Please cite this article in press as: Pas P et al. Striatal activity during reactive inhibition is related to the expectation of stop-signals. Neuroscience (2017), http://dx.doi.org/10.1016/j.neuroscience.2017.08.037

Neuroscience xxx (2017) xxx–xxx

STRIATAL ACTIVITY DURING REACTIVE INHIBITION IS RELATED TO THE EXPECTATION OF STOP-SIGNALS

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Abstract—Successful response inhibition relies on the suppression of motor cortex activity. The striatum has previously been linked to motor cortex suppression during the act of inhibition (reactive), but activation was also seen during anticipation of stop signals (proactive). More specifically, striatal activation increased with a higher stop probability. Here we investigate for the first time whether activation in the striatum during reactive inhibition is related to previously formed expectations. We used a modified stop-signal response task in which subjects were asked trial by trial, after being presented a stop-signal probability cue, whether they actually expected a stop to occur. This enabled us to investigate the subjective expectation of a stop signal during each trial. We found that striatal activity during reactive inhibition was higher when subjects expected stop signals. These results help explain conflicting findings of previous studies on the association between striatal activation and inhibition, since we demonstrate a crucial role of the subjects' expectation of a stop signal and thus their ability to prepare for a stop in advance. In conclusion, the current results show for the first time that striatal contributions to reactive response inhibition are, in part, related to subjective anticipation.

Key words: behavioral Control, FMRI, striatum, motor cortex, proactive inhibition, expectation.

INTRODUCTION

To successfully navigate the world, people often need to control habitual actions or stop them altogether. Broadly speaking, the inhibition of responses can be divided into reactive and proactive (Aron, 2011). Reactive inhibition describes the direct inhibitory response to a stimulus, while proactive inhibition involves the anticipation of having to stop in advance. This anticipation can be derived from past experiences or external cues (Chikazoe et al., 2009; Verbruggen and Logan, 2009; Vink et al., 2014, 2015b), and ordinarily leads to the slowing down of responses (Logan and Cowan, 1984). This interplay of expectancy and inhibition develops throughout childhood (Vink et al., 2014), and has been shown to be impaired in several psychiatric disorders, such as schizophrenia (Vink et al., 2015a).

Functional imaging studies have demonstrated that proactive inhibition involves activity in a network associated with stopping, including the supplementary motor area, dorsal premotor cortex, parietal cortex, right inferior frontal gyrus and the striatum (Vink et al., 2006; Chikazoe et al., 2008, 2009; Jahfari et al., 2010; Zandbelt and Vink, 2010; Duque et al., 2012; Zandbelt et al., 2012). The corpus striatum has been identified as a crucial region in inhibition. Its exact role is still unclear, as it has been implicated in both proactive processes leading up to response inhibition as well as reactive inhibition. Specifically, reactive inhibition during a stop-signal paradigm has been associated with increased activation in the striatum when comparing successful inhibition to failed inhibition trials (Vink et al., 2005). However, this activity has also been linked to an increase in stop-signal probability, with more activation when the probability of a stop-signal occurring was high (Zandbelt and Vink, 2010). Vink and colleagues (2015b) suggest that striatal activation during reactive inhibition is, in part, related to prior anticipatory processing of contextual cues.

To determine whether the striatum is more involved in reactive stopping or anticipatory processes preceding inhibition, it is necessary to investigate them separately. It is difficult to separate these two processes, as many tasks used in inhibition experiments rely on a single outcome measure, pressing a button or refraining from doing so, without taking the subjects' interpretation of a given cue into account. This makes it difficult to attribute a more specific role to the striatum, delineating effects stemming from formed expectations and successful performance on the task. For instance, subjects may interpret cues indicating chances of having to stop differently, depending on success or failure in previous trials. After a number of high-probability trials in succession without an actual stop-cue, the subsequent high-probability cue may hold more weight for a participant. People are known to be bad at predicting random events, known as naive statistics and the gambler's fallacy (Clotfelter and Cook, 1993).

