NeuroImage xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

NeuroImage

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

Event-related potentials associated with performance monitoring in non-human primates

Jessica M. Phillips [a,b], Stefan Everling [a,b,c,*]

[a] Department of Physiology and Pharmacology, Western University, London, Ontario, Canada
[b] Brain and Mind Institute, Western University, London, Ontario, Canada
[c] Robarts Research Institute, London, Ontario, Canada

ARTICLE INFO

Article history:
Accepted 7 April 2014
Available online xxxx

Keywords:
Performance monitoring
Ne
ERPs
Monkeys
Error positivity

ABSTRACT

The abilities to monitor performance outcomes and, when appropriate, impose strategic adjustments in behavior, are core features of the intact human cognitive control system. Errors committed in choice reaction time tasks are typically followed by two scalp potentials, the error negativity (Ne) and error positivity (Pe). These components are considered physiological signatures of the performance monitoring system. Several theories have been proposed to account for these error-related potentials and their functional and behavioral significance. These ideas were inspired by empirical data in humans and other mammalian species, and supported by the results of experiments in which performance monitoring, in humans and computational models, was investigated. However, an appropriate animal model is required to rigorously test the predictions that arise from these theories. Here, using a variant of the anti-saccade task, we demonstrate that event-related signals recorded from macaque monkeys, following errors in choice, resemble the human Ne and Pe. These components were modulated by cognitive variables, namely the degree of cognitive control associated with the applied rule, which implies the existence of hierarchical error processing systems in monkeys, and the degree of response control associated with the saccade. Error-related potential amplitudes were also correlated with remedial action, in a rule-dependent manner. These results demonstrate that error-related potentials in macaque monkeys and human subjects show important similarities, thus supporting the use of the macaque monkey as an animal model for the neurophysiological study of performance monitoring, and potentially, post-error adjustments.

Introduction

Human cognition is fundamentally fallible (Gehring et al., 1993). Accordingly, an important facet of our cognitive control system is the capacity to monitor behavioral outcomes. When undesired or suboptimal outcomes are detected, cognitive control may be summoned by the performance monitoring system so that cognitive resources, and thus behavior, can be adjusted to improve future outcomes (Ridderinkhof et al., 2004). Since its discovery (Falkenstein et al., 1991; Gehring et al., 1993), the error negativity (Ne) has garnered significant interest in the field of cognitive neuroscience (Gehring et al., 2012). The Ne, a scalp potential that is elicited after erroneous responses in choice reaction time (RT) tasks, is thought to be an electrophysiological correlate of performance monitoring (Gehring et al., 2012), and may therefore be linked to the need to increase cognitive control. Consistent with this hypothesis, several authors have reported that the amplitude of the Ne correlates with post-error behavioral adjustments (Debener et al., 2005; Gehring et al., 1993; Ladouceur et al., 2007; Rodriguez-Fornells et al., 2002; West and Travers, 2008) such as post-error slowing (PES) (Rabbitt and Rodgers, 1977), which might be a result of a conscious effort to compensate for poor performance (Botvinick et al., 2001; Dutilh et al., 2012). However, this interpretation of PES is lacking support and has even been opposed in some cases (Gehring et al., 2012; Logan and Crump, 2010).

The Ne is evoked if subjects perform a response that should have been withheld (errors in action or "false alarms") (Scheffers et al., 1996), when subjects select the wrong response option (errors in choice) (Falkenstein et al., 1991; Gehring et al., 1993), and when subjects fail to respond before a temporal deadline (Luu et al., 2000), regardless of the effector used to respond in the task, or the modality in which stimuli are presented (Falkenstein et al., 1991; Gehring et al., 2012). This component is also sensitive to the emphasis placed on speed or accuracy during task performance (Arbel and Donchin, 2009; Falkenstein et al., 1995; Ganushchak and Schiller, 2006; Gehring et al., 1993; Hajcak et al., 2003; Ullsperger and Szymanowski, 2004) and in general, the degree of response control exercised by subjects (Pailing et al., 2002). The Ne is often followed by an error positivity (Pe)

Abbreviations: RT, reaction time; PES, post-error slowing; Pe, error positivity; SD, standard deviation; EC, correct trials preceded by an error; CC, correct trials preceded by a correct trial.

