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# Dopaminergic Genetic Variants and Voluntary Externally Paced Exercise Behavior

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EPIDEMIOLOGY

**ABSTRACT**

VAN DER MEE, D. J., I. O. FEDKO, J.-J. HOTTENGA, E. A. EHLI, M. D. VAN DER ZEE, L. LIGTHART, T. C. E. M. VAN BEIJSTERVELDT, G. E. DAVIES, M. BARTELS, J. G. LANDERS, and E. J. C. DE GEUS. Dopaminergic Genetic Variants and Voluntary Externally Paced Exercise Behavior. *Med. Sci. Sports Exerc.*, Vol. 50, No. 4, pp. 700–708, 2018. **Purpose**: Most candidate gene studies on the neurobiology of voluntary exercise behavior have focused on the dopaminergic signaling pathway and its role in the mesolimbic reward system. We hypothesized that dopaminergic candidate genes may influence exercise behavior through additional effects on executive functioning and that these effects are only detected when the types of exercise activity are taken into account. **Methods**: Data on voluntary exercise behavior and at least one single-nucleotide polymorphism/variable number of tandem repeat (VNTR) were available for 12,929 participants of the Netherlands Twin Registry. Exercise activity was classified as externally paced if a high level of executive function skill was required. The total volume of voluntary exercise (minutes per week) as well as the volume specifically spent on externally paced activities were tested for association with nine functional dopaminergic polymorphisms (*DRD1*: rs265981, *DRD2/ANKK1*: rs1800497, *DRD3*: rs6280, *DRD4*: VNTR 48 bp, *DRD5*: VNTR 130–166 bp, *DBH*: rs2519152, *DAT1*: VNTR 40 bp, *COMT*: rs4680, *MAOA*: VNTR 30 bp), a polygenic score (PGS) based on nine alleles leading to lower dopamine responsiveness, and a PGS based on three alleles associated with both higher reward sensitivity and better executive functioning (*DRD2/ANKK1*: "G" allele, *COMT*: Met allele, *DAT1*: 440-bp allele). **Results**: No association with total exercise volume or externally paced exercise volume was found for individual alleles or the nine-allele PGS. The volume of externally paced exercise behavior was significantly associated with the reward and executive function congruent PGS. This association was driven by the *DAT1* 440-bp and *COMT* Met allele, which acted as increaser alleles for externally paced exercise behavior. **Conclusions**: Taking into account the types of exercise activity may increase the success of identifying genetic variants and unraveling the neurobiology of voluntary exercise behavior. **Key Words:** CANDIDATE GENE, EXERCISE BEHAVIOR, REWARD SENSITIVITY, EXECUTIVE FUNCTIONING

Despite the substantial heritability of exercise behavior (1,2), genetic association studies have not yet been successful in uncovering the causative variants for the initiation and maintenance of voluntary exercise behavior (3,4). Most candidate gene studies on the neurobiology of voluntary exercise behavior to date have focused on the dopaminergic signaling pathway (as reviewed in Ref. [5]). Three of these studies found a significant association between genetic variants in the dopaminergic system and exercise behavior in humans. The first study found that women reporting European ancestry ($N$ = 256) who are homozygous for the *DRD2/ANKK1* "A" allele (which is associated with decreased levels of DRD2 receptors) had 25%–38% lower past-year general physical activity levels compared with carriers of the "C" allele (6). The second study found no significant differences in past-year physical activity levels or exercise habit among 648 Japanese men and women with respect to the *DRD2/ANKK1* gene. However, they did find a significant association between the *DRD2/ANKK1* genotype and exercise habits in the period from childhood to adolescence, in which homozygotes of the "A" allele were again less likely to be exercisers (7). The third study, in 54-month-old children ($N$ = 651), found that individual carriers of the 3.5–4 repeat *MAO-A* variable number of tandem repeat (VNTR; high-activity version) showed lower overall parent-reported activity levels than did the carriers of the 3 repeat *MAO-A* VNTR (low-activity version) (8).

After these promising first findings, subsequent larger studies have failed to find an association with these and other

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genes involved in the dopaminergic system and either daily physical activity or the more narrow trait of voluntary exercise behavior. A study by Jozkow et al. (9) in 900 Polish men investigating the relationship between physical activity and the *DRD2 C313T* and the *DRD4* 48-bp VNTR polymorphisms did not find an association. A study by Huppertz et al. (5) investigated whether functional single-nucleotide polymorphisms (SNP) or VNTR in several dopaminergic genes, including *DRD2/ANKK1*, involved in the mesolimbic reward system could explain the heritability of voluntary exercise behavior. Despite their large number of participants ($N = 8768$), they did not find an association between any of the dopaminergic SNP or VNTR and exercise behavior in leisure time.

A shared limitation of the studies on this topic so far is that they lumped together all regular moderate-to-vigorous exercise activities into a single measure. Landers and Esch (10) have stressed that taking into account the nature of the set of skills required in exercise activity is of major importance when investigating the neurobiology of individual differences in exercise behavior, most notably for the engagement in sports. They hypothesize that the required level of externally versus internally paced skills is of key importance in the endorsement of sports and exercise as a regular leisure time activity. As defined by Galligan (11), each exercise/sports activity is located somewhere on the external–internal paced continuum. Internally paced or self-paced activities are exercise/sports activities in which the performer controls the rate at which the activity is executed. Such activities usually rely on closed skills including, for example, a javelin throw or the discus. In externally paced activities, the environment (which may include opponents or natural elements) controls the rate of performing the activity. The performer must pay attention to external events to control his/her rate of movement. These activities require reactive skills and are usually open skills (i.e., in ball games, the performer must time his actions with the actions of other players and the ball) (11,12). As is clear from these definitions, externally paced exercise activities rely much more on executive functions (e.g., task switching, inhibition, and planning) than more internally paced activities, like jogging.

