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Original Research Paper

Cognitive control and the anterior cingulate cortex: How conflicting stimuli affect attentional control in the rat

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ABSTRACT

Converging evidence supports the hypothesis that the prefrontal cortex is critical for cognitive control. One prefrontal subregion, the anterior cingulate cortex, is hypothesized to be necessary to resolve response conflicts, disregard salient distractors and alter behavior in response to the generation of an error. These situations all involve goal-oriented monitoring of performance in order to effectively adjust cognitive processes. Several neuropsychological disorders, e.g., schizophrenia, attention deficit hyperactivity and obsessive compulsive disorder, are accompanied by morphological changes in the anterior cingulate cortex. These changes are hypothesized to underlie the impairments on tasks that require cognitive control found in these subjects. A novel conflict monitoring task was used to assess the effects on cognitive control of excitotoxic lesions to anterior cingulate cortex in rats. Prior to surgery all subjects showed improved accuracy on the second of two consecutive, incongruent trials. Lesions to the anterior cingulate cortex abolished this. Lesioned animals had difficulty in adjusting cognitive control on a trial-by-trial basis regardless of whether cognitive changes were increased or decreased. These results support a role for the anterior cingulate cortex in adjustments in cognitive control.

1. Introduction

One aspect of cognitive control is the ability to discriminate important information from inessential and then respond (Alexander and Brown, 2010; Kennerley et al., 2006; Rudebeck et al., 2008; Walton et al., 2007a). This process requires the prefrontal cortex to integrate information from memory with current sensory input and respond in an appropriate manner (Alexander and Brown, 2010; Baddeley and Della Sala, 1996; Carter et al., 2000; Goldman-Rakic, 1996; Holroyd et al., 2004). When previously successful responses generate errors or fail to yield reinforcement, cognitive control is required to adapt to these changes in environmental contingencies (Brown and Braver, 2005; Carter et al., 1998; Garavan et al., 2003; Hester et al., 2005; Holroyd et al., 2004; Kennerley et al., 2006; Kolling et al., 2014; Krigolson and Holroyd, 2007; Ridderinkhof et al., 2003; Rudebeck et al., 2008; Walton et al., 2007a).The anterior cingulate cortex (ACC) is one of the subregions of prefrontal cortex that is active when cognitive control is required (Botvinick et al., 2001; Brown and Braver, 2005; Cole and Schneider, 2007; Kerns et al., 2004; Lorist et al., 2005; Magno et al., 2006; Woodward et al., 2008; Yeung and Nieuwenhuis, 2009).

Emitting an error or being in a situation where errors are likely correlates with activation of the ACC (Amiez et al., 2005; Brown and Braver, 2005; Carter et al., 1998; Hester et al., 2005; Holroyd et al., 2004; Yeung et al., 2004). Kennerley et al. (2006) found non-human primates with ACC lesions require more trials to reach asymptotic performance and generate more errors after correct responses than controls. In non-human primates and rats, the ACC is connected to the parietal cortex and dorsolateral prefrontal cortex or the rat homolog, the prelimbic cortex (Hoover and Vertes, 2007; Selemon and Goldman-Rakic, 1988). This connectivity may allow the ACC to recruit these areas following the detection of conflict to increase attentional control (Banich et al., 2000; Carter et al., 1998; Kerns et al., 2004; MacDonald et al., 2000).

The ACC has been implicated in decision making where evaluating the utility of stimuli and responses is required (Bush et al., 2002; Kennerley et al., 2006; Lee et al., 2007). Specifically, ACC is necessary to integrate error, conflict, and reinforcement information leading to the hypothesis that ACC is critical to effortful processing, e.g., in evaluating the utility of an effortful action based on potential reward (Kennerley et al., 2006; Lee et al., 2007). Different factors can devalue reinforcement such as a delayed

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reinforcement or an increased physical effort (climbing a barrier, increasing the number of responses required; Walton et al., 2006). Subjects will perform the more demanding task under conditions when this effort yields a larger reward (Kennerley et al., 2006; Walton et al., 2006). Lesions of the ACC impair calculations of the cost of a behavior to produce inefficient actions (Kolling et al., 2014; Walton et al., 2003, 2009). These data support the hypothesis that the ACC is important for utilizing action-outcome history to optimize reward. One limitation of this prior work is that physical effort not cognitive effort was varied.

Functional imaging studies have shown the ACC is activated in the presence of conflicting stimuli or responses (Botvinick et al., 1999; Botvinick et al., 2001; Chen et al., 2006; Kerns et al., 2004; Mitchell, 2006; van Veen et al., 2001). Botvinick et al. (1999) tested subjects in a task previously described by Gratton et al. (1992) that requires the individual to attend to central directional cues, e.g., left arrow respond on left button. Some trials include flanker arrows that point in the same or opposite direction as the target. On congruent trials, flanker and central stimuli require the same response, but these stimuli provide conflicting information on incongruent trials. Response latencies are shorter on congruent trials than incongruent trials (Botvinick et al., 1999). Participants also respond faster on the second of two consecutively presented incongruent trials (Botvinick et al., 1999, 2001; Gratton et al., 1992; Kerns et al., 2004; Ridderinkhof et al., 2004; Sheth et al., 2012). This speeded reaction is coincident with greater activation of the dorsal region of the ACC (Botvinick et al., 1999; Sheth et al., 2012). It has been hypothesized that the activation of the ACC increases top-down control and narrows the attentional focus so conflicting information is disregarded on the following trial (Botvinick et al., 1999).

