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Interactive effects of age and multi-gene profile on motor learning and sensorimotor adaptation

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ABSTRACT

The interactive association of age and dopaminergic polymorphisms on cognitive function has been studied extensively. However, there is limited research on whether age interacts with the association between genetic polymorphisms and motor learning. We examined a group of young and older adults' performance in three motor tasks: explicit sequence learning, visuomotor adaptation, and grooved pegboard. We assessed whether individuals' motor learning and performance were associated with their age and genotypes. We selected three genetic polymorphisms: Catechol-O-Methyl Transferase (COMT val158met) and Dopamine D2 Receptor (DRD2 G > T), which are involved with dopaminergic regulation, and Brain Derived Neurotrophic Factor (BDNF val66met) that modulates neuroplasticity and has been shown to interact with dopaminergic genes. Although the underlying mechanisms of the function of these three genotypes are different, the high performance alleles of each have been linked to better learning and performance. We created a composite polygene score based on the Number of High Performance Alleles (NHPA) that each individual carried. We found several associations between genetic profile, motor performance, and sensorimotor adaptation. More importantly, we found that this association varies with age, task type, and engagement of implicit versus explicit learning processes.

1. Introduction

Aging is associated with a variety of motor and cognitive declines, many of which have been linked to changes in corticostriatal function and dopaminergic transmission (Bäckman et al., 2006, 2000; Volkow et al., 1998). Several genetic polymorphisms have been identified which affect the dopaminergic metabolism pathway, including Catechol-O-Methyl Transferase (COMT), Dopamine D2 Receptor (DRD2), and Brain Derived Neurotrophic Factor (BDNF) polymorphisms (Savitz et al., 2006). COMT and DRD2 are directly linked to dopamine signaling (Jönsson et al., 1999; Meyer-Lindenberg et al., 2005; Stelzel et al., 2009). BDNF on the other hand, plays an important role in neuroplasticity and is indirectly involved in dopamine function (Egan et al., 2003; Guillin et al., 2001; Hünnerkopf et al., 2007; Hyman et al., 1991).

Previous work has shown that dopaminergic genotypes modulate the availability of dopamine in prefrontal and striatal regions, and are associated with varying levels of motor learning and performance. Joundi et al. (2012) investigated the association of BDNF with visuomotor processes and they found that carriers of the val-met genotype showed reduced rates of visuomotor adaptation during learning and the long term retention phase. However, their performance did not differ from the val-val genotype group at a retention test following a short delay. They also found more pronounced differences between the two genotype groups when they adapted to a larger deviation from the target, suggesting that BDNF

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genotype is associated with explicit processes of adaptation. Their findings further suggest that the association of BDNF with visuomotor adaptation is influenced by the task design (complexity and learning phase). Moreover, McHughen et al. (2011) provided evidence that the well-established effects of the BDNF val-met polymorphism in the early phase of motor learning, where val-met individuals show reduced learning, disappear with long term intense training. Their findings also support the notion that genotype associations with motor learning are influenced by task design (amount of practice).

We have recently reported that COMT val-val and DRD2 TT genotypes were associated with poorer performance in motor sequence learning for young adults (Noohi et al., 2014). We also observed that COMT val-val individuals exhibited slower visuomotor adaptation, however, there was no association of the DRD2 TT polymorphism with visuomotor adaptation. Thus, our findings are in line with previous reports of task specific associations between genetic polymorphisms and differing forms of motor learning and adaptation.

Several studies have shown declines in motor learning and performance with healthy aging (Gage et al., 1989; Kluger et al., 1997; Seidler et al., 2010). However, some older adults sustain learning and performance patterns equivalent to those of young adults (Albert et al., 1995; Dennis et al., 2007; Kattenstroth et al., 2010; Lustig et al., 2009); it is unclear what underlies this "successful aging" in some individuals. Flöel et al. (2005) provided evidence that dopamine levels modulate the rate of motor learning in healthy young and older adults. They showed that older adults with diminished motor memory improved significantly after receiving a single dose of oral L-Dopa. They suggested that individual differences in dopamine transmission could be used as an index of successful aging. These individual differences can be partly captured by an individual's genotype, and more specifically, genotypes that regulate dopamine function.