On the basis of the simple principle that people are more motivated to repeat a behavior that they are good at, a tight fit of one's skills to the exercise activities chosen can be expected to increase the chance of long-term adherence to those exercise activities. Because executive functioning is critical to performance in externally paced sports, ones executive function abilities might drive the motivation to voluntarily engage in such exercise behaviors. Various twin studies have shown substantial heritability of performance in executive function tasks (13,14), and intriguingly, genetic variation in dopaminergic signaling has been widely regarded as a major contributor to this heritability (13,15). In fact, the same genetic polymorphisms that have been investigated in the context of reward processing in the striatal brain regions have been hypothesized to have an effect on executive functioning in prefrontal brain regions. Table 1 summarizes the reported association of functional genetic polymorphisms in the dopamine (DA) system with reward sensitivity and executive functioning. More detail on the variants of these nine polymorphisms and their hypothesized neurobiological effects is provided in Appendix, Supplemental Digital Content, Functional variants in dopaminergic genes and their association with reward sensitivity and executive functioning, http://links.lww.com/MSS/B99.

Table 1 suggests that most of these genetic polymorphisms have a dual effect on reward sensitivity and executive function. These pleiotropic genetic effects are sometimes aligned such that the same allelic variant is associated with both higher reward sensitivity and better executive functioning (*DRD2/ANKK1* (rs1800497) "T" allele, *COMT* (rs4680) "A" allele, *DAT1* (VNTR 40 bp) 440-bp repeat), whereas for other genes, the same allele has opposing or unclear effects on both traits (*DRD1* (rs265981) "G" allele), *DRD3* (rs6280) "C" allele, *DBH* (rs2519152) "T" allele, *DRD4* (VNTR 48 bp) 7 repeat, *DRD5* (VNTR 130–166 bp) 148-bp repeat, *MAOA* (VNTR 30 bp) ≥3.5 repeats). We currently do not know whether the putative effects of these dopaminergic variants on exercise behavior depend more on reward sensitivity or on executive function. We hypothesize that the latter effect cannot be ignored. If dopaminergic effects on executive function are present, the genetic association with voluntary exercise behavior as a whole, which is a mixture of internally and externally paced exercise activities, could be diluted by opposite effects of the same allele on externally versus internally paced exercise activities.

In the current study, we test whether the genetic polymorphisms in dopaminergic pathways listed in Table 1 are associated more strongly with the total weekly minutes of voluntary externally paced exercise behavior than with the total weekly minutes of voluntary exercise behavior as a whole.



TABLE 1. The effect of various functional genetic polymorphism of the DA system and their reported effect on DA levels, reward sensitivity, and executive functioning.

| Polymorphism | Alleles | Variant | Effect on DA | Effect on Reward Sensitivity | Effect on Executive Functioning | Reference in Supplemental Material |
|---|---|---|---|---|---|---|
| DRD1 (SNP rs265981) | A G | A | Lower DA responsiveness | ↑ | ↓ | (1–6) |
| DRD2/ANKK1 (SNP rs1800497) | A G | A | Higher DA responsiveness | ↓ | ↓ | (11–20) |
| DRD3 (SNP rs6280) | T C | C (Gly) | Lower DA responsiveness | ↑ | ? | (22–27) |
| DBH (SNP rs2519152) | T C | T | Higher DA levels | ? | ↓ | (28–34) |
| COMT (SNP rs4680) | A G | A (Met) | Higher DA levels | ↑ | ↑ | (35–39) |
| DAT1 (VNTR 40 bp) | 440 480 | 440 | Higher DA levels | ↑ | ↑ | (39–43) |
| DRD4 (VNTR 48 bp) | 7r vs all other | 7 repeat | Higher DA responsiveness | ↑ | ↓ | (39,45–54) |
| DRD5 (VNTR 130–166 bp) | 148 bp vs all other | 148 bp | Lower DA responsiveness | ↑ | ↓ | (30,56–60) |
| MAOA (VNTR 30 bp) | <3.5 vs ≥3.5 | ≥3.5 | Lower DA levels | ↑ | ↓ | (61–63) |

For detailed information and references, see Appendix, Supplemental Digital Content, Functional variants in dopaminergic genes and their association with reward sensitivity and executive functioning, http://links.lww.com/MSS/B99.

We further expect this to be most prominent in those alleles associated with both higher reward sensitivity and better executive functioning (*DRD2/ANKK1* (rs1800497) "T" allele, *COMT* (rs4680) "A" allele, *DAT1* (VNTR 40 bp) 440-bp repeat).

## MATERIALS AND METHODS

**Participants.** The participants of this study were drawn from the larger cohort of twins and their family members that agreed to participate in the study on individual differences and behavior by the Netherlands Twin Registry (NTR). The Medical Research Ethics Committee of the VU University Medical Centre approved the protocol for data collection. All participants 18 yr and older signed a written informed consent form. For participants younger than 18 yr, the primary caregiver gave written informed consent. Characteristics and recruitment of participants are described elsewhere (16,17). Only individuals with a Dutch/Western European background for whom both genotyping data and at least one measure of leisure time exercise behavior through self-report were available were eligible for inclusion. Because the heritability of exercise behavior is highest during adolescence (70%–80% vs 20% in children and 50%–60% in adulthood [18]), the exercise data drawn from several longitudinal questionnaires were optimized to find genetic associations. The optimization consisted of choosing the data from the questionnaire in which the participants' age was closest to the age of 18 yr. The final sample consisted of 12,929 individuals (4393 families, including 1671 monozygotic twin pairs), 39.8% male participants, with an age range of 12–90 yr (mean ± SD, 32.45 ± 15.95 yr) in which 59.6% were adults (age range, 20–90 yr) and 40.4% were adolescents (age range, 12–19 yr).