* Corresponding author at: Robarts Research Institute, 1151 Richmond Street North, London, Ontario N6A 5B7, Canada.
E-mail address: severlin@uwo.ca (S. Everling).

http://dx.doi.org/10.1016/j.neuroimage.2014.04.028
1053-8119/

(Falkenstein et al., 1991), a scalp component has not been studied or modeled to the same extent (Overbeek et al., 2005). Falkenstein and colleagues proposed that the Pe is actually one manifestation of an evoked P300 wave (Falkenstein et al., 1991), which is thought to reflect a generic response to behaviorally significant events Nieuwenhuis et al., 2005. These components are dissociable, and are thus assumed to reflect different monitoring-related processes (Arbel and Donchin, 2009; Bechara, 2004; Endrass et al., 2007; Gehring et al., 2012; Hajcak et al., 2003; Hester et al., 2005; Krigolson and Holroyd, 2007; Ladouceur et al., 2007; Luu et al., 2000; Nieuwenhuis et al., 2001; Overbeek et al., 2005; Ridderinkhof et al., 2009; Ullsperger, 2006; Vocat et al., 2008).

Several theories have been conceptualized to account for the mechanistic causes and functional significance of the Ne. Computational modeling and functional neuroimaging have provided some support for these ideas (for review, see (Gehring et al., 2012)), however it is not possible to rigorously test these proposals without the adoption of an appropriate animal model (Godlove et al., 2011). Due to the high cost of performance errors in many species, it has been proposed that error-monitoring systems have evolved over time (Gehring et al., 1993). This implies that a neural performance monitoring system should not be a unique feature of the human brain, and that the old world monkey could be a suitable model with which to study this system in detail. However, this has been a contentious issue (Godlove et al., 2011). This is largely a consequence of the accumulation of evidence (1) that the source of the Ne is the anterior cingulate cortex (ACC), and (2) for cytoarchitectonic and potential functional divergence for the human and monkey ACC (Cole et al., 2009, 2010). However, the results from several studies in both monkeys and humans have implicated other medial frontal cortical regions as putative sources of error-related potentials (Bonini et al., 2014; Scangos et al., 2013; Stuphorn et al., 2000).

Recently, Godlove and colleagues have provided the first evidence that macaque monkeys could be well-suited to facilitate investigations of the performance monitoring system (Godlove et al., 2011). This group employed the stop-signal task (Logan and Cowan, 1984), which evokes a Ne in human subjects (Endrass et al., 2005) after a failure to withhold a planned response (i.e., errors in action or false alarms). The authors demonstrated that non-canceled errors are indeed followed by both Ne and Pe components in macaque monkeys. Demonstration of these electrophysiological homologies for post-response ERPs in a variety of behavioral contexts, error types, and modalities (Gehring et al., 2012) would greatly aid in the widespread acceptance of the macaque monkey as a model system with which to examine the neural basis of performance monitoring. It should also be demonstrated that experimental manipulations to which the human Ne is known to be sensitive (Gehring et al., 2012) also alter this component in this candidate model system.

