# Polymorphisms in the Dopamine Receptor 2 Gene Region Influence Improvements during Working Memory Training in Children and Adolescents

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## Abstract

■ Studying the effects of cognitive training can lead to finding better treatments, but it can also be a tool for investigating factors important for brain plasticity and acquisition of cognitive skills. In this study, we investigated how single-nucleotide polymorphisms (SNPs) and ratings of intrinsic motivation were associated to interindividual differences in improvement during working memory training. The study included 256 children aged 7–19 years who were genotyped for 13 SNPs within or near eight candidate genes previously implicated in learning: *COMT, SLC6A3 (DAT1), DRD4, DRD2, PPP1R1B (DARPP32), MAOA, LMX1A,* and *BDNF*. Ratings on the intrinsic motivation inventory were also available for 156 of these children. All participants performed at least 20 sessions of working memory training, and performance during the training was logged and used as the outcome variable. We found that two SNPs, rs1800497 and rs2283265, located near and within the *dopamine receptor 2 (DRD2)* gene, respectively, were significantly associated with improvements during training ($p < .003$ and $p < .0004$, respectively). Scores from a questionnaire regarding intrinsic motivation did not correlate with training outcome. However, we observed both the main effect of genotype at those two loci as well as the interaction between genotypes and ratings of intrinsic motivation (perceived competence). Both SNPs have previously been shown to affect DRD2 receptor density primarily in the BG. Our results suggest that genetic variation is accounting for some interindividual differences in how children acquire cognitive skills and that part of this effect is also seen on intrinsic motivation. Moreover, they suggest that dopamine D2 transmission in the BG is a key factor for cognitive plasticity. ■

## INTRODUCTION

There is a growing literature regarding methods of improving working memory (WM) using computerized training programs. This is of scientific interest as a tool for studying brain plasticity relating to cognitive function and also potentially of practical use considering the importance of WM and attention in everyday life. One method using computerized WM tasks first described by Klingberg and colleagues (Klingberg, 2010; Klingberg et al., 2005; Klingberg, Forssberg, & Westerberg, 2002) consistently results in improvement on nontrained WM tasks and attentive behavior (Brehmer, Westerberg, & Backman, 2012; Green et al., 2012; Hardy, Willard, Allen, & Bonner, 2012; Klingberg et al., 2005), whereas evidence for improvements in problem solving have been inconsistent (Bergman Nutley et al., 2011; Thorell, Lindqvist, Bergman Nutley, Bohlin, & Klingberg, 2009; Klingberg et al., 2005). Similarly, training on a dual *n*-back task has shown improvement in problem solving in some (Jaeggi, Buschkuehl, Jonides, & Perrig, 2008) but not all studies (Redick et al., 2012). Other methods of WM training have shown improvements for updating (Dahlin, Neely, Larsson, Backman, & Nyberg, 2008) and reading (Chein & Morrison, 2010).

It has also become evident that there are considerable interindividual differences in training-induced improvements (Söderqvist, Nutley, Ottersen, Grill, & Klingberg, 2012; Jaeggi, Buschkuehl, Jonides, & Shah, 2011). These are interesting because they could inform about factors important for plasticity but possibly also explain some inconsistencies between training studies. Factors that could influence the interindividual differences include motivation, baseline cognitive performance, diagnostic status, and genetic variation (Söderqvist, Nutley, Ottersen, et al., 2012; Söderqvist, Nutley, Peyrard-Janvid, et al., 2012; Jaeggi et al., 2011).

Dopamine is a neurotransmitter that is important for WM performance (Vijayraghavan, Wang, Birnbaum, Williams, & Arnsten, 2007; Williams & Goldman-Rakic, 1995) but also directly influences the plasticity of the brain, for example, by facilitating dendritic outgrowth (Tritsch & Sabatini, 2012; Scheidtmann, Fries, Muller, & Koenig, 2001; Stroemer, Kent, & Hulsebosch, 1998; Walker-Batson, Smith, Curtis, Unwin, & Greenlee, 1995). This suggests that dopamine might influence the effectiveness of interventions targeting

