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The developmental relationship between central dopaminergic level and response inhibition from late childhood to young adulthood

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ABSTRACT

Dopamine (DA) is known to modulate response inhibition (RI). In contrast to the abundant adult studies, only few developmental studies have focused on this topic. Moreover, the mechanism underlying the modulation of RI by the DA system from childhood to adulthood remains unclear. We aimed to assess whether the relationship between DA and RI during late childhood and young adulthood is similar. Accordingly, DA function was measured using the spontaneous eye blink rate (EBR), whereas RI ability was tested using the Go/Nogo task. Experiment 1 included 149 adults (age range, 18–25 years) who completed the EBR test and the Go/Nogo task; the results showed that higher EBR was associated with lower commission error in the Nogo trials. Experiment 2 included 45 children (age range, 10–12 years) and 37 adults (age range, 18–19 years) who completed the EBR test and Go/Nogo tasks (similar to experiment 1); in both the child and adult groups, higher EBR was related to better RI ability. As EBR is closely related to central DA function, these findings suggest that DA plays a similar role in the processing of RI in late childhood and young adulthood.

1. Introduction

Response inhibition (RI) refers to the inhibition of prepotent responses or events (Barkley, 1997), and involves a choice between action and non-action (Rubia et al., 2001). Dopamine (DA) is an important neurotransmitter in the brain that modulates RI processing (Padmanabhan and Luna, 2013). Studies have shown that individuals with higher DA function have better behavioral performance on RI tasks, higher inhibition-related brain activation, and a larger inhibition-related event-related potentials (ERPs) component, all of which reflect better RI ability (Albrecht et al., 2014; Ghahremani et al., 2012; van Bochove et al., 2013; Zhang et al., 2015; Zhang et al., 2016). With regard to the underlying mechanism, some studies have proposed that DA modulates the processing of RI through the frontal-striatal neural circuitry (Acheson et al., 2015; Albrecht et al., 2014; Ghahremani et al., 2012). For example, in the frontal-striatal motor loop involved in the Go/Nogo task,[2] the supplementary motor area (SMA) sends excitatory glutamatergic input through the dorsal striatum to the ventrolateral thalamus, which projects back to the SMA. In this loop, the dorsal striatum would have either excitatory (dopamine D1 receptor, DRD1) or inhibitory (dopamine D2 receptor, DRD2) influences on striatal firing, which mediates SMA activity (Acheson et al., 2015).

However, in contrast to the amount of adult studies, far fewer studies have focused on the relationship between DA and RI in children and adolescents; moreover, the invasive methods generally used in adult populations (positron emission tomography [PET] or medication) typically cannot be used to study developing populations (Padmanabhan and Luna, 2013). Nevertheless, the fact that the spontaneous eye blink rate (EBR) has been non-invasively confirmed to indirectly reflect the central DA activity (Bodfish et al., 1995; Karson, 1983; Shukla, 1985; Eckstein et al., 2016; Jongkees and Colzato, 2016; Slaghter et al., 2015), which begins during the fetal period, increases rapidly during childhood and adolescence, and then stabilizes during adulthood (Bacher, 2014; Cruz et al., 2011).

Previous pharmacological studies showed that EBR could be altered by both DRD1 and DRD2 agonists/antagonists (Blin et al., 1990; Groman et al., 2014; Jutkiewicz and Bergman, 2004; Kleven and Koek, 1996; Lawrence and Redmond, 1991; Taylor et al., 1999); however one recent PET study showed that EBR was more strongly related to the DRD2 system (Groman et al., 2014). Besides, the EBR is also associated with dopamine D4 7-repeat allele (Dreisbach et al., 2005) and behavioral interventions (rewards and acute exercise) could also alter the EBR (Aarts et al., 2012; Cooper, 1973). In contrast to healthy controls, DA

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[2] The Go/Nogo task is a classical RI task that requires a response to be made when a frequently occurring "Go" is presented, but withheld when a less frequent "Nogo" stimulus is presented (Cragg and Nation, 2008).

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dysfunction could cause increased or decreased EBR in children with immunodeficiency syndrome, fragile X syndrome, ADHD, and iron deficiency anemia, as well as in adults with schizophrenia and Parkinson disease (Chen et al., 2003; Colzato et al., 2008; Dauer and Przedborski, 2003; Freed, 1980; Gauggel et al., 2004; Howes and Kapur, 2009; Kegeles et al., 2010; Lozoff, 2011; MacLean et al., 1985; Roberts et al., 2005; Volkow et al., 1999; Vreugdenhil et al., 1997). Thus, for the evidence of the association between EBR and DA (maybe, in particular the striatal DRD2 system) abovementioned, it is possible to assess the developmental relationship between DA and RI by testing EBR (Eckstein et al., 2016).

Thus far, recent studies have shown that higher EBR is related to better performance on RI tasks in adults and children. In adult studies, Zhang et al. (2015) found that the higher accuracy of the Nogo-trials in the Go/Nogo task was related to higher EBR; van Bochove et al. (2013) showed that the occurrence of spontaneous blinks in one trial predicted the exertion of greater conflict control on the subsequent trial in the flanker task. However, some reports have been inconsistent. Colzato et al. (2009) tested inhibition through a stop-signal task, and found that better inhibition is related to reduced EBR. Moreover, Zhang et al. (2016) showed that EBR was positively correlated with the N2 amplitude of Nogo-trials, instead of the accuracy of the Nogo-trials in the Go/Nogo task in a small sample. In contrast, in child studies, Lozoff and colleagues found that children aged 10 years with iron-deficiency anemia had decreased DA function and lower EBR, as compared to healthy controls (Algarín et al., 2013), and that the accuracy in the Nogo trials in the Go/Nogo task was lower in children with iron-deficiency anemia than in healthy controls (Lozoff, 2011). As the EBR and performance in the Go/Nogo tasks were not simultaneously examined in the 2 abovementioned studies, it could only be inferred that the higher EBR was related to better RI ability in children. Furthermore, Lackner et al. (2010) explored the correlation between the EBR in children aged 3–5 years and their RI ability; this correlation was found to be positive, but marginally significant.