**Phenotyping.** The phenotype of interest for this study was regular voluntary exercise behavior. Data on exercise behavior were collected by self-report questionnaires in which participants were asked to indicate 1) which exercise activities they participated in regularly (maximum number of five activities), 2) how many times per week they participated in the respective activity on average, and 3) how many minutes per instance they participated in the respective activity on average. Previous studies (19) have shown that the test–retest reliability of this questionnaire is high (>0.82) and that its outcome is associated with that of other instruments measuring regular moderate-to-vigorous physical activity (20). On the basis of the questionnaire, a variable coding for regular exercise ("Do you regularly participate in sports/exercise activities—Yes/No") was created, in which regular voluntary exercisers were given a value of 1 (Yes) and nonexercisers were given a value of 0 (No). We were not interested in activities that are 1) irregularly engaged in (such as ski holidays, swimming on holidays), 2) nonleisure time activities (e.g., cycling or walking as a form of transportation), 3) related to gardening or house cleaning, and 4) (for younger participants) compulsory physical education classes. These activities were therefore excluded. Participants who are only engaged in the excluded exercise activities are thus classified as nonexercisers and given a value of 0.

For each exercise activity reported, it was determined whether this activity was internally paced or externally paced. On the basis of the external–internal paced continuum of Galligan (11), we defined four levels of internally vs externally paced exercise to which an activity was assigned: 1) highly externally paced (pace is influenced by both teammates and opponents; e.g., soccer and basketball), 2) intermediate externally paced (pace is influenced by opponents or teammates only; e.g., martial arts and tennis), 3) low externally paced (pace is influenced by dynamic external elements like wind/water/music/synchronic team movements; e.g., sailing and street dance), and 4) internally paced (pace is mostly or entirely self-directed; e.g., running and yoga). In this study, we focus on the end of the continuum, namely, highly externally paced exercise. On the basis of the previously mentioned classification, participants were given a value of 1 (Yes) if they engaged in highly externally paced exercise activities (22.2%) and a value of 0 (No) if they engaged in intermediate (10.1%) or low (8.3%) externally paced activities only or if they did not engage in externally paced exercise (59.4%).

For each indicated exercise activity, the total number of minutes per week participated in the respective activity was calculated by multiplying the number of times per week with the number of minutes per time for that activity. The total number of minutes per week engaged in all exercise behaviors was calculated by summing over all eligible activities an individual was engaged in. The number of minutes per week spent on externally paced activities was calculated by summing over the relevant activities the participant had reported. Because of the high degree of skewedness for all the exercise activity variables, we decided to log10 transform them for further analysis.

**Genotyping and imputation.** The SNP genotyping was done on several platforms, including sequencing for the Netherlands reference genome project Genome of the Netherlands (GONL) (21). Platform priority was set as follows: GONL sequence ($N = 368$) > Illumnia Omni 1M ($N = 257$) > Illumina Human Beadchip 660 ($N = 1439$) > Affymetrix 6.0 ($N = 8940$) > Affymetrix–Perlegen ($N = 1142$). If a sample was done multiple times, the sample with the highest number of genotyped quality-controlled SNP was selected. Samples were removed if they failed to fulfill the following quality control (QC) criteria as described previously (22).

The genotype data of all platforms, except the GONL sequence individuals, were then merged into a single data set. Subsequently, the missing SNP genotypes between each platform were cross-platform imputed using the GONL reference data set (23). A second round of QC was applied to the cross-platform–imputed data (21). After this step, the 386 GONL samples from the NTR were readded to the data for the SNP that survived the QC. Ethnic outliers were detected ($N = 666$) using 10 principal components (PC), which were calculated for each individual in the data using the approach as described in Ref. (24). Subsequently, 20 PC

were computed within the Dutch sample to capture possible population clustering within the Netherlands (24). Finally, a second round of imputations was done with the 1000G phase 3 all ancestries reference panel using the Michigan Imputation Server.

In addition to these SNP, VNTR, namely, the classic DAT1, DRD4, DRD5, and MAOA polymorphisms, were available for 3363–3680 participants. The genotyping was done using polymerase chain reaction assays, and details about the laboratory procedures are previously described in Beijsterveldt et al. (16). Participants with mendelian errors were removed from the analyses. VNTR were tested for Hardy–Weinberg equilibrium (HWE) $P > 0.001$ and minor allele frequency (MAF) > 0.01. None of the VNTR failed the thresholds for HWE and MAF. The HWE and MAF for the SNP and VNTR in the final data set are shown in Table 2.

**Genotype coding and polygenic scores.** The SNP were coded on the basis of the presence of one of the two alleles in the genotype ranging from 0 to 2. The VNTR were coded on the basis of the presence or absence of a specific number of repeats ranging from 0 to 2. An exception was the X-linked MAOA VNTR where male participants received a code of 2 if the specific repeat was present on their single X-chromosome. Coding of the SNP and VNTR is based on concordance with previous research findings on the polymorphism with regard to reward sensitivity, executive functioning, and exercise behavior (Table 1). An overview of the exact coding of the alleles/repeats per polymorphism can be found in Table 2.