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neural functioning. Indeed, drugs that facilitate dopaminergic transmission, such as amphetamine and methylphenidate, are known to enhance the effect of motor training (Stroemer et al., 1998; Walker-Batson et al., 1995). The importance of dopamine for WM training has been investigated using PET, with results showing evidence of changes in cortical D1 receptor binding (McNab et al., 2009) as well as D2 binding in striatal areas (Bäckman et al., 2011) following training. Evidence is also supporting an influence of dopaminergic-related genetic variants on outcomes following a behavioral intervention. For example, studies have shown that *DRD4* genotypes interact with effects of behavioral intervention influencing externalizing behavior and attention (Bakermans-Kranenburg, Van, Pijlman, Mesman, & Juffer, 2008). Regarding WM training, there are now two studies indicating that variants within the *SLC6A3/DAT1* gene affect the response to training (Söderqvist, Nutley, Peyrard-Janvid, et al., 2012; Brehmer et al., 2009). However, both studies are relatively small and are in need of replication. Dopamine is not only associated with cognitive function and plasticity but is also a key neurotransmitter in processes relating to reward and motivation (Wise, 2004), which might indirectly influence both cognition and training-induced improvements.

The aim of this study was to investigate the effects of single-nucleotide polymorphisms (SNPs) in genes linked to dopaminergic function on improvements during WM training. Polymorphisms (SNPs) were selected based on previous literature showing influence on learning and cognition. In addition to SNPs in genes that are directly linked to dopaminergic functions, polymorphisms in the *LMX1A* and *BDNF* genes were also included. The SNP within *LMX1A* was included as an attempt to replicate previous findings on WM training (Bellander et al., 2011). Polymorphisms within *BDNF* were included based on the literature showing BDNF to be an important factor for neural plasticity (Park & Poo, 2013). We also wanted to assess if any genetic effect on training was mediated via an influence on intrinsic motivation by administrating a modified version of the intrinsic motivation inventory (IMI) questionnaire (McAuley, Duncan, & Tammen, 1989).

## METHODS
### Participants and Procedure

Inclusion criteria for the study were (i) a minimum of 20 training sessions with Cogmed RM training (Cogmed Systems), (ii) successful genotyping for included SNPs, and (iii) a participant younger than 20 years. Information regarding the study was sent out via e-mail to, at that time, current customers of Cogmed WM training in Sweden, mostly consisting of schools. This e-mail included information regarding the study and an enquiry into their assistance with spreading information about the study to individual users of the Cogmed training programs. Schools that agreed to assist with this were sent individual envelopes containing study information and consent forms. A responsible contact person at each school distributed these to individuals who were currently training or had previously completed training with Cogmed WM training program. Thirty-four schools participated in the study, and a total of 1387 individual information envelopes were sent out. Informed consent to participate in the study was given by 320 individuals and legal guardians for participants younger than 15 years. After consent was received, the questionnaires and an Oragene saliva self-collection OG-500 kit (DNA Genotek, Inc., Canada) were sent to the participants via mail. Participants returned the completed questionnaires and saliva samples to the researchers using an included response envelope. Completed questionnaires and saliva samples were returned by a total of 251 participants. The study was approved by the regional ethical committee at Karolinska Institutet in Stockholm, Sweden.

### WM Training Paradigm

Participants trained using RM provided by Cogmed, as developed by Klingberg et al. (2002, 2005). This training program consists of 12 different WM demanding tasks covering both visuospatial and verbal domains. Some of the tasks are changed during the training period to increase variability so that 8 of the 12 tasks are trained on each session. Difficulty level (number of items to be remembered) is adapted according to a built-in algorithm that takes an individual's previous performance into consideration. This allows for training to be performed at a level that is close to the capacity limit for each individual.

### Genotyping

DNA was extracted from saliva (OraGene OG-500, DNA Genotek, Inc., Canada) according to the manufacturer's recommendations. The sample used for genotyping originally contained 278 individuals. Genotypes for all SNPs were amplified and detected using a Sequenom Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF) genotyping platform and iPLEX Gold assays as previously described (Darki, Peyrard-Janvid, Matsson, Kere, & Klingberg, 2012). All genotypes were called and confirmed independently by two researchers. As a quality control, 5% of the total sample was regenotyped, resulting in a 100% concordance for all polymorphisms analyzed. A minimum genotype success rate of 80% was used as inclusion criteria for further analysis. Genome build 37.3, dbSNP version 137, and Haploview 4.2 were used to locate polymorphisms to chromosomal positions and gene regions as well as to calculate linkage disequilibrium between markers. The amplification and genotyping of rs1800497 was performed on the opposite DNA strand relative to what is reported in the dbSNP producing the A minor allele.