Here, we recorded EEGs from two macaque monkeys while they performed a variant of the anti-saccade task (Phillips and Everling, 2012; Phillips et al., 2013), which is known to evoke a robust Ne and Pe when human subjects fail to suppress a saccade toward a flashed peripheral stimulus (Endrass et al., 2007; Nieuwenhuis et al., 2001; Wessel et al., 2011). For anti-saccades, the errors of interest are known as direction errors, which may be categorized as *errors in choice* (i.e., the inappropriate response option is chosen) (Endrass et al., 2007). This particular task variant allowed us to extend the findings of Godlove et al. (2011) in several important ways, because the resultant behavior is associated with various unique categories of choice-related errors. First, we were able to compare error trials for saccades that were guided using differing levels of cognitive control (i.e., pro- and anti-saccade errors). As such, we were also able to investigate the relationship between error-related potential amplitudes and post-error slowing for these distinct error trial categories. Second, in this task variant, monkeys use two strategies to process trials (Phillips and Everling, 2012; Phillips et al., 2013). We have referred to responses generated using these different strategies as either "automatic" (fast, stimulus-triggered saccades) or "controlled" (slower, instruction-guided saccades). Thus, we were able to examine ERPs following errors produced under differing speed–accuracy priorities, which allowed us to probe the monkey error-related potentials for modulations that have been consistently reported in the human literature (Arbel and Donchin, 2009; Falkenstein et al., 1995; Ganushchak and Schiller, 2006; Gehring et al., 1993; Hajcak et al., 2003; Ullsperger and Szymanowski, 2004).

Materials and methods

Subjects

Two male macaque monkeys (*Macaca mulatta*), monkey B and monkey Q (weighing 10 and 8 kg, respectively), were subjects in this study. Experimental procedures advanced in accordance with the Canadian Council of Animal Care Policy on the Use of Laboratory Animals and a protocol approved by the Animal Use Subcommittee of the University of Western Ontario Council on Animal Care. Each animal was implanted with 16 low impedance electrodes, which were embedded in the skull. These electrodes were positioned over major dorsal cortical regions, based on stereotaxic coordinates (Paxinos et al., 2000) for EEG recordings (Godlove et al., 2011; Sander et al., 2010; Woodman et al., 2007).

Experimental design

We used an adaptation of an oculomotor switch task (Phillips and Everling, 2012; Phillips et al., 2013), the "saccade-overriding task" introduced by Isoda and Hikosaka (2007) (Fig. 1). The monkeys used two rules to generate saccades in response to a peripheral stimulus. The pro-saccade rule instructed the saccade to be directed toward the stimulus, while the anti-saccade rule instructed the saccade to be directed away from the stimulus, toward the opposite mirror position. The trials were presented in blocks, in which the rule repeated until the monkey had completed between 5 and 10 correct trials. Thus, the block transitions were unpredictable.

Each trial began with the presentation of an uninformative white fixation point (see Fig. 1). The monkey was required to direct his gaze toward this central point to initiate the trial. After a variable delay (750–900 ms), a stimulus was presented to the either left or right of the fixation point at 8° eccentricity. After a delay of 200 ms, the central point was replaced with a colored instruction cue that conveyed the rule on the current trial. A response was considered correct if a saccade was generated within 500 ms of instruction cue onset, if it fell within the appropriate target window (5° by 5°), and the endpoint was maintained for 80 ms. If these criteria were met, a liquid reward was delivered 400 ms after the saccade fell into the target window. If the monkeys' gaze left the fixation window prior to the onset of the instruction cue, the trial was considered an early response error and, accordingly, no reward was delivered.

Implant and surgery

A surgery was conducted for each monkey wherein electrodes were implanted for chronic EEG recordings. Ketamine hydrochloride (10 mg/kg i.m.) was used for initial sedation. Atropine (0.05 mg/kg s.c.) was also administered to reduce bradycardia and salivary secretions. Propofol was used to initiate (2.0 mg/kg i.v.) anesthesia, which was maintained with propofol (0.2 mg/kg/min i.v.) and midazolam (0.35 mg/kg/min i.v.). Heart rate, respiratory rate, blood oxygen, blood pressure and body temperature were monitored throughout the duration of the surgeries. The animals received a regime of antibiotics (cefazolin, 25 mg/kg i.m.) for a 10-day period following the surgeries. The analgesic buprenorphine hydrochloride (0.01 mg/kg i.m.) was also administered for 3 days postoperatively to alleviate any potential

Please cite this article as: Phillips, J.M., Everling, S., Event-related potentials associated with performance monitoring in non-human primates, NeuroImage (2014), http://dx.doi.org/10.1016/j.neuroimage.2014.04.028