Mind the reading mind: a multifaceted and methodologically diverse approach to investigating the role of attentional control and feedback in reading comprehension

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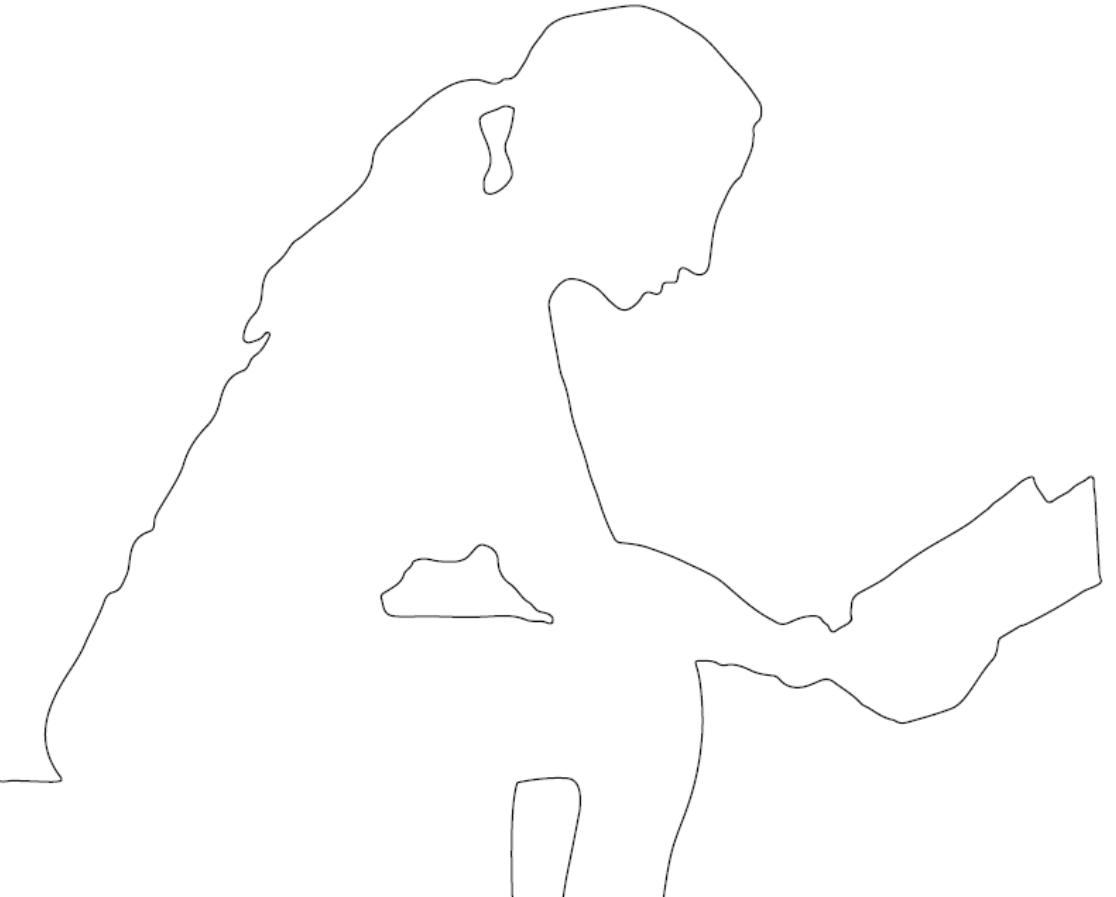

Chapter 3

The Effects of Increased Dopamine-Levels on Attentional Control During Reading and Reading Comprehension

Based on:

Swart, E. K., & Sikkema-de Jong, T. M. (under review). The effects of increased dopamine-levels on attentional control during reading and reading comprehension.

Abstract

The aim of the present study was to gain insight in the neurobiological processes, particularly the dopaminergic processes, underlying attentional control during reading and reading comprehension. In order to test the effects of increased dopamine (DA) in the brain, female university students *(N* = 80*),* half of them carrier the DRD4-7R allele and half of them not, participated in a double blind placebo-controlled within-subject experiment in which they were orally administered levodopa or a placebo before reading a text. After reading the text, participants reported on their attentional control during reading and completed comprehension questions. Pharmacologically increasing DA levels in the brain negatively influenced reading comprehension. This effect was moderate (η_p^2 = .13). Alternatively, increased DA levels in the brain did not affect attentional control. No interaction effects of condition and DRD4 genotype were found, for either attentional control or reading comprehension. Results are discussed from the perspective of the inverted U-shape theory and the possible dopamine-related mechanisms.

Keywords: dopamine, attentional control, reading comprehension, inverted U-shape theory

Note

This study was registered with EudraCT European Clinical Trials Database (Identifier: 2014-001352-36). We acknowledge dr. A. G. Bus for her input to the design of the study at the start of the project.