The role of dopaminergic genetic polymorphisms on performance in older adults has been studied extensively, although previous work has predominantly investigated cognitive rather than motor function. For example, Nagel et al. (2008b) showed that age magnifies associations between genotype and memory, and suggested that carriers of low-dopamine alleles have more pronounced deficits in learning and memory in older age. However, other studies have failed to replicate these age by gene interactions (see Appendix A for a summarized selection of studies that were/were not able to replicate these findings). Thus it is difficult to predict whether there might be age by gene interactions for associations between dopaminergic polymorphisms and motor skill learning. The studies reporting increasing genotype associations with behavior in advancing age (Lindenberger et al., 2008) suggest that young adults might engage some compensatory mechanisms to overcome the effects of "low dopamine" alleles, whereas for older adults general declines reduce the effectiveness of compensation (Cabeza et al., 2002; Collier et al., 2007; Park and Reuter-Lorenz, 2009; Reuter-Lorenz and Cappell, 2008). However, this hypothesis remains to be critically evaluated.

Apart from previous animal studies (Boger et al., 2011; Chen et al., 2005; Li et al., 2010a, 2010b; Markowska and Breckler, 1999; Watanabe et al., 1991), only a few studies have investigated whether there is an age by genotype interaction in the motor domain for human subjects (Alcalay et al., 2014; Schuck et al., 2013). Schuck and colleagues showed that the interactive effect of dopaminergic genotypes (DAT VNTR and DARPP-32) and age is more pronounced in explicit components of motor sequence learning than implicit. Alcalay et al. (2014) assessed the association of a Parkinson's risk gene with motor and cognitive performance, and found that CH/H PARKIN carriers exhibited slower progression of Parkinson's disease and less motor and cognitive impairments than non-carriers. These suggest that motor learning and performance are influenced by age and genotype, however, it is not clear whether the results would hold across differing dopaminergic polymorphisms and a range of motor learning paradigms.

Given the evidence that motor sequence learning and sensorimotor adaptation rely on dopaminergic processes (Carbon et al., 2004; Joundi et al., 2012; Marinelli et al., 2009; Noohi et al., 2014; Tremblay et al., 2010), we investigated the association of COMT, DRD2, and BDNF polymorphisms with motor learning and performance in healthy young and older adults. To more robustly explain variations in dopamine modulation that links to an individual's behavior, we employed the polygene approach (David et al., 2013; De Quervain and Papassotiropoulos, 2006; Hamrefors et al., 2010; Lluís-Ganella et al., 2010; Nikolova et al., 2011; Noohi et al., 2014; Papenberg et al., 2013; Pearson-Fuhrhop et al., 2013); that is, we created a count score of the number of purportedly high performance alleles (i.e. alleles that have been previously linked to better performance in cognitive and motor tasks) that an individual carries across COMT, DRD2, and BDNF. We hypothesized that age-related declines in motor learning and performance would be associated with the presence of fewer "high performance alleles" in our three genes of interest. Given our findings with young adults (Noohi et al., 2014), we also predicted that these associations would vary between motor sequence learning and sensorimotor adaptation for both young and older adults.

2. Methods

2.1. Participants

Subjects were recruited from the University of Michigan student population and the National Institutes of Health Claude D. Pepper Older Americans Independence Center. Considering the effect of gender and ethnicity on genotype modulations (Barnett et al., 2007; Farrer et al., 1997; Garte, 1998; Kates et al., 2006; Laing et al., 2012), we limited our recruitment to females with Caucasian ethnicity. From a total of 142 individuals (72 YA, 70 OA) who participated in our study, those with a score of <27 in the Mini Mental State Examination (MMSE), history of neurological disorders, contaminated DNA samples, or incomplete/missing data were excluded. The final sample size consisted of 68 young (21 ± 1.9 yrs) and 63 older adults (71 ± 4.9 yrs). We included "Estrogen therapy" as a covariate in our analyses as it has been shown to improve dopamine function in post-menopausal women (Duff and Hampson, 2000; Tsang et al., 2000; Yaffe et al., 1998). All participants signed a written informed consent form that was approved by the University of Michigan Institutional Review Board.

2.2. Genotyping

As described in our previous report (Noohi et al., 2014), we collected participants' saliva samples with Oragene DNA self-collection kits. We identified the single nucleotide polymorphisms (SNPs) of COMT (rs4680), DRD2 (rs1076560), and BDNF (rs6265) genes for the provided DNA samples. Table 1 presents that the distribution of alleles for each gene within the two age groups was in accordance with Hardy-Weinberg equilibrium. Taking the COMT-met, DRD2-G, and BDNF-val alleles as the "high performance" alleles, we defined a polygene index representing the Number of High Performance Alleles (NHPA) that each individual carries. As depicted in Table 2, the total number of high performance alleles (i.e. NHPA score) can vary between 0 and 6. None of the subjects in our sample of young adults were carriers of 0 or 1 NHPA; only two older adult subjects were carriers of 0 ($n=1$)