## Motivation Measure

An adapted version of the IMI was used to assess the participants' intrinsic motivation in relation to the training (McAuley et al., 1989). The scale was translated to Swedish, and the questions were adapted to address the WM training specifically.

## Statistical Analyses

Influence of the candidate SNPs were analyzed using univariate general linear models in SPSS version 21, with a max index score used as the dependent variable. The max index score reflects the mean of the three most successful trials on a visuospatial grid task and a verbal backward digit span task during the two best training days. These two tasks are chosen as they represent performance on both visuospatial and verbal WM performance and as these two tasks are performed at each session throughout the training period. The training data that were used as outcome measures consisted of a continuous recording of performance of every trial from every day. This performance could be affected not only by the WM capacity of the individual but also on temporary fatigue, lack of motivation, or distractions. To get a measurement of the WM capacity, we used the average level of the three most successful trials with highest level as "max level" on each day. To get a measure of global maximum performance ("max index"), we averaged the 2 days with highest "max level." We expected this to reduce noise and temporary dips in performance that would be included if using a measure based on mean performance only on the last day of training.

To control for effects of regression toward the mean, we included baseline performance (start index) as a covariate in the analyses. The start index consists of the "max level" during the second and third days. Performance on the second and third days (rather than the first day) was used to allow enough practice trials to get familiar with the tasks and stimuli and to allow for the program to establish a baseline performance.

We also performed a post hoc correlation of the start and max index with mean performance during Day 1 and Day 20 (last day with complete data from all participants). The correlation between mean Day 1 performance and start index was $r = .875$, and the correlation between mean performance Day 20 and max index was $r = .912$.

In addition to start index, age and one SNP were also included as covariates in the analyses. Thus, for each SNP, an analysis was performed using a univariate general linear model, with max index score as dependent variable and start index, age, and the particular SNP entered as covariates as independent variables. This was repeated for each SNP leading to a total of 13 analyses.

To assess influence of motivation on training, we assessed the effect of the different subscales on the IMI on training improvements separately using general linear models similar to those described above, with max index as dependent variable and start index, age, and IMI subscale score as covariates.

To assess possible interactions between motivational and genetic effects, general linear models including interaction analyses were planned for any SNP found to be a significant predictor of training improvement. This was performed for the two SNPs in the *dopamine receptor 2 (DRD2)* gene region and the perceived competence subscale, also controlling for start index and age.

