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The neurochemical basis of the contextual interference effect

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ABSTRACT

Efficient practice organization maximizes learning outcome. Although randomization of practice as compared to blocked practice damages training performance, it boosts retention performance, an effect called contextual interference. Motor learning modulates the GABAergic (gamma-aminobutyric acid) system within the sensorimotor cortex (SM); however, it is unclear whether different practice regimes differentially modulate this system and whether this is impacted by aging. Young and older participants were trained on 3 variations of a visuomotor task over 3 days, following either blocked or random practice schedule and retested 6 days later. Using magnetic resonance spectroscopy, SM and occipital cortex GABA+ levels were measured before and after training during the first and last training days. We found that (1) behavioral data confirmed the contextual interference effects, (2) within-day occipital cortex GABA+ levels decreased in random and increased in blocked group. This effect was more pronounced in older adults; and (3) baseline SM GABA+ levels predicted initial performance. These findings indicate a differential modulation of GABA levels across practice groups that is amplified by aging.

1. Introduction

Learning new motor skills is essential across the lifespan. Practice characteristics (e.g., practice type and frequency, feedback, and practice organization) are the most prominent factors affecting skill learning outcome (Kantak and Winstein, 2012; Magill, 2010; Schmidt and Lee, 1999; Wulf and Shea, 2002). Extensive research has focused on determining which practice conditions can lead to enhanced motor skill learning and better long-term retention (Guadagnoli and Lee, 2004). This is particularly important in the context of aging because the capacity to improve motor skills is diminished with aging, although the current highly dynamic society requires lifelong learning (Desrosiers et al., 1999; Fozard et al., 1994; King et al., 2013). Hence, optimizing training protocols to facilitate skill learning is of utmost importance.

Converging evidence from learning studies has shown that although randomization of practice of a set of skills as compared to blocked practice induces inferior performance during the acquisition phase, it boosts subsequent retention performance, an effect called contextual interference (CI) (Wright et al., 2016). In spite of reports of age-related decline in motor performance and skill acquisition (Seidler et al., 2010; Swinnen, 1998), it has been shown that older adults benefit from the CI effect to a similar degree as their younger counterparts (Lin et al., 2012; Pauwels et al., 2015).

Despite the large interest in the CI effect, very little is known about its underlying neural correlates [for a review see Lage et al. (2015)]. Functional magnetic resonance imaging (fMRI) studies have suggested higher frontoparietal activity, particularly in the primary motor cortex, premotor cortex, and supplementary motor area, in random as compared to blocked practice of motor sequence tasks (Cross et al., 2007; Lin et al., 2011; Wymbs and Grafton, 2009). Furthermore, it has been reported that random practice promotes neural plasticity in both young adults (YAs) and old adults (OAs), although the training-induced brain activation changes differ between these groups (Lin et al., 2012).

Synaptic plasticity is the underlying neurophysiological basis of learning, and it highly relies on the balance between excitation and inhibition networks in the brain (Carcea and Froemke, 2013; Dorrn et al., 2010). It has been shown that regulation of gamma-aminobutyric acid (GABA), the primary inhibitory

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neurotransmitter in the brain (McCormick, 1989), plays a key role in shaping and controlling neural excitation and maintenance of the excitatory-inhibitory balance (Brunel and Wang, 2003; Buzsáki et al., 2007). In this regard, it has been shown that modulation in the GABAergic system plays a key role in motor cortical long-term potentiation–like plasticity (Ballini et al., 2008) and motor learning (Floyer-Lea et al., 2006; Rosenkranz et al., 2007; Ziemann et al., 2001). So far, 2 studies have used the transcranial magnetic stimulation (TMS) technique to quantify modulations in the motor cortical excitatory-inhibitory balance and compare it across different CI practice schedules. Lin et al. reported decreases in short-interval intracortical inhibition, which is considered an indirect measure of $GABA_A$ activity, and increases in motor cortical excitability in response to random as compared to blocked practice, which was more pronounced in OAs than YAs (Lin et al., 2011, 2012). In contrast, Coxon et al. reported greater motor cortical disinhibition in a blocked as compared to a random group (Coxon et al., 2014). Although these TMS studies suggest differential modulations in the motor cortical excitatory-inhibitory balance in different practice schedules, measures of GABA levels within prominent brain areas obtained using novel magnetic resonance techniques could complement and shed new light on these findings.

Edited magnetic resonance spectroscopy (MRS) enables noninvasive and accurate quantification of regional concentration of GABA (Mescher et al., 1998). So far, only 2 studies have used MRS to investigate motor learning-induced changes in GABA levels within the sensorimotor cortex (SM). Floyer-Lea et al. (2006) reported a rapid decrease in GABA levels following learning a force reproduction tracking task. Sampaio-Baptista et al. (2015) investigated long-term modulation of GABA levels in low- and high-intensity practice groups, who trained on a juggling task for 6 weeks. Their findings indicated a decrease in GABA levels in the low-intensity but not in the high-intensity group. To the best of our knowledge, no study has made use of MRS measures of GABA to investigate the CI effect in motor learning. Furthermore, because an age-related decline in regional GABA levels has been reported in previous animal and human studies (Gao et al., 2013; Grachev and Apkarian, 2001; Porges et al., 2017), it remains to be investigated whether aging affects the neurochemical modulation during CI practice schedules.

