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Research report

The right angular gyrus controls spontaneous eyeblink rate: A combined structural MRI and TMS study

Tamami Nakano [a,b,*]

[a] Graduate School of Frontier Biosciences, Osaka University, Suita, Osaka, Japan
[b] Graduate School of Medicine, Osaka University, Suita, Osaka, Japan

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ABSTRACT

Spontaneous eyeblink rates vary greatly between people, from several to a few dozen blinks per minute. Nevertheless, it remains unknown which brain region controls generation of spontaneous eyeblinks. To investigate this issue, the present study examined brain anatomy, which reflects inter-individual variability in eyeblink rate using structural magnetic resonance images with voxel-based morphometry (VBM) in 57 participants. The gray matter volume of the right angular gyrus (rAG) was positively associated with an increased eyeblink rate. Next, we examined whether eyeblink rate decreased when activity in the rAG was disrupted by transcranial magnetic stimulation (TMS) with a protocol of continuous theta burst stimulation: TMS of the rAG decreased eyeblink rate by 16%. In contrast, sham stimulation did not significantly affect eyeblink rate. The results from the structural MRI and TMS experiments suggest that the rAG is involved in controlling the generation of spontaneous eyeblinks in humans.

1. Introduction

People spontaneously generate an eyeblink every few seconds, averaging 20 blinks per minute. It is generally accepted that eyeblinks are necessary for ocular lubrication, but spontaneous eyeblinks actually occur several times more frequently than necessary for lubrication (Doane, 1980). Thus, the functional role of most spontaneous eyeblinks is unknown.

Blink rate varies with the level of attention and arousal (Stern, Walrath, & Goldstein, 1984). Moreover, spontaneous blinks tend to occur at attentional breakpoints, such as the end of a sentence while reading (Hall, 1945), a pause in speech while listening to someone talk (Nakano & Kitazawa, 2010), and during implicit breakpoints while viewing videos (Nakano, Yamamoto, Kitajo, Takahashi, & Kitazawa, 2009). These behavioral phenomenon indicate that internal

* *Corresponding author*. Dynamic Brain Network Laboratory, Graduate School of Frontier Biosciences, Osaka University, 1-3 Yamadaoka, Suita, Osaka 565-0871, Japan.
E-mail address: tamami_nakano@fbs.osaka-u.ac.jp.
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information processing must modulate the time and frequency of the spontaneous eyeblink generation.

An important clue for elucidating the neural mechanisms of spontaneous eyeblinks is the large inter-individual variability in blink rate, ranging from several to a few dozen blinks per minute (Nakano, Kuriyama, Himichi, & Nomura, 2015; Ponder & Kennedy, 1928). Several previous studies have reported that dopamine activity in the basal ganglia affects spontaneous eyeblink rate. Exposure to dopamine agonists immediately increases blink rate in monkeys and humans (Karson, 1983; Karson, Staub, Kleinman, & Wyatt, 1981). Blink rate correlates positively with dopamine levels in the basal ganglia of monkeys (Taylor et al., 1999). Moreover, patients with Parkinson's disease, which leads to dopamine deficiency in the basal ganglia, often show a lower than normal blink rate (Karson, 1983; Karson et al., 1981). When the basal ganglia receive an input from the cerebral cortex, it activates brainstem blink circuits through an inhibitory input to the superior colliculus (Basso, Powers, & Evinger, 1996). Thus, individual variability of dopamine levels in the basal ganglia may affect the level of gating for blink generation. Patients with Parkinson's disease exhibit pervasive movement disorders such as shaking, rigidity, slowness of movement, and difficulty walking. Nevertheless, there is no report that the variability in the blink rate in healthy people correlates with the performance of other movements. These observations raise the possibility that other factors may also contribute to the large inter-individual variability in blink rate.