In addition, two polygenic scores (PGS) were calculated. The first PGS ("low DA response PGS") was calculated by summing the number of alleles associated with lower DA responsiveness (*DRD1* (rs265981) "A" allele, *DRD2/ANKK1* (rs1800497) "G" allele, *DRD3* (rs6280) "C" allele, *DRD4* (VNTR 48 bp) no 7 repeat, *DRD5* (VNTR 130–166 bp) 148 bp) or higher DA levels (*DBH* (rs2519152) "T" allele, *COMT* (rs4690) "A" allele, *DAT1* (VNTR 40 bp) 440 bp, *MAOA* (VNTR 30 bp) <3.5 repeats) for each participant, referred to as the number of increaser alleles. To calculate the second PGS ("executive and reward congruency PGS"), we summed the number of alleles associated with both higher reward sensitivity and better executive functioning (*DRD2/ANKK1* (rs1800497) "G" allele, *COMT* (rs4680) "A" allele, *DAT1* (VNTR 40 bp) 440-bp repeat) for each participant, referred to as the number of increaser alleles.

**Statistical analysis.** To map the differences in exercise behavior (defined as % regular exercisers, % regular externally paced exercisers, number of minutes spent on exercise as a whole and number of minutes spent on externally paced exercise) with regard to sex and age (binned in three age groups: 18 to <25 yr, 25 to <55 yr, and 55 yr and older), a chi-square and an ANOVA analysis were performed, respectively.

General linear model analyses were performed in SPSS for Windows (version 23.0; SPSS Inc) to investigate the association between the genetic polymorphisms and PGS versus the total weekly minutes of voluntary exercise behavior as a whole and/or the total weekly minutes of voluntary externally paced exercise behavior. In each linear model analysis, the genetic polymorphisms and PGS were entered as independent variables separately. Nonexercisers ($N$ = 4926) are retained in these analyses and given a weekly volume of zero. As a sensitivity analysis, we repeated the analyses in exercisers only.

In the genetic association analyses, the following variables were included as covariates: sex (0, male; 1, female), age, age squared, sex–age interaction, and the first 20 genetic PC. Family was included as a random factor to account for clustering due to relatedness. Preliminary analyses showed that correction for the batch effect of genotyping SNP was not necessary. For the analyses including VNTR, the following variables were included as covariates: sex, age, age squared, sex–age interaction, and batch effect for study origin. Family was included as a random factor to account for clustering due to relatedness. For a subset of the participants in the VNTR analyses, the first 20 genetic PC were available due to concurrent availability of genome-wide SNP data (~70%). For this subset, all analyses were repeated including the previously mentioned covariates with the addition of the 20 PC.

We corrected for multiple testing by dividing the $P$ value by the number of polymorphisms and two PGS (0.05/11), resulting in a significance threshold of $P = 0.005$.

## RESULTS

Table 3 depicts the differences between sex and age groups with regard to voluntary exercise behavior. Male participants spent more minutes per week engaged in exercise behavior



TABLE 2. Number of individuals with complete genotype and phenotype data (N), their mean age (SD), % male, allele/VNTR coding, MAF, and the P value of the test for HWE.

| Gene | N | Age, $\mu$ (SD) | Male, % | Minor Allele | 0 (Allele/Repeat) | 1 (Allele/Repeat) | 2 (Allele/Repeat) | MAF | HWE |
|---|---|---|---|---|---|---|---|---|---|
| DRD1 (rs265981) | 10,244 | 34.46 (16.00) | 38.8 | A | GG | AG | AA | 0.36 | 0.05 |
| DRD2/ANKK1 (rs1800497) | 10,247 | 32.37 (15.98) | 39.5 | A | GG | AG | AA | 0.19 | 0.23 |
| DRD3 (rs6280) | 10,247 | 32.46 (16.00) | 38.8 | C | TT | TC | CC | 0.31 | 0.36 |
| DBH (rs2519152) | 10,245 | 32.46 (16.00) | 38.8 | C | CC | TC | TT | 0.47 | 0.43 |
| COMT (rs4680) | 10,246 | 32.46 (16.00) | 38.8 | A | GG | AG | AA | 0.45 | 0.68 |
| DAT1 (VNTR 40 bp) | 3586 | 27.78 (14.87) | 43.1 | 440 bp | Two 480 bp | 440–480 bp | Two 440 bp | 0.25 | 0.37 |
| DRD4 (VNTR 48 bp) | 3363 | 28.61 (15.08) | 43.7 | 7r | No 7r | One 7r | Two 7r | 0.18 | 0.54 |
| DRD5 (VNTR 130–166 bp) | 3680 | 28.60 (14.97) | 42.2 | 148 bp | No 148 bp | One 148 bp | Two 148 bp | 0.49 | 0.43 |
| MAOA (VNTR 30 bp) | | | | | | | | | |
| Male | 1564 | 29.38 (15.59) | — | ≥3.5r | One <3.5r | — | One ≥3.5r | 0.34 | n.a. |
| Female | 2052 | 28.28 (14.55) | — | ≥3.5r | Two <3.5r | <3.5r to ≥3.5r | Two ≥3.5r | 0.37 | 0.86 |

n.a., not applicable.

