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Conflict monitoring mechanism at the single-neuron level in the human ventral anterior cingulate cortex

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A B S T R A C T

Life requires monitoring and adjusting behavior in the face of conflicts. The conflict monitoring theory implicates the anterior cingulate cortex (ACC) in these processes; its ventral aspect (vACC) specializes in emotional conflict. To elucidate the underpinning neural mechanism, we recorded vACC extracellular activity from 12 patients with mood disorders or epilepsy who performed the face-emotional Stroop task. Behaviorally, both conflict detection and adaptation to conflict were evident. The firing rate of neurons in the vACC represented current conflict, i.e., current-congruency. The late onset of the effect is compatible with a role in monitoring. Additionally, early responses of some neurons represented the immediate history of conflicts, i.e., previous-trial-congruency. Finally, in some neurons the response to the current-trial was modulated by previous-trial-congruency, laying the ground for adjusting-to-conflicts. Our results uncover a single neuron level mechanism in the vACC that encodes and integrates past and present emotional conflicts, allowing humans to accommodate their responses accordingly.

Introduction

Adaptive behavior requires constant experience-based adjustments, a function that has been attributed to the anterior cingulate cortex (ACC). The ventral ACC (vACC), which participates in various aspects of emotional processing (Levy et al., 2007), specializes in the emotional aspects of experience-base adjustments. Neuroimaging studies have particularly implicated the vACC in implicit, automatically evoked emotional regulation (Etkin et al., 2015), as seen in the face-emotional-Stroop task. In this task participants classify the facial expression of face pictures superimposed by matching or mismatching word labels, creating congruent and incongruent experimental conditions, respectively. The emotional conflict created by incongruent trials is generally associated with slower reaction time (RT) and lower accuracy. Intriguingly, the degree of slowing is modulated by previous-trial-congruency, indicating experience-based adaptation, that is, emotional regulation (Etkin et al., 2015). Notably, a parallel adaptation effect is frequently seen in congruent trials, manifested as a faster performance in congruent trials that follow congruent trials rather than incongruent trials (Etkin et al., 2010). The two complementary effects are collectively termed here 'adaptation to congruency'. Adaptation to congruency is accompanied by increased activity in the vACC in fMRI, pointing to the functional significance of this region in emotional regulation (Etkin et al., 2006; Egner et al., 2008). A lesion study expanded these findings and showed that the vACC is not only important but is essential for emotional regulation (Maier and di Pellegrino, 2012) and performance in the Stroop task (Swick and Jovanovic, 2002); however, results are mixed and inconsistent across studies. Additional support for the role of vACC in emotional regulation is found in major depressive disorder (MDD). MDD pathology is characterized, among other

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symptoms, by impaired emotional regulation (Campbell-Sills et al., 2006; Kovacs et al., 2008; Ehring et al., 2010) and converging findings point to the vACC as a critical region in MDD (Mayberg, 1997; Pizzagalli, 2011), since it demonstrates altered volumetric (Drevets et al., 2008), metabolic (Drevets et al., 2002) electrophysiological (Jaworska et al., 2012), functional activity (Etkin and Schatzberg, 2011; Mitterschiffthaler et al., 2008) and connectivity (Greicius et al., 2007) patterns. Intriguingly, in the face-emotional-Stroop task, patients with MDD show similar emotional regulation as healthy participants, manifested as adaptation to congruency during both congruent and incongruent trials (Etkin and Schatzberg, 2011). Important to the current study, MDD patients show activity modulation in the vACC similar to healthy participants in adaptation to congruency, but only during congruent trials, while in incongruent trials they recruit compensatory mechanisms located in lateral frontal areas (Etkin and Schatzberg, 2011). In order to combine the data of the MDD patients with another group of patients (see below) and to generalize the results to the healthy population, the current study focused on congruent trials only.

The phenomenon of adaptation to congruency is not specific to emotional conflicts; in fact, it was first demonstrated in cognitive conflicts. This phenomenon inspired the formulation of the conflict monitoring theory (Botvinick et al., 2001), according to which the ACC detects conflicts and passes this information to the dorsolateral prefrontal cortex, thereby dynamically adjusting the allocation of control mechanisms on subsequent processing of information. This renowned theory gained much support from behavioral, lesion and neuroimaging studies (Botvinick et al., 2001; Carter and van Veen, 2007; Kerns et al., 2004), though support from the latter should be taken with a grain of salt for several reasons. First, the fMRI activity demonstrated in the ACC during conflict may reflect neural events other than spiking activity (Logothetis and Wandell, 2004), which cannot be passed to other brain regions as required by the conflict monitoring theory (Nakamura et al., 2005). Furthermore, fMRI signal represents the cumulative activity of neural ensembles, and therefore, increased activity during conflict may merely be due to simultaneous activation of two populations of neurons, each representing an independent potential response, rather than detecting the conflict itself (Nakamura et al., 2005). And finally, an fMRI study showed that the increased activation in the dACC during incongruent condition was related to the prolonged RT in that condition, rather than conflict per se (Grinband et al., 2011), though there is a dispute whether the findings and interpretations of the study contradict the conflict monitory theory (Yeung et al., 2011). In addition, inconsistently with the theory's predictions, several non-human primate studies failed to find conflict–responding neurons in the dACC (Nakamura et al., 2005; Ito et al., 2003). Yet, in accordance with the theory, a recent microelectrode recording study in humans uncovered neurons in the dACC that encode current and recent conflicts. When the activity in these neurons was modulated by the previous trial, it predicted behavioral adaptation (Sheth et al., 2012). Nevertheless, this was a single study with six patients undergoing cingulotomy to treat refractory obsessive compulsive disorder, recording was limited to dACC, and the task examined only a cognitive conflict.

