Neuropsychologia 48 (2010) 1144–1159

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

Errors recruit both cognitive and emotional monitoring systems: Simultaneous intracranial recordings in the dorsal anterior cingulate gyrus and amygdala combined with fMRI

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ARTICLE INFO

Article history:
Received 9 June 2009
Received in revised form
17 November 2009
Accepted 11 December 2009
Available online 21 December 2009

Keywords:
False alarms
Commission errors
Error detection
Cognitive control
Emotional effects
Dorsal anterior cingulate cortex
Amygdala
Epilepsy
Human intracranial EEG
fMRI

ABSTRACT

We studied error monitoring in a human patient with unique implantation of depth electrodes in both the left dorsal cingulate gyrus and medial temporal lobe prior to surgery. The patient performed a speeded go/nogo task and made a substantial number of commission errors (false alarms). As predicted, intracranial Local Field Potentials (iLFPs) in dorsal anterior cingulate indexed the detection of errors, showing an early differential activity around motor execution for false alarms, relative to correct responses (either hits or correct inhibitions). More surprisingly, we found that the left amygdala also participated to error monitoring (although no emotional stimuli were used), but with a very different neurophysiological profile as compared with the dorsal cingulate cortex. Amygdala iLFPs showed a precise and reproducible temporal unfolding, characterized by an early monophasic response for correct hits around motor execution, which was delayed by ~300 ms for errors (even though actual RTs were almost identical in these two conditions). Moreover, time-frequency analyses demonstrated a reliable and transient coupling in the theta band around motor execution between these two distant regions. Additional fMRI investigation in the same patient confirmed a differential involvement of the dorsal cingulate cortex vs. amygdala in error monitoring during this go/nogo task. Finally, these intracranial results for the left amygdala were replicated in a second patient with intracranial electrodes in the right amygdala. Altogether, these results suggest that the amygdala may register the motivational significance of motor actions on a trial-by-trial basis, while the dorsal anterior cingulate cortex may provide signals concerning failures of cognitive control and behavioral adjustment. More generally, these data shed new light on neural mechanisms underlying self-monitoring by showing that even "simple" motor actions recruit not only executive cognitive processes (in dorsal cingulate) but also affective processes (in amygdala).

1. Introduction

Error detection is an essential cognitive function for adaptive and flexible behaviors (Gratton, Coles, & Donchin, 1992; Rabbitt, 1966; Ullsperger & von Cramon, 2004). Error detection allows a rapid adjustment of actions based on their perceived outcome, and may therefore play a critical role in reinforcement learning (Cohen & Ranganath, 2007; Holroyd & Coles, 2002). In this model, errors modify the strength of stimulus-response mappings, thereby altering and improving subsequent actions in an appropriate manner. Error detection has been shown, by electrophysiology (Debener et al., 2005; Dehaene, Posner, & Tucker, 1994; Falkenstein, Hoormann, Christ, & Hohnsbein, 2000; Gehring & Fencsik, 2001; van Veen & Carter, 2002, 2006), lesion (Cohen, Ridderinkhof, Haupt, Elger, & Fell, 2008; Swick & Turken, 2002 but see Fellows & Farah, 2005), functional neuroimaging (Brown & Braver, 2005; Carter et al., 1998; Stevens, Kiehl, Pearlson, & Calhoun, 2007; Ullsperger & von Cramon, 2001) and intracranial recording studies (Brazdil et al., 2002; Wang, Ulbert, Schomer, Marinkovic, & Halgren, 2005), to critically rely on the dorsal anterior cingulate cortex (ACC) and surrounding medial prefrontal cortex (PFC; Bush, Luu, & Posner, 2000; Ridderinkhof, Nieuwenhuis, & Braver, 2007; Taylor, Stern, & Gehring, 2007).

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doi:10.1016/j.neuropsychologia.2009.12.020

Although the exact neurocognitive process subserved by the dorsal ACC remains currently debated, its selective involvement in error detection and conflict monitoring is now well established.

According to the error-based reinforcement learning model (or alternatively, the risk prediction/error avoidance model, see Ridderinkhof, van den Wildenberg, Segalowitz, & Carter, 2004) the dorsal ACC receives feedback from the striatum and mesencephalic dopamine system (Brown & Braver, 2005; Holroyd & Coles, 2002), consistent with a functional link between cognitive monitoring and affective-motivational processes. In this model, errors are followed by a phasic suppression of dopamine, which increases the dorsal ACC activity, and in turn elicits the error-related negativity (ERN), a well-known scalp ERP marker of error detection (see Falkenstein et al., 2000). Thus, the ERN is thought to reflect a cognitive signal that rapidly informs about a discrepancy between actual and expected outcomes, and thus promotes learning (Frank et al., 2005; Holroyd & Coles, 2002).

