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Self-rated intensity of habitual physical activities is positively associated with dopamine $D_{2/3}$ receptor availability and cognition

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ABSTRACT

Between-person differences in cognitive performance in older age are associated with variations in physical activity. The neurotransmitter dopamine (DA) contributes to cognitive performance, and the DA system deteriorates with advancing age. Animal data and a patient study suggest that physical activity modulates DA receptor availability, but data from healthy humans are lacking. In a cross-sectional study with 178 adults aged 64–68 years, we investigated links among self-reported physical activity, D2/D3 DA receptor ($D_{2/3}$DR) availability, and cognitive performance. $D_{2/3}$DR availability was measured with [^{11}C]raclopride positron emission tomography at rest. We used structural equation modeling to obtain latent factors for processing speed, episodic memory, working memory, physical activity, and $D_{2/3}$DR availability in caudate, putamen, and hippocampus. Physical activity intensity was positively associated with $D_{2/3}$DR availability in caudate, but not putamen and hippocampus. Frequency of physical activity was not related to $D_{2/3}$DR availability. Physical activity intensity was positively related to episodic memory and working memory. $D_{2/3}$DR availability in caudate and hippocampus was positively related to episodic memory. Taken together, our results suggest that striatal DA availability might be a neurochemical correlate of episodic memory that is also associated with physical activity.

1. Introduction

Cognitive performance and its underlying brain structures and functions deteriorate in old age, although there are considerable differences between individuals (Lindenberger, 2014; Nyberg et al., 2012; Rönnlund et al., 2005). These differences may partly be due to lifestyle factors such as physical activity. Positive associations between habitual physical activity and cognitive performance have been observed in numerous observational studies (Bauman et al., 2016; Blondell et al., 2014; Boraxbekk et al., 2016; Memel et al., 2016; Prakash et al., 2015; Sofi et al., 2011; Willey et al., 2016). These findings are substantiated by results from intervention studies that have documented positive effects of exercise on cognitive performance in healthy elderly persons (Ahlskog et al., 2011; Carvalho et al., 2014; Düzel et al., 2016; Jonasson et al., 2016; Liu-Ambrose et al., 2008; Maass et al., 2015; P. J. Smith et al., 2010; Voss et al., 2014; but see Young et al., 2015) as well as in dementia patients (Farina et al., 2014; Groot et al., 2016; Heyn et al., 2004; but see Forbes et al., 2014). Thus, between-person differences in physical activity may partly account for differences in cognitive performance in aging. However, a number of important questions need further exploration, such as the relative importance of intensity and frequency of physical activity and the biological mechanisms that link physical activity to cognition.

Several intervention studies have shown that physical exercise affects the brain's structural integrity, with most evidence obtained for grey-matter volume (Colcombe et al., 2006; Erickson et al., 2011;

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Kleemeyer et al., 2016; Niemann et al., 2014), and with less evidence for white-matter volume (Colcombe et al., 2006; Erickson et al., 2014; Voelcker-Rehage and Niemann, 2013; Voss et al., 2013). Observational studies suggest that self-reported physical activities are positively related to grey matter volume, most consistently so to frontal (Flöel et al., 2010; McEwen et al., 2015; Rovio et al., 2010; Walhovd et al., 2014) and hippocampal (B. M. Brown et al., 2014; Demirakca et al., 2014; Killgore et al., 2013) volume.

Physical exercise also affects the brain's neurotransmitters, especially monoamines such as DA (Lin and Kuo, 2013). Acute effects of exercise on increased release of DA in striatum have been shown in rodents (Meeusen et al., 1997), but did not replicate in a study on humans (Wang et al., 2000). Also effects of long-term exercise regimes have been reported in rodents; an early study found enhanced $[^3H]$spiperone binding at $D_{2/3}$DR's in striatal post-mortem tissue of rats that had completed a 12 weeks of motorized treadmill training as compared to non-training rats (Gilliam et al., 1984). Furthermore, endurance training increased D_2DR receptor density in striatum of rodents in another study using the same marker and measuring DA levels and metabolites (MacRae et al., 1987). A recent study in rats demonstrated that the beneficial effect of voluntary exercise on learning was disrupted by infusion of a D_2-antagonist into the striatum (Eddy et al., 2014), suggesting D_2 receptor-dependent signalling in striatum as a mediator of exercise-related effects on cognition in these animals. Also, cortical levels of DA are elevated after four weeks of running-wheel exercise in wild-type rats, but not in animal models of Huntington's disease in which the DA system is disrupted (Renoir et al., 2011). Animal studies of Parkinson's disease (PD) have shown that exercise decreases PD symptoms and counteracts the detrimental effects of neurotoxins that are used to induce the disease in the animal models (Gerecke et al., 2010; Mabandla et al., 2004; Tajiri et al., 2010; Yoon et al., 2007). In line with this pattern, a recent exercise intervention study in humans documented increased $D_{2/3}$DR BP_{ND} in abstinent methamphetamine users that completed an 8-week exercise training program (n = 10) as compared to a control group (n = 9) with the same diagnose residing in the same treatment facility (Robertson et al., 2016). This study suggests that striatal dopaminergic deficits related to methamphetamine addiction might be ameliorated by physical exercise. Epidemiological studies have found associations between physical activity and reduced risk for PD (Xu et al., 2010; Chen et al., 2005; Thacker et al., 2008), suggesting a protective effect of physical activity.