The present study aims to elucidate the neural mechanism by which the vACC acts to monitor emotional conflicts and adjust the response to conflicting emotional information based on recent experience. To this end we recorded extracellular neuronal activity in the vACC in two groups of patients that underwent surgical procedure in order to ameliorate treatment-resistant medical conditions. The first group was composed of 8 patients with treatment-resistant MDD or bipolar disorder. In recent years, deep brain stimulation of the subcallosal cingulate gyrus (consisted of the subgenual ACC (sgACC) and adjacent parts of the pregenual ACC (pgACC), the two components of the vACC) has been used to ameliorate depressive symptoms in such patients (Mayberg et al., 2005; Lozano et al., 2012; Puigdemont et al., 2012). The second group was composed of 4 patients suffering from medically intractable epilepsy undergoing implantation of depth electrodes in order to identify the seizure foci for subsequent surgery. While waiting for spontaneous seizures to occur, some patients are willing to perform cognitive tasks. Using the unique clinical setups created by these surgical procedures, we recorded extracellular neuronal activity in the vACC from the 12 patients while they performed the face-emotional-Stroop task (see Materials and methods for additional details), searching for the neural mechanism of monitoring and adapting to emotional conflicts. A region that provides such a neural mechanism must have neurons that: 1) show a congruency effect, manifested as a greater change in spike rate for incongruent as compared to congruent trials; 2) represent previous-trial-congruency, manifested as a greater change in spike rate for post incongruent as compared to post congruent trials; or 3) show modulation of congruency effect by previous-trial-congruency. Behaviorally, patients showed both congruency and experience-based adaptation to congruency effects. Corresponding spike rate patterns in vACC neurons propose neural basis for these behavioral phenomena.

Materials and methods

Participants

The study incorporated two groups of patients; each recruited and participated in the experiment at a different medical center. The first group was recruited at Toronto Western Hospital, Ontario, Canada. It was composed of six patients with treatment resistant MDD (4 females, age range 31–57y) and two patients suffering from treatment resistant bipolar disorder (2 females, ages 28 and 56y) undergoing implantation of deep brain stimulation (DBS) electrodes in the vACC (Table 2). The second group was recruited at Tel Aviv Sourasky Medical Center, Israel. It was composed of four patients with treatment resistant epilepsy (3 females, age range 28–45y) who were implanted with chronic depth electrodes for 1–3 weeks to determine the seizure focus for possible surgical resection. All patients had normal intelligence, normal or corrected to normal visual acuity (i.e., when needed, patients wore glasses in the operating room or in their bedroom, according to the setting, see below) and no structural brain abnormalities, indicated by MRI. The study was approved by the Human Research Ethics Committee of the University Health Network, University of Toronto (for the MDD/bipolar group) and by the Tel Aviv Sourasky Medical Center Institutional Review Board (for the epilepsy group). Participants were assessed on the basis of informed consent, which was obtained according to the Declaration of Helsinki.

The face-emotional-Stroop task

Stimuli: Face stimuli consisted of black and white face images from the Nim-Stim Set of Facial Expressions (Tottenham et al., 2009), cropped to an oval shape, preserving only main facial parts. Each of the four male and four females whose images used in the study posed a fearful facial expression in one image and a happy facial expression in another image, resulting in 16 different face images. Each face image had two versions, one with the word “Happy” and the other with the word “Fear”, printed with red ink, superimposed on its center, resulting in 32 stimuli. In the MDD/bipolar group, each stimulus appeared 5 times in the full version of the experiment performed, yielding 160 trials. In the epilepsy group each stimulus appeared 2–3 times in each task-condition (see below), yielding 160 trials. The same stimuli were used in the practice session.

Task MDD/bipolar group: In this task, faces with either happy or fearful facial expression were presented, overlaid with the words “Happy” or “Fear”. Facial expression and the content of the written word either matched (termed: congruent) or did not match (termed: incongruent). Participants were required to press a button in order to indicate whether the facial expression was happy or fearful, while ignoring the word. Owing to the intricate clinical setup and in order to minimize the participant's effort, the assignment of buttons to “happy” and “fear” facial expression was presented at the bottom of the screen during the entire