TABLE 3. Sex and age differences in voluntary exercise behavior.

| | N | % Exercisers | % Exercisers Engaged in Externally Paced Activities | No. Weekly Minutes Exercise, $\mu$ (SD) | No. Weekly Minutes Externally Paced Exercise, $\mu$ (SD) |
|---|---|---|---|---|---|
| All participants | | | | | |
| All | 12,929 | 61.9 | 22.2 | 132.44 (172.39) | 45.01 (100.35) |
| Male | 5144 | 62.0 | 30.8 | 152.67 (194.06) | 64.10 (116.59) |
| Female | 7786 | 61.9 | 16.5* | 119.07 (154.99)* | 32.39 (85.71)* |
| 18–25 yr | 6143 | 72.4 | 35.2 | 173.52 (182.14) | 78.55 (126.43) |
| Male | 2490 | 75.1 | 46.9 | 207.40 (201.25) | 109.40 (141.41) |
| Female | 3653 | 70.6 | 27.2 | 150.43 (163.93) | 57.53 (110.29) |
| 25–55 yr | 5650 | 54.2 | 11.5 | 97.77 (148.07) | 16.28 (55.40) |
| Male | 2118 | 51.8 | 17.8 | 102.78 (160.94) | 24.79 (66.69) |
| Female | 3532 | 55.7 | 7.7 | 93.17 (139.69) | 11.19 (46.63) |
| 55+ yr | 1136 | 43.4** | 4.9** | 87.69 (179.93)** | 6.48 (35.39)** |
| Male | 536 | 41.0 | 7.5 | 95.52 (209.88) | 9.02 (36.45) |
| Female | 600 | 45.5 | 2.7 | 80.70 (147.97) | 4.22 (34.30) |
| Exercisers only | | | | | |
| All | 8007 | — | 35.8 | 213.85 (174.86) | 72.68 (119.38) |
| Male | 3187 | — | 49.7 | 246.42 (194.13) | 103.47 (113.67) |
| Female | 4820 | — | 26.6* | 192.32 (157.21)* | 52.32 (104.03)* |
| 18–25 yr | 4449 | — | 48.6 | 239.59 (173.13) | 108.46 (137.21) |
| Male | 1870 | — | 62.5 | 276.17 (186.91) | 145.68 (146.09) |
| Female | 2579 | — | 38.5 | 213.06 (157.21) | 81.48 (123.61) |
| 25–55 yr | 3065 | — | 21.2 | 178.39 (160.81) | 30.02 (72.43) |
| Male | 1097 | — | 34.3 | 198.44 (176.15) | 57.86 (86.52) |
| Female | 1968 | — | 13.9 | 167.22 (150.47) | 20.08 (61.04) |
| 55+ yr | 493 | — | 11.4** | 202.07 (226.99)** | 14.94 (52.57)** |
| Male | 220 | — | 18.2 | 232.73 (274.83) | 21.98 (54.40) |
| Female | 273 | — | 5.9 | 177.36 (176.11) | 9.27 (50.43) |

*Chi-square analysis showed that male and female participants differed significantly, $P < 0.001$.
**Post hoc Bonferroni ANOVA analyses showed that all age groups differed significantly, $P < 0.001$.

than did female participants, both in exercise as a whole and externally paced activities. Both male and female participants show a significant decrease in the time spent on exercise behavior with increasing age, and this decrease is much mo re pronounced when looking at externally paced exercise only.

The genetic association analyses for each of the nine genes separately showed no evidence for an association of the dopaminergic alleles with either exercise as a whole or externally paced exercise (Table 4). The low DA response PGS also did not yield a significant association with either exercise behavior as a whole or externally paced exercise behavior.

In contrast, the executive and reward congruency PGS did show a significant association with the number of minutes per week spent on externally paced exercise behavior ($P = 0.003$; Table 4, Fig. 1A). The association of this PGS remains significant and consistent in direction after correcting for the genetic PC and when computed in exercisers only ($P = 0.005$; Table 4). However, the observed association seems to be entirely attributable to the *DAT1* and *COMT* genes with no additional contribution of *DRD2/ANKK1*. When testing this assumption, a PGS based on *DAT1* and *COMT* indeed showed an even stronger effect (total population: $N = 3562$, $B = 0.057$, SE = 0.0195, $P = 0.003$; exercisers only: $N = 2287$, $B = 0.089$, SE = 0.0263, $P = 0.001$; Fig. 1B). Independently, an increase in the number of *DAT1* and *COMT* alleles that are positively associated with reward and executive functioning (440-bp allele and MET allele, respectively) is associated with an increase in minutes spent on externally paced exercise (Figs. 1C, D). However, both executive and reward congruency PGS measures are indicative of an inverted U-shape, in which having both the minimal and the maximal number of increaser alleles is nonbeneficial.

## DISCUSSION

In this article, we aimed to expand the body of research on causative biological factors for the initiation and maintenance of voluntary exercise behavior. We focused on genetic variants with functional effects on dopaminergic signaling with reported downstream effects on executive functioning and reward sensitivity. We gained new insight by explicitly taking into account the types of voluntary exercise activity participants were regularly engaged in.

In a large data set ($N$ = 12,929), we classified all self-reported voluntary exercise activities as either highly externally paced or otherwise based on the external–internal paced continuum of Galligan et al. (11). This continuum takes into account the nature of the set of skills required in exercise activities, specifically executive function skills. We hypothesized that the effects of executive skills on the motivation to engage in exercise cannot be ignored if the exercise activities depend on these skills. Genetic association with nine functional dopaminergic allelic variants and two PGS based on these variants yielded only a single result that survived multiple testing and correction for possible stratification. The PGS of increaser alleles in *DRD2/ANKK1, COMT* and *DAT1* for executive function and reward sensitivity showed a consistent association with a higher volume of externally paced exercise activities. The effect seemed to be driven entirely by the *COMT* Met and *DAT1* 440-bp alleles, with the *DRD2/ANKK1* "A" allele having no additional contribution.