In brief, according to the abovementioned studies, it can be inferred that the central DA activity reflected by EBR might have a similar relationship with RI in children and adults. This inference is consistent with the development of the brain. From the late childhood to the adolescent period, the thickness of the cortex in the brain increases, and synaptic pruning—referring to the selective elimination of unnecessary neuronal connections—occurs (particularly in the prefrontal cortex [PFC]); both these actions could increase the efficiency of individuals in RI tasks (i.e. smaller response time and higher accuracy) (Cragg and Nation, 2008; Luna and Sweeney, 2004; Luna et al., 2015). These 2 changes are reportedly closely related to DA. For example, recent studies have shown that cortex thickness is positively related to striatal DA activity (Casey et al., 2013; Choi et al., 2016; Fernández-Jaén et al., 2016; Morales et al., 2015), and that synaptic pruning is partly modulated by DA activity through the GABAergic neurons (Thompson et al., 2004). As DA activity in the PFC and striatum increases from late childhood to adulthood (Padmanabhan and Luna, 2013; Thompson et al., 2004), the increase in DA activity would promote the refinement of the brain structure, along with the improvement of the efficiency in RI task; therefore it would lead to better RI in individuals with higher DA. Hence, the inference that children and adults have similar relationships in terms of the association between higher EBR and better RI, is reasonable.

However, due to the limitations of previous studies, this interference should be more directly and strongly verified in a study wherein children and adult participants are simultaneously recruited and the same paradigm of RI tasks is adopted in the 2 groups. Accordingly, in the present study, we aimed to explore the relationships between DA system activity (measured using EBR) and RI (measured using the Go/Nogo task) in children and adults in 2 experiments. In experiment 1, we primarily sought to validate the relationship between EBR and Go/Nogo task performance observed in the study by Zhang et al. (2015) of a large sample of young adults. Furthermore, in experiment 2, we compared the relationships between EBR and the performance on the Go/Nogo task in children (aged 10–12 years) and young adults (aged 17–19 years). Based on previous findings, we hypothesized that individuals with higher and lower EBR would exhibit a better and poorer RI ability, respectively, in the late childhood group and young adult group.

2. Experiment 1

2.1. Participants

In experiment 1, we enrolled 149 healthy Chinese participants (70 men and 79 women) aged between 18 and 25 years from Southwest University (mean age, 22.56 years; standard deviation (*SD*), 1.27 years). Among these participants, 61 were involved in a previous study (Zhang et al., 2015) and 88 were new recruits. Prior to the experiment, the participants were asked to complete a questionnaire, which indicated that none of the participants smoked, took psychoactive drugs, had mental disease, had flu symptoms, wore contact lenses, and had coffee or tea or alcoholic beverages before the experiment on the experimental day.

2.2. Ethics statement

The experiment was approved by the institutional review board of the Faculty of Psychology of Southwest University. All the participants read and signed an informed consent form prior to participation and received financial compensation (20 Yuan, RMB) for their participation after the experiment.

2.3. Procedure

The participants underwent an EBR test and thereafter completed the Go/Nogo task. The examinations were administered through a Dell desktop PC with a 14.1-inch monitor and a display resolution of 1920 × 1080 pixels. The background color of all the stimuli was gray. The participants responded using a keyboard.

2.3.1. EBR test

Given that the EBR increases with an increase in the arousal and fatigue levels as well as in the evening (Barbato et al., 2000; De Paova et al., 2009), the participants underwent the EBR tests between 9:00 A.M. and 5:30 P.M.; moreover, the participants were asked to rest until they felt energetic or were given the option to participate in the experiment on another day in case they felt tired before the experiment. During the EBR test, the participants were seated in front of a computer screen, located at a distance of approximately 1 m. They were asked to look at a black cross (4 × 4 cm) displayed at the center of the computer screen, while in a relaxed state.

The eye blinks were recorded using the Brain Product System and were analyzed through 4-min eye-open segments by using a Brain Vision Analyzer (Brain Products GmbH, Munich, Germany). A total of 4 Ag–AgCl electrodes were used to record eye movement. A vertical electrooculogram (EOG), which recorded the voltage difference between the 2 electrodes placed above and below the left eye, was used to detect the eye blinks. A horizontal EOG, which recorded the voltage difference between the electrodes placed lateral to the external canthi, was used to measure horizontal eye movement (Colzato et al., 2009). An eye blink was defined as a waveform that includes an upward deflection, followed by a downward deflection that crosses the zero baseline. The time duration between the upward and downward deflection is no more than 400 ms; and the voltage change between them is more than 100 μV (Barbato et al., 2000). Individual EBR values were calculated by dividing the number of eye blinks that occurred during the 4-min measurement into 4 intervals (Colzato et al., 2009; Chermahini & Hommel, 2010).