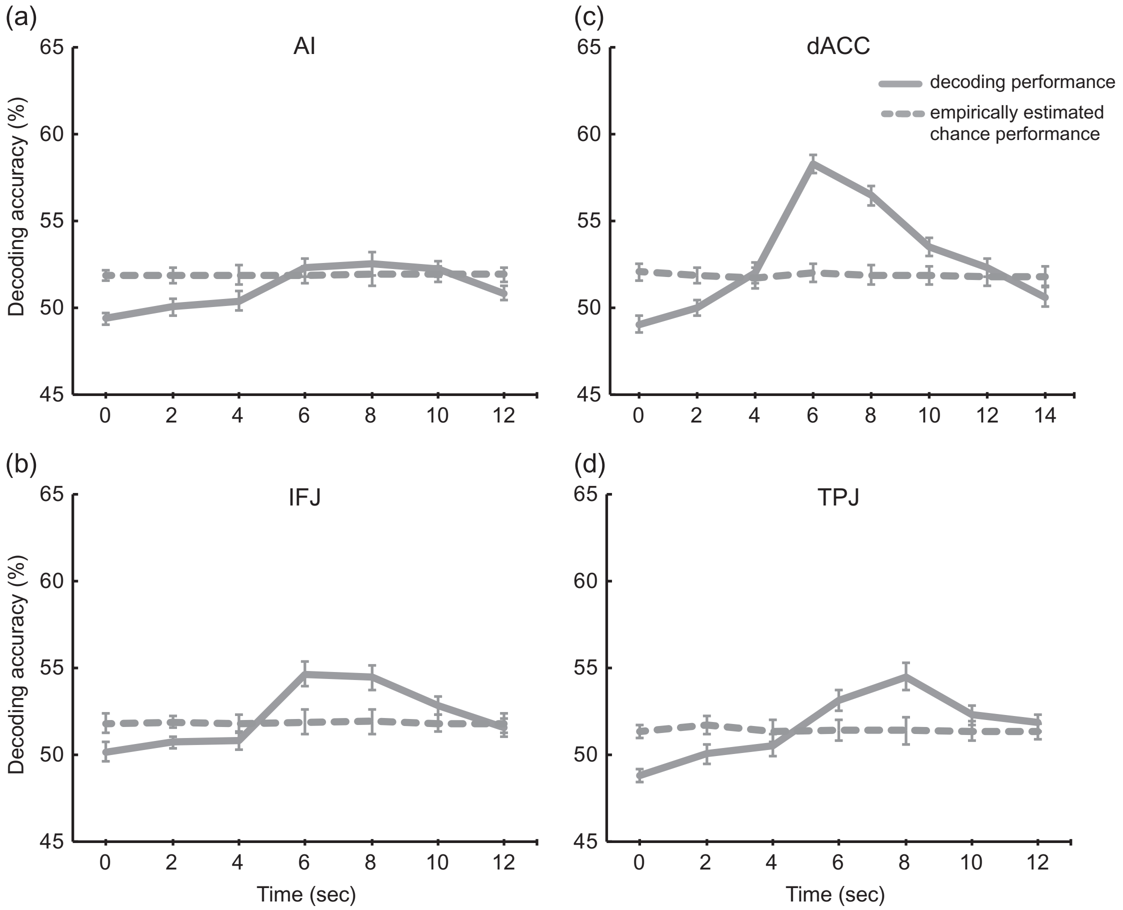

Figure 8. Event-related MVPA results. (*a*) AI decoding performance. (*b*) IFJ decoding performance. (*c*) dACC decoding performance. (*d*) TPJ decoding performance. The cue onset is at time point zero. Error bars represent standard errors of the mean.

alert for the presence of a potentially or de facto behaviorally relevant event, calling for further processing of that event. This account does not only fit well with the AI's transient, robust response to attention capturing events, it also accommodates the sustained activity of this region to socioaffective stimuli. Specifically, when a novel, salient or task-relevant stimulus is presented, the AI alerts the brain's information processing system of the occurrence of that event. Then, the system engages in the process of analyzing/interpreting the stimulus (see below), followed by the orchestration of an appropriate response to that event if it is deemed behaviorally relevant, terminating the episode. If the stimulus is identified as behaviorally irrelevant, the alerting signal is no longer needed. This account not only explains the response of the AI to target presentations and task cues (Dosenbach et al. 2006; Nelson et al. 2010; Dubis et al. 2014; Han and Marois 2014), but also to the standard oddball movie clips. In this context, the AI responds to the onsets and offsets of these oddballs because these represent changes to the subject's ongoing environmental stasis that require evaluation. There is no sustained AI response throughout the presentation of these oddballs, however, as there is no accumulation of evidence that they are behaviorally meaningful. By contrast, when one is confronted with extended oddballs depicting human suffering or aversive stimuli—stimuli that are likely to be behaviorally meaningful—the AI continues to fire, calling for a behavioral reaction to respond to the situation under conditions in which it cannot be acted upon.