In the present study, YAs and OAs were trained on a visuomotor bimanual tracking task following either a blocked or a random practice schedule. MRS data from 2 voxels of interest, SM and the occipital cortex (OCC), were collected before and after the training session during the first and last day of training. We investigated (1) whether involvement in the different practice schedules differentially modulated training-induced GABA levels and (2) whether the potential training-induced GABA modulations were age-dependent. In view of the neurochemical-behavioral associations, we assessed whether baseline GABA levels and/or training-induced changes in GABA levels predicted performance and/or learning outcome. Based on results of previous motor learning studies (Floyer-Lea et al., 2006; Sampaio-Baptista et al., 2015), we expected to find a general learning-related decrease in GABA levels within the SM in both practice groups. However, as previous studies investigating the neural correlates of the CI effect reported that greater neuroplastic changes occur in the random as compared to blocked practice group (Lin et al., 2011, 2012), we expected to find a more pronounced GABA decrease in the random as compared to blocked practice group. Previous MRS studies using tasks without crucial visual processing requirements have considered OCC as a control voxel (Levy et al., 2002; Puts et al., 2011). However, this bimanual tracking task involves substantial processing of visual information (Beets et al., 2015; Santos Monteiro et al., 2017), so the visual areas are critically engaged during the task execution. In addition, random as compared to blocked practice is accompanied with more elaborate processing of afferent information as a result of shifting between task variants from one trial to another (Pauwels et al., 2018). Therefore, we anticipated that random practice would recruit visual processing regions to a larger extent, resulting in greater modulations in GABA levels within the OCC voxel.

With respect to aging, we expected that OAs, as compared to YAs, have lower baseline GABA levels within both voxels (Gao et al., 2013; Grachev and Apkarian, 2001). However, as increased brain activity is typically observed in OAs as compared to YAs during performance of motor tasks in general (Goble et al., 2010; Heuninckx et al., 2005, 2008; Van Impe et al., 2013) as well as during acquisition of a bimanual tracking task similar to the one used here (Santos Monteiro et al., 2017), we anticipated greater modulations in GABA within both voxels in OAs. With regard to neurochemical-behavioral correlates, we hypothesized that baseline GABA levels would predict initial performance (Kim et al., 2014; Stagg et al., 2011) and that learning-induced changes in GABA levels would predict learning outcome (Kim et al., 2014; Stagg et al., 2011). This is the first time that the modulation of MRS-derived GABA concentration and its age-related mediation is studied in the context of CI.

2. Materials and methods

2.1. Participants

Thirty-two YAs (21.8 ± 1.8 years; range 18–27 years) and 28 OAs (mean = 66.5 ± 4.1; range 60–74 years) participated in this study. Within each age group, participants were randomly assigned to 1 of the 2 CI practice conditions: (1) blocked practice or (2) random practice. Consequently, 4 different groups were tested: YA-blocked, YA-random, OA-blocked, and OA-random. Participants had normal or corrected-to-normal vision and reported no history of neurological disease or psychiatric disorders. Handedness was assessed using the Oldfield Handedness scale (Oldfield, 1971). Hand laterality scores did not differ between the practice conditions within each age group [YA: $p = 0.478$; OA: $p = 0.103$]. In addition, the Montreal Cognitive Assessment (Nasreddine et al., 2005) test was conducted to screen for mild cognitive impairment. The OAs were without any cognitive or motor impairment. Montreal Cognitive Assessment scores did not differ between practice schedule conditions within each age group (YA: $p = 0.800$; OA: $p = 0.303$). Participants were blind to the purpose of the experiment. Before testing, written informed consent was obtained from each participant. The protocol was approved by the local ethical committee of KU Leuven, Belgium, and was in accordance with the Declaration of Helsinki (2009).

2.2. Experimental procedure

The participants followed a training protocol consisting of 5 sessions in total (for an overview of the study protocol, see Fig. 1A). During the first session (Day 0), participants were screened for handedness, cognitive performance, and contraindication to magnetic resonance imaging (MRI). This was followed by a baseline test in a dummy scanner. Day 0 was followed by 3 days of practice, that is, Day 1, Day 2, and Day 3. For practical reasons, Day 1 and Day 2 were consecutive days, whereas there was 1 day of rest between Day 2 and Day 3. The first (Day 1) and the last (Day 3) days of practice were conducted in the actual MRI scanner, whereas the second day (Day 2) was performed in a dummy scanner. Finally, a delayed retention (DR) test was administered 6 days after the last day of practice in the actual MRI scanner without MRS scanning. A 6-day retention interval was chosen to make meaningful inferences