TABLE 4. The effect of genotype on the total weekly number of minutes spend on voluntary exercise behavior.

| | No. Minutes Exercise | | | | No. Minutes Externally Paced Exercise | | | | No. Minutes Externally Paced Exercise in Exercisers Only | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Gene (Allele) | N | B | SE | P | N | B | SE | P | N | B | SE | P |
| DRD1 (A) | 10,244 | −0.011 | 0.0171 | 0.51 | 10,244 | −0.008 | 0.0147 | 0.59 | 6362 | −0.010 | 0.0211 | 0.64 |
| DRD2/ANKK1 (A) | 10,247 | 0.005 | 0.0211 | 0.82 | 10,247 | −0.002 | 0.0179 | 0.90 | 6364 | −0.006 | 0.0255 | 0.81 |
| DRD3 (C) | 10,247 | −0.020 | 0.0177 | 0.26 | 10,247 | −0.020 | 0.0155 | 0.20 | 6364 | −0.025 | 0.0219 | 0.25 |
| DBH (T) | 10,245 | 0.014 | 0.0168 | 0.39 | 10,245 | −0.004 | 0.0144 | 0.77 | 6362 | −0.013 | 0.0206 | 0.52 |
| COMT (A) | 10,246 | −0.012 | 0.0171 | 0.47 | 10,246 | 0.024 | 0.0145 | 0.093 | 6363 | 0.041 | 0.0208 | 0.050 |
| DAT1 (440 bp) | 3586 | 0.053 | 0.0316 | 0.095 | 3586 | 0.085 | 0.0309 | 0.006 | 2300 | 0.104 | 0.0403 | 0.010 |
| DAT1 (440 bp) | 2511 | 0.034 | 0.0388 | 0.37 | 2511 | 0.093 | 0.0393 | 0.018 | 1683 | 0.122 | 0.0479 | 0.011 |
| DRD4 (7r) | 3363 | −0.022 | 0.0388 | 0.58 | 3363 | 0.061 | 0.0357 | 0.086 | 2118 | 0.099 | 0.0495 | 0.045 |
| DRD4 (7r) | 2512 | −0.017 | 0.0442 | 0.71 | 2512 | 0.058 | 0.0439 | 0.19 | 1683 | 0.103 | 0.0578 | 0.075 |
| DRD5 (148 bp) | 3680 | 0.002 | 0.0282 | 0.95 | 3680 | 0.006 | 0.0259 | 0.82 | 2364 | −0.003 | 0.0352 | 0.93 |
| DRD5 (148 bp) | 2568 | −0.011 | 0.0342 | 0.74 | 2568 | 0.015 | 0.0326 | 0.65 | 1723 | 0.021 | 0.0423 | 0.62 |
| MAOA (≥3.5r) | 3616 | −0.007 | 0.0244 | 0.77 | 3616 | −0.011 | 0.0234 | 0.64 | 2327 | −0.021 | 0.0313 | 0.50 |
| MAOA (≥3.5r) | 2523 | 0.004 | 0.0290 | 0.90 | 2523 | 0.010 | 0.0287 | 0.71 | 1699 | 0.010 | 0.0366 | 0.78 |
| Low DA response PGS | 2512 | 0.009 | 0.0117 | 0.45 | 2512 | 0.019 | 0.0113 | 0.09 | 1685 | 0.024 | 0.0145 | 0.10 |
| Low DA response PGS | 2403 | 0.009 | 0.0119 | 0.47 | 2403 | 0.019 | 0.0115 | 0.09 | 1614 | 0.021 | 0.0148 | 0.15 |
| Executive and reward congruency PGS | 3586 | 0.005 | 0.0172 | 0.78 | 3586 | 0.047 | 0.0162 | 0.003 | 2300 | 0.071 | 0.0220 | 0.001 |
| Executive and reward congruency PGS[a] | 2511 | −0.008 | 0.0208 | 0.71 | 2511 | 0.058 | 0.0208 | 0.005 | 1683 | 0.084 | 0.0267 | 0.002 |

SNP: model corrected for sex, age, age squared, age–sex interaction, and 20 PC on Dutch ancestry; VNTR and PGS: model corrected for sex, age, age squared, age–sex interaction, and batch effect. Significant effects ($P < 0.005$) are depicted in bold.

[a]Indicates model including VNTR additionally corrected for the 20 PC on Dutch ancestry (which were only available for a subset of the participants, hence the smaller sample sizes).

