NEUROSCIENCE
INTERNATIONAL BRAIN IBRO RESEARCH ORGANIZATION
RESEARCH ARTICLE
J. Yoshida et al. / Neuroscience xxx (2018) xxx–xxx

Area-specific Modulation of Functional Cortical Activity During Block-based and Trial-based Proactive Inhibition

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Abstract—Animals can suppress their behavioral response in advance according to changes in environmental context (proactive inhibition: delaying the start of response), a process in which several cortical areas may participate. However, it remains unclear how this process is adaptively regulated according to contextual changes on different timescales. To address the issue, we used an improved stop-signal task paradigm to behaviorally and electrophysiologically characterize the temporal aspect of proactive inhibition in head-fixed rats. In the task, they must respond to a go cue as quickly as possible (go trial), but did not have to respond if a stop cue followed the go cue (stop trial). The task alternated between a block of only go trials (G-block) and a block of go-and-stop trials (GS-block). We observed block-based and trial-based proactive inhibition (emerging in GS-block and after stop trial, respectively) by behaviorally evaluating the delay in reaction time in correct go trials depending on contextual changes on different timescales. We electrophysiologically analyzed task-related neuronal activity in the primary and secondary motor, posterior parietal, and orbitofrontal cortices (M1, M2, PPC, and OFC, respectively). Under block-based proactive inhibition, spike activity of cue-preferring OFC neurons was attenuated continuously, while M1 and M2 activity was enhanced during motor preparation. Subsequently, M1 activity was attenuated during motor decision/execution. Under trial-based proactive inhibition, the OFC activity was continuously enhanced, and PPC and M1 activity was also enhanced shortly during motor decision/execution. These results suggest that different cortical mechanisms underlie the two types of proactive inhibition in rodents.

Key words: rodent, cerebral cortex, proactive inhibition, stop-signal task, multi-neuronal recording.

INTRODUCTION

Proactive inhibition, a type of behavioral inhibition, delays the start of a behavioral response (i.e., reaction time) under a condition that may suddenly require suppression of the intended response (Verbruggen and Logan, 2008b; Aron, 2011; Jahanshahi et al., 2015b). This rational behavior is advantageous in that it allows the animal to reliably make the appropriate choice (i.e., execution or suppression of the response) by slowing reaction time. To date, stop-signal tasks have often been adopted to investigate behavioral inhibitions, including proactive inhibition (Vince, 1948; Lappin and Eriksen, 1966; Logan et al., 1984; Verbruggen and Logan, 2008b). In such tasks, subjects must typically respond quickly to a go cue (go trial), but if a stop cue, given randomly, follows the go cue, they must suppress the response (stop trial). Reaction time in a go trial is longer following a stop trial than following a go trial in humans (Riger and Gauggel, 1999), monkeys (Emeric et al., 2007; Nelson et al., 2010), and rodents (Mayse et al., 2014). This effect rapidly disappears within a few trials, suggesting that proactive inhibition can emerge in a trial-based change in context; hereafter, we refer to this as a "trial-based proactive inhibition". On the other hand, in humans, reaction time is longer during blocks of go trials with occasional stop trials than during blocks of only

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Abbreviations: M1, primary motor cortex; M2, secondary motor cortex; PPC, posterior parietal cortex; OFC, orbitofrontal cortex; frSST, free response stop-signal task.

https://doi.org/10.1016/j.neuroscience.2018.07.039
0306-4522/

Please cite this article in press as: Yoshida J et al. Area-specific Modulation of Functional Cortical Activity During Block-based and Trial-based Proactive Inhibition. Neuroscience (2018), https://doi.org/10.1016/j.neuroscience.2018.07.039

go trials (Verbruggen et al., 2005; Verbruggen and Logan, 2008a). Also, an instruction cue indicating the possibility of a stop trial (as a rule instruction) causes proactive inhibition in monkey and human (Chikazoe et al., 2009; Verbruggen and Logan, 2009; Zandbelt et al., 2013). These effects appear to last as long as the context continues. These observations suggest that proactive inhibition can emerge in a block/rule-based change in context; we refer to this as a "block-based proactive inhibition". Therefore, it is possible that proactive inhibition can be induced adaptively by contextual changes on different timescales.