## RESULTS

### Participants

A total of 224 individuals with an equal gender distribution (117 boys and 107 girls) fulfilled all criteria. Participants were between 7 and 19 years old (mean age = 12.45, $SD = 2.16$). According to parental reports, 24 of the included participants had a neuropsychiatric diagnosis (some multiple; ADHD/ADD $n = 14$, dyslexia $n = 5$, autism or Asperger syndrome = 5, others $n = 4$). The IMI questionnaire was introduced while data collection was ongoing and is therefore only available for a subsample of 152 individuals.
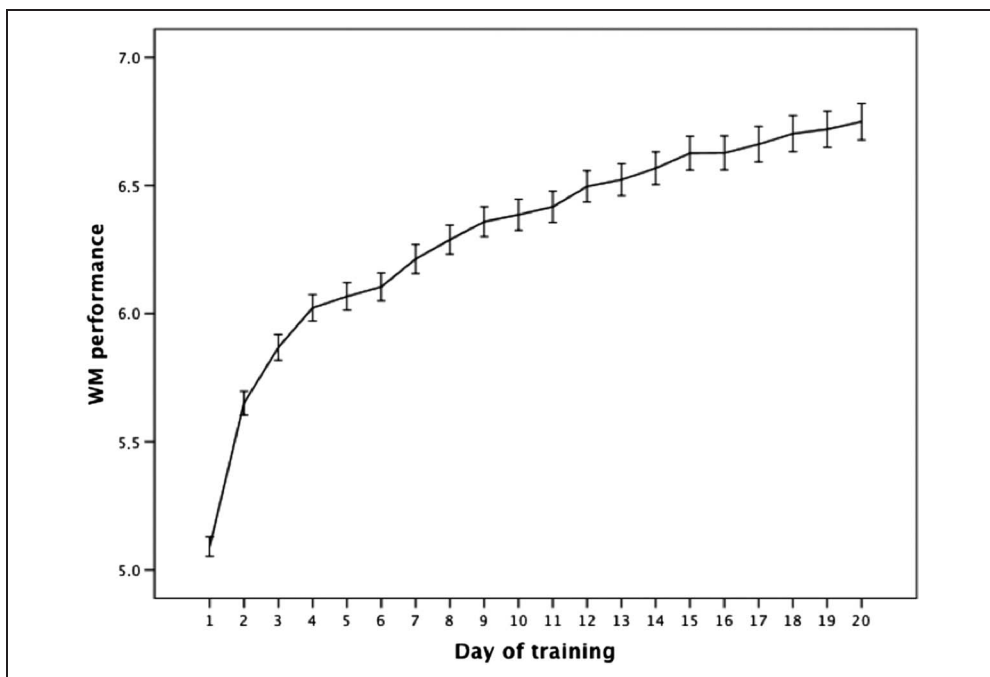
### WM Training

Participants completed an average of 24.7 training sessions ($SD = 1.06$), where each session lasted for an average of 36.5 min ($SD = 8.8$). Typically, participants improved their performance throughout the whole training period (Figure 1). Improvements on the index measure increased 33% on average, but with a large variance (Figure 2). Improvements were significantly correlated with age ($r = .15$, $p = .028$), and age was therefore included as a covariate in the analyses described below.

### Genetic Influence on Training Improvements

Thirteen SNPs (Table 1) were genotyped with an average success rate of 97%. Two SNPs, rs2283265 and rs1800497 (also known as the Taq1A polymorphism), significantly predicted training improvements after controlling for multiple comparisons. Both SNPs are located within or in the immediate vicinity of *DRD2*. For both SNPs, homozygosity for the minor (A) allele was rare ($n = 7$ and $n = 9$ for rs2283265 and rs1800497, respectively), and AA homozygotes were therefore merged with heterozygotes for analysis. According to our genotyping, these two SNPs are in moderate linkage disequilibrium ($r^2 = .76$). For both SNPs, the presence of the minor A-allele (in one or two copies) was associated with superior improvements in WM (Figure 3). None of the two SNPs showed a significant association with baseline performance (both $ps > .1$).

**Figure 1.** Mean performance on WM during training. The $y$ axis show average highest performance on the visuospatial and verbal WM tasks contributing to the index measure. The $x$ axis shows day of training. Error bars illustrate $\pm 1$ *SEM*.



## Motivational Measures

Four subscales from the IMI were included: interest/enjoyment, perceived competence, effort/importance, and value/usefulness. Out of these four subscales, there was a trend toward association with the training improvements for the perceived competence scale only, $F(1, 147) = 7.90, p = .06$ (all other $p$ values $> .1$). In this subscale, participants were asked to rate their own ability to perform the task and how well they think they did in comparison with others. Next, we performed analyses using general linear models including scores on the perceived competence scale as well as the two significant *DRD2* SNPs. These analyzed main effects as well as interaction effects of the SNPs and perceived competence on training improvements. For rs2283265 and rs1800497, respectively, these analyses showed a main effect of SNP, $F(1, 149) = 5.09, p = .026; F(1, 148) = 5.90, p = .016$; a main effect of