Moreover, because DA is involved in human higher-order cognitive functions, such as episodic memory (Bäckman et al., 2011; Bäckman et al., 2010; Bäckman et al., 2006; Cervenka et al., 2008; Lisman et al., 2011; Nyberg et al., 2016; Shohamy and Adcock, 2010) and working memory (Cools & D'Esposito, 2011; Liggins, 2009; Takahashi, 2013; Takahashi et al., 2008), beneficial effects of physical activity on cognitive performance may be related to the effects of physical activity on DA functioning. In a previous publication using data from the Cognition, Brain, and Aging (COBRA) study, we observed, in a large age-homogeneous sample with 181 participants, that $D_{2/3}$DR availability in caudate nucleus and hippocampus is related to episodic memory performance (Nyberg et al., 2016), extending previous findings from smaller studies with age-heterogeneous samples.

The dose-response patterns regarding intensity, frequency, and duration are not yet sufficiently characterized (Prakash et al., 2015; Young et al., 2015). In observational studies, both frequency and intensity of physical activity have been associated with cognitive performance. Some studies report associations with frequency of light-intensity physical activities (e.g. Johnson et al., 2016; S. Lee et al., 2013), some with mild-to-moderate-intensity activities (e.g. Geda et al., 2010; Makizako et al., 2015), some with frequency of moderate-to-vigorous activities (e.g. B. M. Brown et al., 2012; Kerr et al., 2013). Only few studies examined physical activity intensity independently from frequency and report associations with cognition (Angevaren et al., 2010; Angevaren et al., 2007; B. M. Brown et al., 2012; van Gelder et al., 2004).

Given the involvement of DA in cognition, and the likely presence of positive effects of physical activity on cognitive performance, possibly through enhanced DA integrity, we investigated the correlative triad of physical activity, DA, and cognition in healthy older humans. We assessed $D_{2/3}$ DA receptor ($D_{2/3}$DR) availability with positron-emission tomography (PET) using the radiotracer $[^{11}C]$raclopride that is typically used for D2-assessment in striatum, but has also been used for hippocampal D2-assessment in the COBRA study (Nyberg et al., 2016). In the present study, we examined on 178 participants of the COBRA study (Nevalainen et al., 2015), whether frequency and intensity of habitual physical activity are associated with episodic memory and with $D_{2/3}$DR availability in caudate, hippocampus, but also putamen. In addition, we examined associations of physical activity to working memory and perceptual speed, even though performance in these domains were not related to $D_{2/3}$DR availability in previous analyses of our data (Nyberg et al., 2016).

2. Methods

The design, recruitment procedure, imaging protocols, cognitive tests, and questionnaires used in the COBRA project have been reported elsewhere (Nevalainen et al., 2015). Here we only describe the methodological details that are directly relevant to the results of the current study. The study was approved by the local Ethical and Radiation Safety Committee of Umeå, Sweden, and all participants provided signed written informed consent before participation.

2.1. Participants

In COBRA, 181 healthy, older individuals (64–68 years; mean: 66.2, standard deviation: 1.2; 81 women) were randomly selected from the population register of Umeå in northern Sweden. Eligible were persons without pathological deviations in brain and cognitive functions, or circumstances that could bias task performance or obstruct imaging sessions (e.g., metal implants). The study participants had a lower prevalence of hypertension than reported for the Swedish population (Carlsson et al., 2008), and normal or slightly higher body-mass index (>30 in 14.4% of the participants). According to nation-wide panels, 60,1% of 55–64 year-old and 58,2% of 65–74 year-old persons report engaging in physical activities comparable with going for a walk for at least 6 h a week (Statistics Statistics-Sweden, 1999). In COBRA, 75,14% reported to engage for at least 6 h a week in physical activity (walking, bicycling, jogging, strength training, sports), thus suggesting that our participants are relatively active (see Table 2).

Data for 3 individuals were excluded. These were persons with imperfect segmentation of magnetic resonance images and PET/MR image coregistration ($n = 2$), as well as deviant brain structure ($n = 1$). Thus, the effective sample included 178 participants (Table 1).

The timing of the assessments was as follows: Participants came to the laboratory on two non-consecutive days (mostly two days in between testing, for n = 32 more than 2 days were in-between). At the first day, participants performed a part of the cognitive testing, underwent structural and functional MRI scanning. Between the two days, they filled out a questionnaire on socio-demographic, personality, and lifestyle variables. At the second day of assessment, participants completed cognitive testing, medical anamnesis, testing of physical parameters and finally underwent a PET scan (Nevalainen et al., 2015).

2.2. Physical activity questionnaire

We used an activity questionnaire designed for the purpose of the COBRA study and tailored to life in northern Sweden. This questionnaire included 43 activities, chunked into the categories of intellectual, physical, and social activities. Participants were asked to indicate for how many hours (options: 1–14 h with 1-h increments, or 15 + hrs) they would engage in each of the activities during a typical summer week. Summer was taken as a reference season because the opportunities for