This alerting function account of the AI is also broadly consistent with the results of Experiment 2. Specifically, the AI showed equivalent activation amplitude and pattern in the face of task-relevant cues associated with different actions (i.e., holding or switching attentional sets). The finding that AI activity was indifferent to cue identity further supports the proposition that the primary role of the AI is to alert the system of potentially (as in Experiment 1) or de facto (as in Experiment 2) behaviorally meaningful events, as such alerting needs not also contain the appropriate cognitive operations or actions that should be taken to respond to the situation.

Our account of AI function is also supported by a recent study that the maintenance of tonic alertness is a crucial function of the cingulo-opercular network (Sadaghiani and D'Esposito 2014). Specifically, the activity of this network was found to increase when target stimuli were presented unpredictably with jittered blank intervals compared with when they were presented with regular intervals. This result accords with our claim that the AI is primarily involved in signaling potentially significant events, as the demand for detecting targets and alerting the system should increase as the target presentation becomes unpredictable. Our findings further suggest that the AI is primarily involved in alerting the system of a (potentially) significant event irrespective of whether those events are phasic or tonic, and irrespective or whether those events are emotionally laden or not. In addition, the present findings provide a clear functional dissociation between the role(s) that AI plays from the one(s) that the dACC is involved in, as discussed below.

Dissociation of AI and dACC Functions

The AI and dACC have often been observed to work in tandem, leading to the idea that these 2 regions are the core components of a network contributing to salience detection, the implementation of task sets, or the initiation of task control (Dosenbach et al. 2006; Seeley et al. 2007; Sridharan et al. 2008; Nelson et al. 2010; Sadaghiani and D'Esposito 2014). Here, we provide evidence that these 2 regions fulfill at least partly distinct functional roles. While we argue that AI activity is related to alerting the organism to the occurrence of a potentially or de facto behaviorally meaningful event, similar transient activity in dACC may be primarily related to the switching of attention to/from the event. Contrary to the AI in Experiment 1, dACC only showed transient responses to both affective and standard oddballs, especially to their offsets. Furthermore, this region showed greater activity to the Switch cue than to the Hold cue in Experiment 2, a pattern that was not observed in AI. It is therefore possible that the dACC (along with the mSPL) is primarily involved in switching of attentional set, perhaps more so when the switch is from a distracting, task-irrelevant event to goal-oriented behavior, consistent with the hypothesis that this area promotes switching between endogenous and exogenous sources of cognitive control (Sridharan et al. 2008). However, these results are also consistent with a broader account of dACC function in updating internal models of task set and the environment in order to enact behavioral change (O'Reilly et al. 2013; Kolling et al. 2016). In this framework, the dACC's response with task-irrelevant oddballs result from a need to update internal models of the environment (and its impact on the goal-oriented task) whereas its greater activity in switch cues of Experiment 2 results from the need to update the task set.

Whichever the precise function(s) that dACC may subserve, our findings clearly suggest that those are at least partly distinct from those in the AI, and that they should not be considered as forming an insulated network with a singular function (Dosenbach et al. 2006; Sridharan et al. 2008; Nelson et al. 2010). Finally, our results further suggest that the other components of a proposed cortico-striatal-thalamo-cortical circuit (Peters et al. 2016), namely, the thalamus and putamen, are functionally more aligned with the AI than with the dACC, the latter being the “odd man out” of this circuit. Evidently, that circuit may be primarily tuned to triggering an alerting signal to the presence or potential presence of a significant event.

In conclusions, the present study proposes a clarification of the functional roles of the AI and dACC, and contrasts these functions from those of other attention areas. Specifically, we suggest that the AI—possibly along with the thalamus and putamen—alerts the information processing system to the occurrence of a potential or de facto behaviorally relevant event, perhaps initiating the cascade of events for task control (Sridharan et al. 2008; Nelson et al. 2010; Sadaghiani and D'Esposito 2014) that would ensure appropriate behavioral resources are devoted to the signaled event. According to this scheme, the signal from AI would be communicated—either directly or indirectly—to the dACC for altering internal models of the environment and/or behavior, to the TPJ for facilitating the cognitive evaluation of the event, to the mSPL for enacting a switch in behavior task set to in response to the event, and to the lateral prefrontal cortex (IFJ) for implementing an appropriate behavioral response if needed. It is thus this alerting function of the AI that could underlie this region's association with a wide variety of cognitive and affective processes.

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Notes

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