**Figure 2.** Histogram illustrating the spread in improvements on the index score following training.
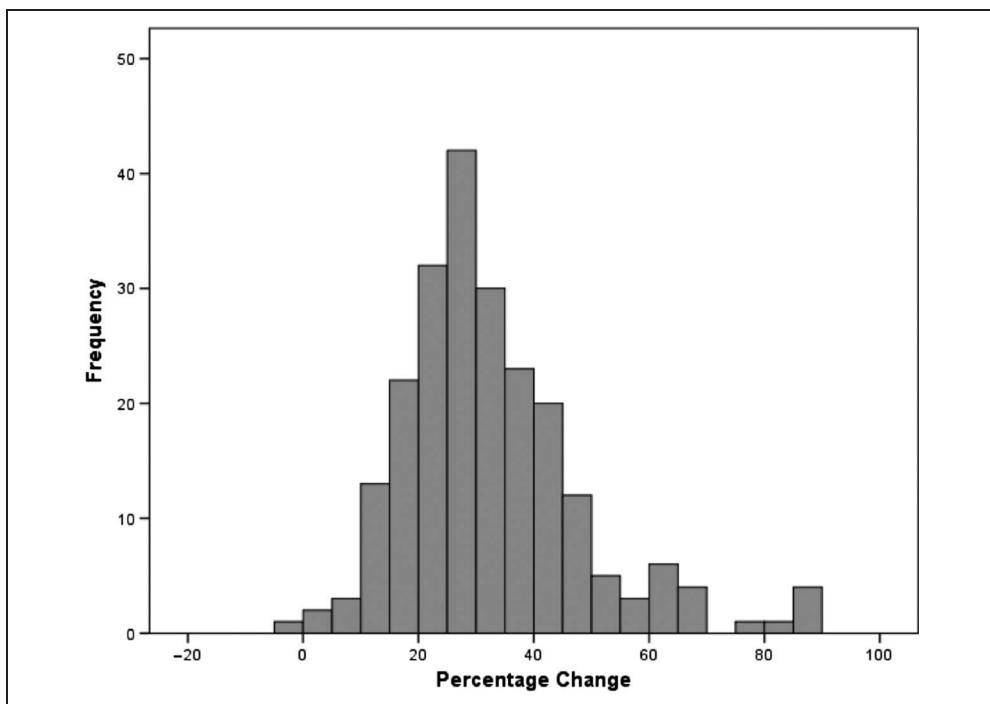
**Table 1.** Candidate SNPs Analyzed for Association with Training Improvements

| Gene | SNP | Position | Location in the Gene | F | p |
|------|-----|----------|----------------------|---|---|
| SLC6A3 (DAT1) | rs27072 | Chr5: 1394522 | in 3′-UTR | 0.251 | .617 |
| | rs40184 | Chr5: 1395077 | intron 14 | 0.307 | .580 |
| | rs3863145 | Chr5: 1392711 | 200 bp downstream of 3′-UTR | 2.179 | .141 |
| DRD4 | rs11246226 | Chr11: 641191 | 500 bp downstream of 3′-UTR | 4.106 | .044 |
| | rs936465 | Chr11: 643568 | 3 kbp downstream of 3′-UTR | 5.808 | .017 |
| | rs7124601 | Chr11: 629273 | Intron 1 | 2.805 | .095 |
| PPP1R1B (DARPP32) | rs3764352 | Chr17: 37790939 | Intron 5 | 2.453 | .119 |
| MAOA | rs6609257 | ChrX: 43612708 | 6.6 kbp downstream of gene | 0.002 | .965 |
| ANKK1 | rs1800497 (TAQ1A) | Chr11: 113270828 | Exon 8 | **9.172** | **.003** |
| DRD2 | rs2283265 | Chr11: 113285536 | Intron 5 | **13.179** | **.0004** |
| LMX1A | rs4657412 | Chr1: 165177033 | Intron 7 | 0.787 | .376 |
| BDNF | rs6265 | Chr11: 27679916 | Exon 5 | 1.090 | .298 |
| COMT | rs4680 | Ch22: 18331271 | Exon 4 | 0.28 | .598 |

$F$ and $p$ values from the univariate general linear models are presented for each SNP. SNPs significant after correction for multiple comparisons ($p < .004$) are highlighted in **bold**.

perceived competence, $F(1, 149) = 11.36$, $p = .01$; $F(1, 148) = 11.89$, $p = .001$; and significant interactions between the two, $F(1, 149) = 7.41$, $p = .007$; $F(1, 148) = 7.91$, $p = .006$. Performing the general linear model analyses separately for the A-allele carriers and the GG homozygotes

revealed that, for both SNPs, there was a significant association with perceived competence and actual improvements for the A-allele carriers only ($ps < .01$), whereas no such association was seen for the GG homozygotes ($ps > .1$; Figure 4). There were no significant interactions