To generate an eyeblink voluntarily, the cerebral motor areas including frontal eye field (FEF) and cingulate motor area send commands for motor initiation to the basal ganglia (Hanakawa, Dimyan, & Hallett, 2008; Kato & Miyauchi, 2003). Nevertheless, these brain regions do not show any activation related to spontaneous eyeblinks. In contrast, our previous investigations demonstrate that a distributed cortical area including the default-mode network and hippocampus show activation related to spontaneous eyeblinks while viewing a video (Nakano, 2015; Nakano, Kato, Morito, Itoi, & Kitazawa, 2013). A previous clinical case study consistently reported that a patient with a lesion of the angular gyrus (AG), a major component of the default-mode network, seldom generates eyeblink spontaneously (Watson & Rapcsak, 1989). In addition, microelectronic stimulation of the macaque homolog of the AG induced eyeblinks in monkeys (Shibutani, Sakata, & Hyvarinen, 1984). Thus, we speculate that some of these cortical regions are involved in the generation of spontaneous eyeblinks and are responsible for the inter-individual variability in blink rate.

To test this hypothesis, the present study first examined which brain regions correlated with individual variability in the rate of spontaneous eyeblink by using voxel-based morphometry (VBM) in 57 healthy participants. Next, we investigated a causal relationship between spontaneous eyeblink rate and the brain region identified by VBM: spontaneous eyeblink rate by disrupting neural activity in this region using transcranial magnetic stimulation (TMS) with a protocol of continuous theta burst stimulation (cTBS).

2. Methods and materials

2.1. Structural MRI study

2.1.1. Participants

The VBM study involved 57 volunteers (28 females, mean ± S.D. age, 22.1 ± 1.3 years) who had previously participated in MRI experiments conducted by our laboratory and allowed use of their T1-weighted anatomical images in this study. The sample size number matched the estimation of sample size ($n = 55$) calculated using a strict power level of .99, an error probability of .05, and an anticipated correlation value of .5. All participants provided written informed consent for participation. The present study was approved by the ethics committee of Graduate School of Frontiers and Biosciences, Osaka University. The study was also conducted in accordance with the Declaration of Helsinki.

2.1.2. Task

To keep arousal and attentional levels at a similar level among participants, the spontaneous eyeblink rate for each participant was measured while they viewed a video taken from the British TV comedy "The Best Bits of Rowan Atkinson in Mr. Bean" (2004, Universal Studios) for 30 min. Participants were informed that their eye movements would be measured while watching the video. They were not told that their blinking was being measured. Eyeblink behavior of 42 participants was monitored using a near-infrared eye-tracking system (NAC Image Technology, Japan) with a sampling rate of 240 Hz. Using a procedure developed in previous eyeblink studies in our laboratory, each eyeblink was detected automatically according to the combination of a rapid decrease in pupil size followed by an increase within 400 msec (Nakano et al., 2013). Eyeblink behavior of an additional 15 participants was monitored using a vertical electro-oculogram (EOGs) systems (BIOPAC150, USA) with a sampling rate of 1000 Hz, in which two active surface electrodes were attached to the skin above and below the left eye, with the reference electrode on the left ear lobe. Each eyeblink was detected based on the same analysis techniques used in our previous studies by the combination of a rapid decrease in participants' EOG signals followed within 400 msec by an increase (Nakano et al., 2009). Because blinking is obvious behavior involving a salient and distinguishable change in both pupil diameter and EOG signals, the blink rates obtained from two different measurements were combined in the present study.

2.1.3. MRI Acquisition and image analysis

Structural brain images were collected for each participant using a T1-weighted 3D MP-RAGE sequence on a Siemens 3-T whole-body scanner (TR = 2 sec, TE = 4.38 msec, flip angle = 8°, field of view = 256 mm, resolution = 1 mm × 1 mm × 1 mm). Image and statistical analyses were performed using the VBM in SPM12 (statistical parametric mapping package, UCL), implemented in MATLAB R2015a (MathWorks, USA). First, the brain images were automatically reoriented to AC-PC line, and segmented into gray matter, white matter and cerebrospinal fluid. Next, a customized template was created based on the gray matter segmentations using a diffeomorphic anatomical registration method