Abnormalities in proactive inhibition have been reported in several human diseases in which the balance of behavioral execution and inhibition is impaired, e.g., parkinsonism (Jahanshahi et al., 2015a), Tourette's syndrome (Ganos et al., 2014), alcoholism (Hu et al., 2015), and eating disorders (Bartholdy et al., 2016). Accordingly, it is of great importance, pathophysiologically as well as physiologically, to elucidate the neural mechanism underlying proactive inhibition. Recent functional imaging studies in healthy subjects revealed that brain structures such as the cerebral cortex, striatum, and midbrain are involved in block-/rule-based proactive inhibition during stop-signal tasks (Vink et al., 2005; Chikazoe et al., 2009; Stuphorn and Emeric, 2012; Zandbelt et al., 2013; van Belle et al., 2014; Vink et al., 2015). In particular, proactive inhibition involves cortico-basal ganglia loops originating from different cortical areas, e.g., the premotor cortex, supplementary motor area, parietal cortex, and inferior frontal gyrus (for reviews, see Aron, 2011; Jahanshahi et al., 2015b; Meyer and Bucci, 2016). However, only a small number of studies attempted to clarify the neural mechanism of proactive or similar inhibition at the single-neuron level. For example, neuronal activity was electrophysiologically examined with regard to trial-based proactive inhibition in monkeys performing stop-signal tasks (Chen et al., 2010; Pouget et al., 2011; Stuphorn and Emeric, 2012), and post-error slowing, a delay in reaction following an error go response, in behaving rats (Narayanan and Laubach, 2008; Narayanan et al., 2013). Those studies never considered the differences in proactive inhibition according to contextual changes on different timescales. Consequently, it remains unknown whether the block- and trial-based types of proactive inhibition are regulated by common or distinct neuronal mechanism(s).

To address this issue, we established an improved version of the stop-signal task, which enabled us to evaluate the block-based (long timescale) and trial-based (short timescale) types of proactive inhibition separately in the same rats. Combining this behavioral task with multi-neuronal recordings, we observed different patterns of modulation of neuronal activity in the frontal and parietal cortical areas during proactive inhibition on different timescales.

EXPERIMENTAL PROCEDURES

Animals and surgery

All experiments were approved by the Animal Research Ethics Committee of Tamagawa University (animal experiment protocol H22/28-32), and were carried out in accordance with the Fundamental Guidelines for Proper Conduct of Animal Experiment and Related Activities in Academic Research Institutions (Ministry of Education, Culture, Sports, Science, and Technology of Japan) and the Guidelines for Animal Experimentation in Neuroscience (Japan Neuroscience Society). All surgical procedures were performed under appropriate isoflurane anesthesia, and all efforts were made to minimize suffering (see below). Our procedures for animal experiments were established in our previous studies (Isomura et al., 2009, 2013; Kimura et al., 2012, 2017; Saiki et al., 2014, 2018; Nonomura et al., 2017; Soma et al., 2017).

Seven adult Long-Evans rats (277 ± 29 g, males) were kept in their home cages under an inverted light schedule (lights off at 9 a.m.; lights on at 9p.m.). These rats were briefly handled by an experimenter (10 min, twice) before surgery. To attach a head-plate (CFR-2, Narishige, Tokyo, Japan) for head-fixation, animals were anaesthetized with isoflurane gas (4.5% for induction and 2.0–2.5% for maintenance, Pfizer Japan Inc., Tokyo, Japan) using an inhalation anesthesia apparatus (Univentor 400 anesthesia unit, Univentor, Zejtun, Malta), and then placed on a stereotaxic frame (SR-10R-HT, Narishige). For local anesthesia, lidocaine (AstraZeneca, Osaka, Japan) was administered around the surgical incisions. Reference and ground electrodes (Teflon-coated silver wires, A-M systems, WA, USA; 125 μm in diameter) were implanted above the cerebellum. During anesthesia, body temperature was maintained at 37 °C using an animal warmer (BWT-100, Bio Research Center, Tokyo, Japan). Analgesics and antibiotics were applied postoperatively as required (meloxicam, 1 mg/kg s.c., Boehringer Ingelheim Japan, Tokyo, Japan; gentamicin ointment, 0.1% us. ext., MSD, Tokyo, Japan). After recovery from surgery (6 days later), the rats were deprived of drinking water in their home cage, but they were able to obtain a sufficient amount of water as rewards for daily task performance. If necessary, the rats were provided an agar block (containing 15 ml water) to maintain > 80% of their original body weight. Food was available in the home cage *ad libitum*.

Behavioral task

To examine proactive inhibition, we established the free response stop-signal task (frSST) (Fig. 1A), in which rats could easily learn to perform go and stop responses adaptively in a head-fixed condition. In the frSST, the rats had to correctly manipulate a "spout-lever" (an operandum unified with a reward; Kimura et al., 2012) with their right forelimb under head-fixation to acquire reward water from the tip of the spout-lever. The spout-lever was movable horizontally (full range 12 mm; positions defined as follows: 0% for front end, 100% for rear end). We defined the 'push' area as the range 0–20%, the 'hold' area as 65–79%, the 'lick' area as 80–100% (Fig. 1A, left). For data analysis, we defined the push-reaction border as 50%, and the pull-reaction border as

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