**Figure 3.** Performance on a backward digit span and visuospatial grid task during the training period, according to rs2283265 genotypes. Error bars show ±1 *SEM*.
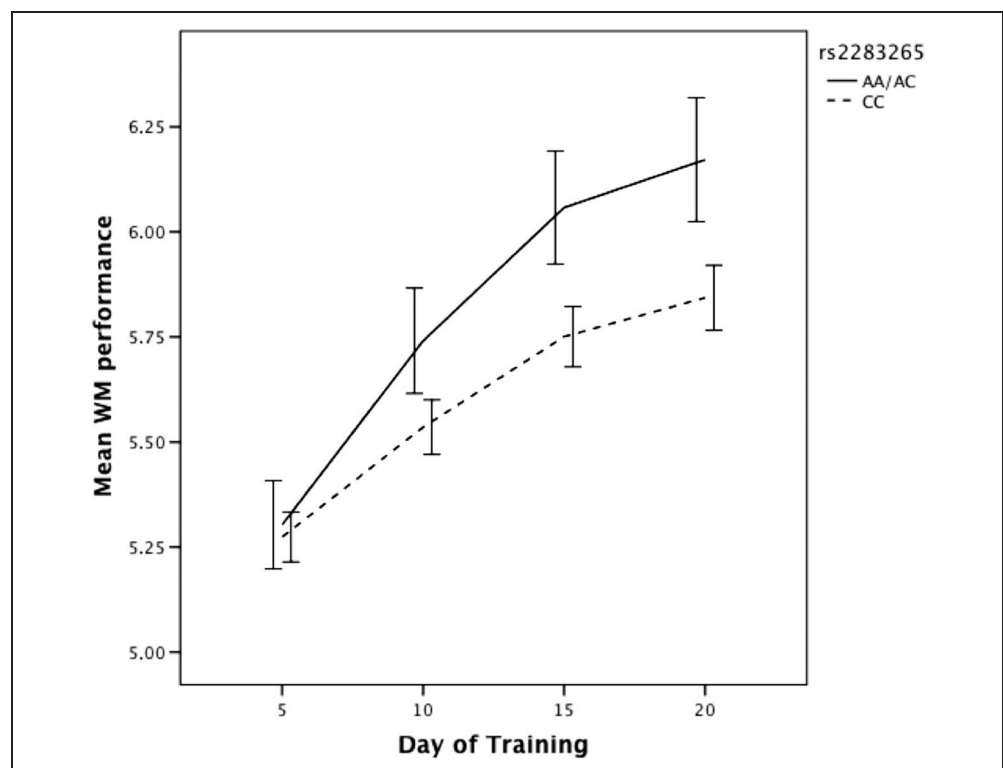
**Figure 4.** The estimated perceived competence is shown on the $x$ axis in relation to actual improvements on the training tasks on the $y$ axis. Data points and line fitting are illustrated according to rs1800497 genotypes.
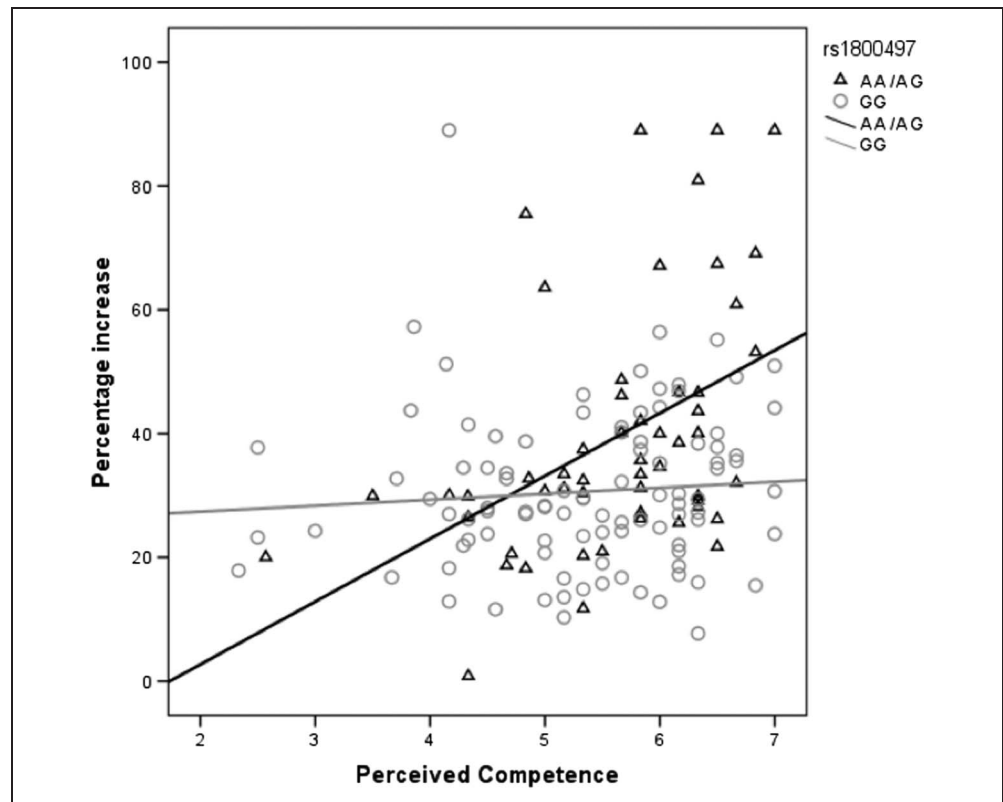