While fMRI studies support a role for the ACC in conflict monitoring, focal lesion studies in humans do not necessarily show deficits on classic tests of conflict monitoring such as the Stroop task (Fellows and Farah, 2005; Glascher et al., 2012; Stuss et al., 2001). The functional sparing found in these studies may be because the test session did not interleave congruent and incongruent trials thus minimizing the need for trial-by-trial cognitive control. When congruent and incongruent trials are intermixed, participants with ACC lesions show slower reaction times than controls on both types of trials and fail to show reaction time improvements on the second of two consecutive incongruent trials (Alexander et al., 2007; di Pellegrino et al., 2007). Subjects with damage to the ACC have also been shown to be less accurate on incongruent trials than control subjects (Swick and Jovanovic, 2002).

Studies in rats have shown that ACC inactivation or lesions impairs the ability of these subjects to disregard previously reinforced stimuli (Newman and McGaughy, 2011; Ragozzino and Rozman, 2007). Additionally, rats with ACC inactivation or lesions maintain ineffective response strategies longer than controls (Bussey et al., 1997; Chudasama et al., 2003; Newman and McGaughy, 2011; Ragozzino and Rozman, 2007). Together these data support the hypothesis that ACC may be crucial for recognizing situations where the behavioral response is not effective and a shift in cognitive processing is required (Dias and Aggleton, 2000; Kennerley et al., 2006; Kolling et al., 2014; Lee et al., 2007).

Few studies have attempted to establish a translational model of conflict monitoring in rats (Haddon and Killcross, 2006; Kashtelyan et al., 2012; Marx et al., 2012). The current work is aimed at redressing possible shortcomings in these previous tasks as described in brief here. In some cases, animals were not reinforced for correct responses or not consistently reinforced during the simultaneous presentation of stimuli (Haddon and Killcross, 2006; Kashtelyan et al., 2012). Reinforcement is consistent in our task to prevent extinction. Previously, stimuli of different modalities were paired with different reinforcers (i.e. sucrose or food pellets) (Haddon and Killcross, 2006). Innate preferences for the different reinforcers may alter responding such that subjects are biased to attend to stimuli associated with the preferred reinforcer, thus decreasing the effects of conflicting information when the non-preferred reinforce is the target modality. As a result, we reinforced all stimuli in an equivalent manner. In some cases response latencies were not measured and non-standard formulas were used to calculate accuracy (Haddon and Killcross, 2006). Finally, all of the prior studies failed to analyze inter-trial effects of congruent and incongruent trials (Haddon and Killcross, 2006; Kashtelyan et al., 2012; Marx et al., 2012). As previous focal lesion studies in humans suggest trial by trial adjustments to cognitive control are the aspect of cognition most sensitive to ACC damage, it is important to include these analyses as they may be critical to revealing impairments (Alexander et al., 2007; di Pellegrino et al., 2007). In the present study, dependent measures and trial-by-trial analyses were performed in a manner similar to those obtained in humans to facilitate comparison between species (Botvinick et al., 1999; Kerns et al., 2004; Roelofs et al., 2006; van Veen et al., 2001).

Currently, we describe the characterization of a novel, cognitive control task for rats with attentional demands similar to those in Gratton's flanker task (Botvinick et al., 1999; Gratton et al., 1992) and determine the effects of excitotoxic lesions to the ACC on performance in this task. Accuracy and response latencies from neutral or congruent trials were compared to those on incongruent trials. In addition, trial-by-trial analyses were completed to determine if rats, like humans, show improved performance on the second of two consecutive incongruent trials and to determine if subjects were sensitive to decreases in cognitive demands, e.g., performed better on non-conflict trials subsequent to a conflict trial. After this characterization, half of the subjects received excitotoxic lesions to the ACC to determine the impact of this damage on the conflict monitoring task. We also assessed performance in a conditional discrimination task with distraction. In this task, subjects experienced the simultaneous presentation of a target stimuli and a novel, salient distractor. In contrast to the conflict monitoring task, the distracting stimuli in the conditional discrimination task were not associated with a response or prior reinforcement. We hypothesized that damage to the ACC would impair performance in the conflict monitoring task, but not the test of distractibility with a novel, but never before reinforced stimulus. Additionally, we hypothesized that ACC lesions would decrease the ability of subjects to respond to trial-by-trial changes in cognitive demands similar to impairments found in humans after excision of the dorsal ACC (Sheth et al., 2012).

2. Research design and methods

2.1. Apparatus and materials

Operant chambers (Med Associates, St. Albans, VT) equipped with two retractable levers, a houselight (2.8 W), a 45 mg pellet dispenser, a 2900 Hz sonalert tone generator, and three panel lights (2.8 W) were used. The food dispenser, panel lights, tone generator, and retractable levers were all located on the same wall (see Fig. 1A). The houselight was located on the opposite wall. Records of signal presentation, lever operation, and food pellet (Dustless Precision Pellets, 45 mg; Bio-serv, Frenchtown, NJ) delivery were maintained using a personal computer with Windows XP (Microsoft, Seattle, WA) and the Med-PC IV software (Med Associates).

2.2. Behavioral training

20 male Long Evans rats were trained in an operant chamber on two sets of conditional discriminations (see Fig. 1A). All animals were food restricted to maintain at least 90% of their free fed weight prior to training.