There are also strong anatomical connections between rostral parts of ACC and other limbic structures involved in affect and motivation, such as the amygdala and insula (Ongur & Price, 2000; van Hoesen, Morecraft, & Vogt, 1993; see also Ochsner & Gross, 2005; Kienast et al., 2008). Based on this evidence, some theories proposed that ACC activity following errors could also reflect an appraisal of the affective significance or salience of errors (Hajcak & Foti, 2008; Hajcak, Moser, Yeung, & Simons, 2005; Li et al., 2008; Luu, Tucker, Derryberry, Reed, & Poulsen, 2003; Pizzagalli, Peccoralo, Davidson, & Cohen, 2006; Polli et al., 2008, 2009; Taylor et al., 2006). Consistent with this notion, the amplitude of the ERN is modulated not only by manipulations such as the frequency of errors (as predicted by the error-based reinforcement learning model, see Gehring, Goss, Coles, Meyer, & Donchin, 1993; Hajcak, McDonald, & Simons, 2003), but also by motivational and emotional factors unrelated to the dopaminergic reward system, such as changes in state or trait anxiety (see Hajcak, McDonald, & Simons, 2003; Hajcak, McDonald, & Simons, 2004; Vocat, Pourtois, & Vuilleumier, 2008; see also Pizzagalli et al., 2006). Further, in a recent scalp ERP study in healthy participants, Hajcak and Foti (2008) found that the startle blink reflex was enhanced following errors during a flanker task, suggesting that error monitoring could also activate the defensive motivational system responsible for the startle reflex (Lang, Bradley, & Cuthbert, 1990). Because both the amygdala and insula are implicated in anxiety and defensive behaviors, these limbic regions might also contribute to error detection processes taking place in dorsal ACC (Fales et al., 2008; Kienast et al., 2008; Ochsner & Gross, 2005). Indirect evidence in support of this theory comes from a few neuroimaging studies that showed increased activity to errors not only in ACC and PFC, but also in deeper limbic brain structures such as the amygdala, insula, and thalamus (Garavan, Ross, Murphy, Roche, & Stein, 2002; Li et al., 2008; Menon, Adleman, White, Glover, & Reiss, 2001; Polli et al., 2008). In a recent fMRI study, Polli et al. (2009) reported an interesting association between the amygdala and rostral ACC during action monitoring, although reliable differences between the left and right amygdala were found in this study. Whereas activation in the right amygdala and right rostral anterior cingulate cortex predicted greater accuracy, the left amygdala activation predicted a higher error rate (see Polli et al., 2009). These results further emphasize that beyond the dorsal/rostral ACC, the amygdala is also involved in action monitoring, and they suggest different roles of the left vs. right amygdala in this process.

However, to date, few data exist to support a role for the human amygdala in error processing and, more generally, action monitoring. It still remains unknown whether mesio-temporal lobe structures, directly involved in emotional processing and learning (Phelps & LeDoux, 2005), might be recruited following errors (see Polli et al., 2008, 2009), and if so, at which latencies relative to the dorsal cingulate cortex. To our knowledge, only one single neurophysiological study reported intracranial ERPs to errors with recordings from mesio-temporal lobe structures, including the amygdala and hippocampus, in epileptic patients (Brazdil et al., 2002). Using a visual oddball task, these authors observed that medial temporal regions generated an ERN-like component (as well as a later positivity) to rare commission errors, with a similar latency (85–120 ms post-response) than the scalp ERN (simultaneously recorded at CPZ electrode sites in these patients). The authors suggested that mesio-temporal lobe, in addition to ACC, may constitute an integral component of the brain's error checking system (Brazdil et al., 2002), but their electrophysiological data provided no specific distinction between error monitoring processes in these different regions.

Here, we could further examine this issue by having the unique opportunity to record iLFPs concurrently from the left amygdala, left hippocampus, and left dorsal anterior cingulate gyrus in a rare patient (SG), who was implanted with depth electrodes concurrently in these regions prior to surgery (Fig. 1). Our patient performed a speeded go/nogo task with non-emotional stimuli, previously validated in healthy participants and specifically designed to study error monitoring functions in clinical populations (Vocat et al., 2008). We predicted that error-related activity in the dorsal anterior cingulate gyrus should share some electrophysiological characteristics with the scalp ERN (such as an early latency relative to motor execution, as well as a dominant theta and beta spectral content; see Debener et al., 2005; Luu, Tucker, & Makeig, 2004; van Veen & Carter, 2002), while a distinct pattern might arise in the amygdala, with early and/or later latencies (Hajcak & Foti, 2008). The unique combination of electrodes in patient SG allowed us to directly compare for the first time, in the same individual, the precise electrophysiological responses evoked by commission errors in these distant brain regions. Furthermore, to ensure that iLFPs recorded in these sites reflected local activity rather than electrical propagation from other nearby regions, SG also underwent an fMRI experiment during the same speeded go/nogo task, so as to confirm a differential involvement of the dorsal cingulate cortex and amygdala in error processing. Finally, because patient SG had all depth electrodes implanted in the left hemisphere, we also recorded iLFPs from the right amygdala and hippocampus in a second patient (Fig. 1) during the same go/nogo task, allowing us to verify whether the pattern of activity found in the left amygdala of SG could be replicated for the opposite (right) amygdala, or was instead specific for the left hemisphere, contralateral to the hand used to make key-press responses.

2. Methods

Our two patients (SG and VM) were examined by invasive intracranial EEG monitoring with depth and subdural electrodes, in the context of presurgical investigations, following the usual clinical procedure at Geneva University Hospital (Brodbeck, Lascano, Spinelli, Seeck, & Michel, 2009; Seeck & Spinelli, 2004). At the time of testing, both patients were free of any medication, according to a standard weaning protocol during the intracranial recordings. No seizure was observed during or between our recordings. In addition, patient SG also participated to an fMRI session, after removal of the electrodes. Because of clinical schedule, VM could not undergo fMRI.

2.1. *Case descriptions*

2.1.1. *Patient SG*

SG is a 39-year-old right-handed man suffering from complex partial seizures in the left temporal lobe. Several neuropsychological and clinical neurological exams showed normal cognitive functions and normal intelligence. He had febrile convulsions as a child (10 months old), and presented with episodes of faintness and loss of consciousness when 20 years old. In recent years, SG had many hyperkinetic seizures (up to 10 per month) which were characterized by an initial prickling of the upper right lip, interruption of current activities, language distortions (occasionally with swearwords), and finally complex motoric activities. During postictal periods,