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Abbreviations: 2D-EPI, two-dimensional echo-planar imaging; MRI, magnetic resonance imaging.

http://dx.doi.org/10.1016/j.neuroscience.2017.08.037
0306-4522/

The current study aims to investigate the role of the striatum during reactive response inhibition, and test whether its activation may in part reflect anticipatory processing triggered by previous contextual cues (Zandbelt and Vink, 2010). To achieve this we have modified a standard stop-signal response task (Vink et al., 2015b). A subjective measurement was added to the task after subjects were presented with the cue indicating stop-signal probability. Subjects were asked whether they expected a stop-signal to occur, using "yes", "no" or "don't know". With this subjective measurement, we could investigate the effect on proactive inhibition of both an objective stop-signal probability and the participant's interpretation of these cues. We previously found that subjective expectation yielded differences in striatal activation during the anticipatory period when presented with a cue indicating the probability of having to stop, with more striatal activity when subjects expected a stop-signal to subsequently occur (Vink et al., 2015b). Expecting stop-signals was also shown to aid successful inhibition, with a higher accuracy during expected stops. In our current study, we will use the same paradigm to investigate the role of the striatum during the response period of the task. This enables us to not only separate correct and incorrect responses, but also to differentiate expected and unexpected stops.

25 Healthy volunteers (20 males) performed a modified delayed-response stop-signal anticipation task while being scanned with functional MRI (Zandbelt et al., 2012). At the beginning of each trial, a cue is presented indicating stop-signal probability (0% or 50%), and subjects are asked to indicate whether or not they expect a stop-signal to occur (yes/no/don't know). We chose a 50% stop-signal probability to ensure a sufficiently high number of stops. After a variable delay following the cue, a stimulus is presented either requiring subjects to respond (go trials) or refrain from responding (stop trials). The effect of stop-signal probability and stop-signal expectation on brain activation during the stimulus–response period is investigated for both go trials and stop trials in the left and right striatum, and motor cortex, with regions of interest taken from (Zandbelt et al., 2011).

Hypotheses

Similar to previous work on inhibition performance on similar tasks (Zandbelt and Vink, 2010; Zandbelt et al., 2011), we expect to find differences in striatal and motor cortex activation when comparing correct and incorrect stops. Striatal activity during inhibition has been associated with accuracy (Vink et al., 2005; Zandbelt and Vink, 2010), and we have previously found that the subjective expectation of stop-signals also leads to higher striatal activation during the cue period (Vink et al., 2015b). In the current study, we will focus on the response period. With expected stops, subjects will rely on proactive processes that involve the striatum, better preparing them for response inhibition and slowing down their responses. We therefore anticipate finding more striatal activation when subjects expect a stop to occur, compared to unexpected stops. As the striatum is thought to modulate motor cortical responses, we also predict a corresponding diminished motor cortex activation for expected stops, compared to unexpected stops (Zandbelt and Vink, 2010).

EXPERIMENTAL PROCEDURES

Subjects

Twenty-five healthy volunteers (Age M = 21.6 years, SD = 2.7; 5 females) participated in the experiment. All subjects were right-handed, reported no history of psychiatric or neurologic disorders and gave written informed consent. The study was approved by the ethics committee of the University Medical Center Utrecht. This study conformed to the 2013 WMA Declaration of Helsinki.

Stop-signal anticipation task

Subjects performed a modified stop-signal anticipation task, in order to measure proactive and reactive inhibitory control (see Fig. 1). The task and experimental procedures were as described before (Vink et al., 2015b). In short, subjects are instructed to make timed responses to a moving bar (referred to as go trials). In some trials, the bar stops on its own (referred to as the stop-signal) and subjects have to refrain from responding. A cue is presented at the start of each trial indicating the probability that the bar will stop, either a '0' indicating no chance of a stop-signal occurring, or '*' indicating the possibility that a stop-signal could occur. Subjects were asked immediately after the cue to answer the question: 'Do you expect a stop-signal?' by pressing a button corresponding to 'yes' or 'no'. This provided us with information concerning the subjects' subjective stop-signal expectation. If subjects failed to respond within 1000 ms, the trial was coded as 'don't know'. Also, if subjects thought that the chance that the bar would stop was 50%, i.e. if they had no expectation at all, they were allowed to refrain from making a choice and the trial would continue in the same fashion. In total, 180 trials were presented, 60 trials with 0% stop-signal probability and 120 trials with a 50% stop-signal probability. These trials were ordered in a pseudo-random sequence that was fixed across subjects. Task difficulty was managed in a stepwise fashion, with a varying delay between the stop cue and the target depending on correct or incorrect trials. This ensured overall stop accuracy to be around 50% for each individual participant. The duration between stop-cue and target at which the participant is able to attain a 50% accuracy is known as the Stop-Signal Response Time (SSRT) (Logan and Cowan, 1984), and used as a measurement of inhibition performance.

Data acquisition

Imaging was performed on a 3.0 T Achieva whole-body magnetic resonance imaging scanner (Philips Medical Systems, Best, The Netherlands) at the University Medical Center Utrecht. The image acquisition parameters were identical to those described in (Vink et al., 2015b). In short, functional ($T2^*$-weighted) echo

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