between age and two SNPs in association with training improvements.

## DISCUSSION

This study showed that two polymorphisms related to DRD2 functioning significantly influenced improvements during WM training. In addition to a main effect of each polymorphism, there was also an interaction with the participants' perceived competence. For participants with the "rapid learning" genotype, higher improvement was correlated with higher rating of competence, whereas such association was not present for participants with other genotypes. Although the current sample can still be argued to be small for genetic analyses, it is to our knowledge the largest study looking at genetic influence of cognitive training so far.

According to the dbSNP (www.ncbi.nlm.nih.gov/SNP/) and UCSC Genome Browser (genome.ucsc.edu), the rs1800497/Taq1A polymorphism is located approximately 10 kb proximal to the *DRD2* gene and predicted to cause a p.Glu713Lys amino acid substitution in the *ANKK1* gene. The Taq1A^{+} allele A has been linked to reduced D2 binding potential and reduced receptor availability (Jonsson et al., 1999). Furthermore, a pharmacological study showed a higher reactivity, in terms of increased BOLD signal in the BG, after treatment with cabergoline, a DRD2 receptor agonist, in subject carrying the Taq1A^{+} polymorphism (Cohen, Krohn-Grimberghe, Elger, &

Weber, 2007). The 1A[+] genotype has also been linked to reduced learning from negative feedback as well as reduced reversal learning (Jocham et al., 2009; Klein et al., 2007). The rs2283265 polymorphism, on the other hand, has been associated with alternative splicing occurring in exon 6 of the *DRD2* gene (Zhang et al., 2007). This splicing variant leads to two different isoforms influencing neural activity differently, one long variant that is primarily expressed presynaptically and a short variant that is expressed postsynaptically. Although both isoforms influence the inhibition of GABA transmission in striatal areas, the short variant in particular has been linked to inhibition of glutamate release, thus influencing the excitability of the neurons (Centonze et al., 2004). Zhang et al. (2007) analyzed postmortem brain tissue and found that the minor allele of the rs2283265 polymorphism was linked to a decreased expression of the short isoform (Zhang et al., 2007). In addition, carriers of the minor allele homozygotes or heterozygotes showed significantly greater BOLD signal in both prefrontal and striatal areas while performing an $n$-back WM task. Although numerous PET studies have shown a positive correlation between striatal D2 density and cognitive performance in both healthy and clinical samples (Cropley, Fujita, Innis, & Nathan, 2006), the opposite pattern has been observed for sequence learning for which a negative correlation between performance on a motor sequence learning task and D2 binding potential in striatal areas has been observed (Karabanov et al., 2010). This is consistent with our findings in which the minor alleles, which have

previously been linked to decreased D2 receptor density, were found to predict greater improvements during training.