The *COMT* and *DAT1* alleles here associated with higher weekly externally paced exercise volume have been previously linked to higher DA levels, better executive functioning, and higher reward sensitivity. The *COMT* gene encodes the DA degrading catechol-*O*-methyltransferase enzyme and is highly expressed in the prefrontal cortex and to a lesser extent

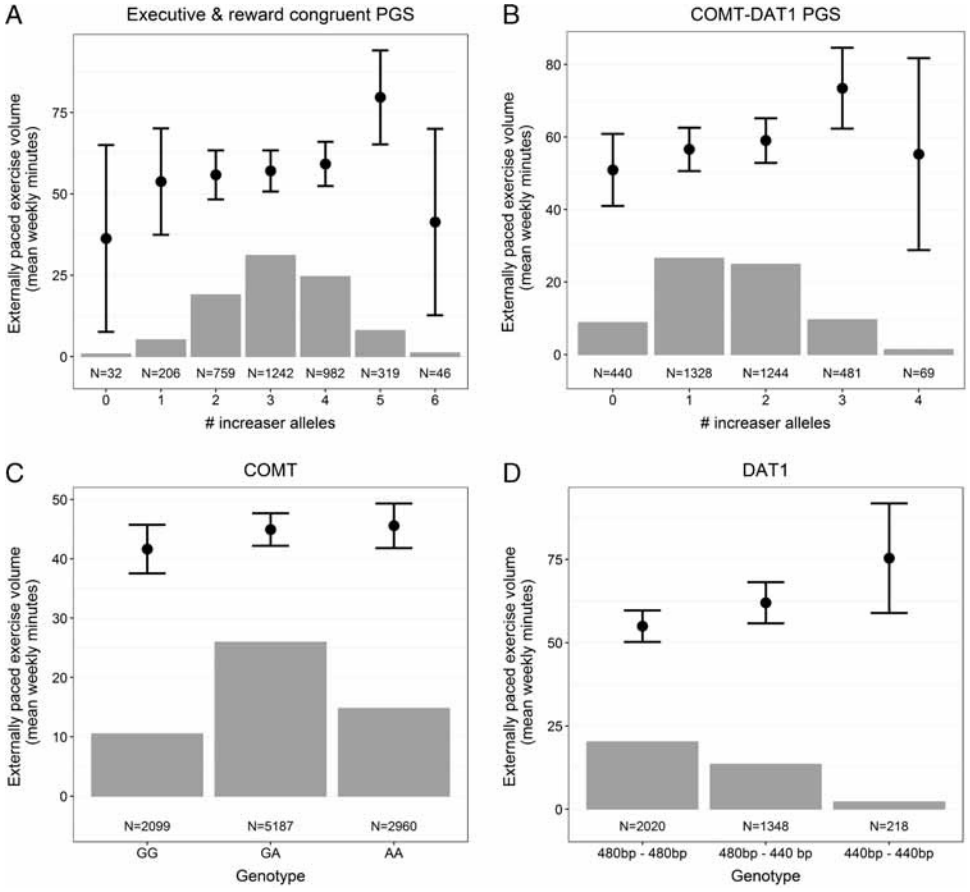


**FIGURE 1—The association between genotype and externally paced exercise volume. A and B, *Dots with error bars* show a positive relationship between the number of executive and reward congruent PGS (composed of *DRD2/ANKK1*, *COMT*, and *DAT1*) and *COMT-DAT1* PGS increaser alleles, respectively, and externally paced exercise volume. The *solid bars* depict the number of participants for each PGS allele count. C and D, *Dots with error bars* show a positive relationship between the COMT A and DAT1 440-bp alleles and externally paced exercise volume. The *solid bars* depict the number of participants for each genotype. Error bars depict 95% confidence interval.**

in the striatum (25). The Met variant degrades DA less efficiently compared with the COMT-Val enzyme, resulting in higher DA levels (26). Homozygosity of the *COMT* Met allele has been associated with both better performance on neuropsychological measures of executive function (Trail Making Test, Part B) or the Delis–Kaplan Executive Function System Trail Making subtest (Trial 4)) (27), better performance on the Frontal Assessment Battery (28), and relatively increased reward learning (29) and reward responsiveness (30).

The *DAT1* gene encodes the DA active transporter, which clears DA from the synapse by depositing it back into the cell. It is thought to be particularly important as a regulator of phasic DA release in subcortical regions where DAT1 is most abundant (31,32). The 440-bp allele is less transcriptionally active compared with the 480-bp allele (25) resulting in lower DA reuptake and thus higher DA levels in the synapse. The less transcriptionally active 440-bp allele is associated with better performance on a continuous performance task in children with attention-deficit hyperactivity disorder (15), a less steep decline in performance over time on the Psychomotor Vigilance Test in healthy adults (33), and higher reward anticipation and responsiveness (30).

Across the largest part of the range of combined genotypes, the *COMT* Met and *DAT1* 440-bp synaptic DA level increaser alleles had an additive effect on externally paced exercise behavior (Fig. 1B). However, the additivity of COMT and DAT1 seems to break down in the combination of the two most extreme homozygotes of *COMT* Met/Met and *DAT1* 440 bp/440 bp. Double homozygotes spent much less than the expected time on externally paced exercise. Caution is in order in interpreting this finding. There were relatively few ($N = 69$) participants in this genotype group, and the within-group individual differences were large. Our finding nonetheless resonates with similar previous findings. A study by Yacubian et al. (25) found an inverted U-shape-typed interaction effect of *COMT* and *DAT1* haplotypes on striatal reward sensitivity during a reward sensitive guessing task. Specifically, the combination of the *COMT* Met allele with the *DAT1* 480-bp allele and the *COMT* Val allele with the *DAT1* 440-bp allele showed blunted responses.

A comparable interaction between the *COMT* Met and the *DAT1* 440-bp allele has been observed with regard to executive functioning. During a verbal fluency task, the *COMT* Met allele homozygotes that also carried the *DAT1* 440-bp allele showed more activation in the left parietal cortex compared with *COMT* Met allele homozygotes with two copies of the *DAT1* 480-bp allele (34). Similar interactions have been found in the hippocampus and tentatively in the prefrontal cortex during two memory tasks (35).

The deviant pattern in the double *COMT/DAT1* homozygotes has been explained by an interaction between tonic and phasic striatal DA levels (36). When tonic DA levels are higher than average because of the COMT Met enzyme, phasic DA release is likely to be more strongly inhibited through stimulation of presynaptic autoreceptors. However, reduced synaptic DA clearance due to the DAT1 440-bp variant might augment phasic DA levels leading to an optimal balance between phasic and tonic striatal DA levels resulting in optimal dopaminergic signaling.

The association of exercise behavior with the *COMT* and *DAT1* alleles was limited to externally paced exercise activities. No association of the increaser alleles in *COMT* and *DAT1* for executive function and reward sensitivity was seen with the total weekly minutes of voluntary exercise behavior as a whole, which includes the large group of exercisers (42.5%) engaged in internally paced activities (like jogging, swimming, and bicycle racing). In fact, none of the nine polymorphisms, or a PGS based on their increaser allele effects on DA availability, were associated with total volume of exercise behavior. This is consistent with the prior two largest studies on the association between dopaminergic variants and moderate-to-vigorous physical activity (9) or voluntary exercise behavior (5).

That the association with dopaminergic candidates can be restricted to a particular type of exercise activity immediately suggests that the age and sex composition of a sample may influence the association. In our data, we observed that both younger and male participants were the most likely to be engaged in a form of externally paced exercise behavior. Younger and male participants also spent more minutes per week on externally paced exercise behavior when compared with older and female participants, respectively. These observations confirm previous suggestions from twin studies that the genetic contribution to the total volume of exercise behavior changes over time (37) and that the influence of genetic variants may be different at different ages. Many genes are differentially expressed across the life-span, for instance, through epigenetic modifications (38,39). It is clearly advisable to take into account not only the type of exercise behaviors in genetic association studies on exercise behavior, but also sex and age effects on the preferred activities. This advice should not be restricted to candidate genes in the dopaminergic system.

A question that remains unsolved is whether the association of the two dopaminergic genes with externally paced exercise behavior is more strongly mediated by the effects of the *COMT* and *DAT1* variants on executive function skills rather than reward sensitivity, or that both pathways are of relevance. In this article, we suggest that executive skills are of influence on the motivation to engage in exercise activities that depend on these skills on the basis of the simple principle that people are more motivated to repeat a behavior that they are good at. However, dopaminergic effects on reward sensitivity could also directly act to influence either the acute affective response to exercise or the "feeling good" often reported shortly after exercise has terminated. Large individual differences in the acute affective response to exercise and feeling good after exercising have been reported, which are partly heritable (40). The *COMT* and *DAT1* variants could well be part of that heritability, because engagement in exercise behavior leads to the production of DA (41). Genetic variation in the mesolimbic reward system could amplify the feelings of reward more in exercisers than others, increasing the motivation to repeat this behavior (42).

The previously mentioned reasoning contrasts with recent insights from contemporary exercise psychology. Evidence from a systematic review favored the acute response to exercise as the stronger determinant of future exercise behavior than the affective state after exercise (43). Most people, including regular exercisers, report feeling "bad" rather than "good" during exercise when compared with their positive affect at rest (44). An aversion to exercise, in the absence of immediate utility, would make evolutionary sense as it leads to energy conservation (45). If exercising is not rewarding at all, it would seem doubtful that genetic effects on reward sensitivity play a major role. However, we cannot exclude the possibility that more positive affect is awarded during externally paced exercise activities than during internally paced activities. Externally paced activities differ in more aspects from internally paced activities than just their dependency on good executive function. They are far more often present in competitive team sports than in solitary and/or noncompetitive exercise. Rewarding effects of the social context and feelings of mastery (e.g., winning a game) may therefore be more abundant in externally paced exercise. To untangle the relative importance of genetic effects on executive function versus reward sensitivity for the engagement in different types of exercise behavior, more in-depth phenotyping of exercise activities may be necessary, that is, establishing whether they are performed in a competitive or recreational setting and in which social context.

The strengths of the current study include the large sample size, carefully chosen functional genetic polymorphisms influencing the DA circuit, executive functioning and reward sensitivity, and well-defined classification of exercise behavior on the external–internal paced continuum. Furthermore, we corrected for ancestry and repeated the VNTR analyses in a subset of the participants for whom the first 20 genetic PC were available. Lastly, we performed a sensitivity analysis in exercisers to determine whether the observed effects were not due to exercise status (yes/no). A limitation of this study is that it was built on a theoretical framework deriving largely from candidate gene studies, not just with regard to exercise behavior but also with regard to reward sensitivity and executive function. Large-scale meta-analytic consortia using a hypothesis-free genome-wide association study approach have only rarely confirmed findings of hypothesis-driven candidate gene studies which have been notably difficult to replicate (46,47). The value of theoretical frameworks building on candidate gene findings can therefore be contested.

We present the first large-scale study that investigated the effect of genetic polymorphisms in the dopaminergic signaling pathway with time spent on voluntary externally paced exercise behavior. We conclude that genetic variation in dopaminergic signaling involved in both executive functioning and reward sensitivity may influence the preference for this type of exercise behavior. More generally, we conclude that taking into account the type of exercise activities, rather than total volumes expressed (e.g., weekly amount of time exercising), can increase the success of genetic association studies aiming to unravel the neurobiology of voluntary exercise behavior.

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The results of the present study do not constitute endorsement by the American College of Sports Medicine and are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

EPIDEMIOLOGY

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