We did not replicate previous findings of association with training improvements and polymorphisms of the *LMX1A* (Bellander et al., 2011) and the *SLC6A3* (*DAT1*) genes (Söderqvist, Nutley, Peyrard-Janvid, et al., 2012; Brehmer et al., 2009). The study reporting on an association with *LMX1A* was based on a very small sample of 29 adults (Bellander et al., 2011), and these findings should therefore be interpreted with caution. More surprisingly, we did not replicate findings of associations with the *SLC6A3* (*DAT1*) gene and training-related improvements that have previously been suggested in two studies (Söderqvist, Nutley, Peyrard-Janvid, et al., 2012; Brehmer et al., 2009). However, the study by Söderqvist et al. differed from the current one in multiple ways. First, Söderqvist et al. included participants who had trained on both WM and nonverbal reasoning, and analyses were performed for these combined. Second, this previous study included a younger age range, from 4 to 4.5 years compared with the current 7–19 years. This difference might be especially relevant as it is known that the dopamine system undergoes dynamic changes during childhood and adolescence (Jucaite, Forssberg, Karlsson, Halldin, & Farde, 2010) and that the effect of dopamine-related genes can change during development (Dumontheil et al., 2011). Finally, although only a small sample in the current study was reported to have a formal neuropsychiatric diagnosis, training is typically provided to pupils that teachers or other staff at schools judge as having poor WM or problems with inattention. Therefore, individuals in the current sample are likely to have higher levels of inattention than the studies by Söderqvist et al. and Brehmer et al. that included typically developing children and adults.

The associations of cognitive plasticity to both *DRD2* and *SLC6A3* (*DAT1*) are consistent in the sense that these two are closely related both functionally and anatomically. First, the DAT1 transporter determines presynaptic uptake and thus how much dopamine is available to act on the postsynaptic receptors, including DRD2. The D2 receptors are expressed throughout the cortex, but the density is many times higher in the BG (McNab et al., 2009; Farde, Hall, Ehrin, & Sedvall, 1986). Similarly, the density of DAT1 transporters has been mapped by radioactive cocaine and was shown to be predominantly located to the BG (Shumay, Chen, Fowler, & Volkow, 2011). Genetic polymorphisms of *DAT1* also affect the transporter density of the BG (Shumay et al., 2011).

One limitation of this study was that data regarding intrinsic motivation were collected after training was completed. In theory, the performance during training could thus affect the ratings on the IMI. However, most participants improved during training (Figure 2), and it was not possible for an individual to judge their improvement relative to others. Thus, their improvement in relation to others' is not likely to affect their ratings.

Furthermore, only one subscale, the perceived competence, correlated positively with degree of improvements during training, whereas such a relation was not found for the other subscales of interest/enjoyment, effort/importance, and value/usefulness. This shows that it was not general expectancy or general intrinsic motivation but one specific aspect of motivation that was associated with higher improvement. Adding to this specificity was the interaction with significant association of rating and training improvement only in A-carriers, but not in GG-carriers (Figure 4). It is thus unlikely that training performance affected scoring, but rather that differences in dopamine D2 receptor functioning lead to different degrees of motivation or different reactions to the positive and negative feedback given during training, which in turn influence learning.

Taken together, the results of genetic effects point to the BG and the dopamine D2 receptors as key factors for cognitive plasticity. This is also consistent with imaging studies showing that the caudate nucleus is active during training (Olesen, Westerberg, & Klingberg, 2004) and that the amount of activation in the putamen correlated with the amount of transfer from WM training (Dahlin et al., 2008). A PET study also found that WM training increased the amount of dopamine release in BG during WM training (Bäckman et al., 2011). The BG-thalamic loop is important for implicit memory and habit formation (Graybiel, 2008; Packard & Knowlton, 2002). The present genetic evidence supports a key role also for training of executive functions. These findings show that genetic polymorphisms of *DRD2* affect the amount of improvement during WM training and that part of this effect is mediated via an interaction with intrinsic motivation. Together with previous results, it indicates the importance for dopaminergic transmission in the BG as key for cognitive plasticity.

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