Introduction

Reading texts requires the reader to control attention for a longer period of time in order to encode and integrate the information into a coherent mental representation of the text (see e.g., van den Broek et al., 2005). This mental representation is constructed by extracting meaning from the text, and the quality of the mental representation is related to the ability of the reader to learn from texts (van den Broek et al., 2005). Research has shown that people who are better able to control their attention during reading learn more from the texts they read (e.g., Sanders et al., 2017; Zhou et al., 2020). Arrington et al. (2014) showed that attentional control, specifically the ability to sustain attention for a longer period of time, and the ability to prevent irrelevant thoughts or information from interfering with performing a task, had a direct positive effect on reading comprehension. Adolescents who were better able to regulate attention, scored higher on reading comprehension. Conners (2009) argued that attentional control should be seen as a third and fundamental component of reading comprehension, just as decades of research have shown for the two components of reading comprehension according to the Simple View of Reading (Gough & Tunmer, 1986). In line with Arrington et al. (2014) and Conners (2009) research on attentional control and reading comprehension, in the present study we defined attentional control as an umbrella construct referring to the allocation of attentional processes and resources, including inhibition of irrelevant and interfering information, selectivity of attention for task-relevant information and sustaining attention for longer periods of time.

Several lines of research have focused on training attentional control via action video games (Green & Bavelier, 2012), mindfulness and meditation (Chiesa et al., 2011), and cognitive training (e.g., Karbach & Verhaeghen, 2014). Results of the research have shown positive effects of training on performance on neuropsychological tasks demanding attentional control, yet few however have examined whether or not this improved performance transfers to other, real-world tasks (see Owen et al., 2010).

Specific to reading comprehension, the effects of attentional control training have varied. For example, Zanesco et al. (2016) found that mediation training improved attentional control during reading, yet the improved attentional control did not lead to improved reading comprehension. Sanders et al. (2017) found that instructing readers to monitor their attention during reading resulted in better attentional control during reading, but negatively influenced reading comprehension, whereas instructing readers to focus on the construction of a mental representation of the text resulted in improved reading comprehension, but had no effect on attentional control. Finally, Mrazek et al. (2013) found positive effects of a mindfulness training on both attentional control during reading and reading performance.

In sum, the research thus far has not provided a clear picture of the relation between attentional control training and reading comprehension. The mixed results may relate to the complex role that dopamine (DA) plays in attentional control (Cools & D'Esposito, 2011). For example, one of the methods used to train attentional control in the studies just described was meditation, an intervention in which people consciously try to control their attention. A side effect of meditation is a large increase in DA levels in the brain (Kjaer et al., 2002). In the present study we aim to investigate the role of DA in attentional control to gain more insight in individual differences in attentional control during reading and how this is related to reading comprehension.

The Role of DA in Attentional Control

DA plays a key role in sustaining attention over prolonged periods of time during completion of tasks, such as reading long stretches of text, that require working memory to integrate information and update knowledge in memory (Boulougouris & Tsaltas, 2008; Westbrook & Braver, 2016). Studies with patients who suffer from reduced DA transmission in the brain due to for instance Parkinson's disease, ADHD, or brain lesions have shown that the ability to focus attention decreases, and distractibility increases, when the transmission of DA in the brain is impaired (Nieoullon, 2002). The prefrontal cortex, which is a DA rich area in the brain, is particularly involved in attentional control, and is highly sensitive to fluctuations in DA (see also Cools & D'Esposito, 2011; Shaywitz & Shaywitz, 2008).

DA levels in the brain can be pharmacologically manipulated by administering drugs containing levodopa. Levodopa is a precursor of DA, acting on DA receptors in, amongst other brain areas, the prefrontal cortex. Levodopa can restore decreased uptake of DA in the brain, resulting in higher DA levels and enhanced cognitive performance. This effect has been found in both clinical samples and healthy adults (see Moustafa et al., 2013). In line herewith, we wondered whether higher DA levels in the brain during reading might be beneficial for attentional control during reading. Although the number of DA administration studies involving cognitive outcomes has increased over the last ten to fifteen years, the exact influence of DA levels in different brain areas that are related to attentional processes (e.g., prefrontal cortex, anterior cingulate cortex, basal ganglia or caudate nucleus; see Shaywitz & Shaywitz, 2008) on performance on different kinds of cognitive tasks has not yet become clear (see Diamond et al., 2004; Nieoullon, 2002; Westbrook & Braver, 2016). Performance on some neuropsychological tasks that require attention (e.g., the dots-mix task) appeared to be sensitive to fluctuations in DA levels (particularly fluctuations in the prefrontal cortex; see Diamond et al., 2004), while

performance on other tasks (e.g., a card sorting task tapping into cognitive flexibility) was not (Ko et al., 2009;).

The Role of DA in Memory Formation

DA is not only involved in attentional processes, but also in related processes such as memory formation (see e.g., Boulougouris & Tsaltas, 2008; Nieoullon, 2002). Similar to the results of the studies on DA and attention, the results of studies on DA and memory formation are mixed (see e.g., Cools & Robbins, 2004). For example, both Breitenstein, Flöel et al. (2006) and Knecht et al. (2004) found positive results associated with increased levels of DA on memory. Breitenstein, Flöel et al. (2006) found that healthy adults who were administered either levodopa or D-amphetamine (both aimed to increase DA levels in the brain) performed better on a word-learning task than adults in a placebo control group. Participants learned faster, learned more, and had better retention after one month when administered either levodopa or D-amphetamine. Similarly, Knecht et al. (2004) found that healthy adults who were administered levodopa learned faster, learned more, and had better retention than those in a placebo control group.

Other studies, however, have found no or negative effects of increased levels of DA. For example, Linssen et al. (2014) found that pharmacologically increasing DA levels in healthy adults with the same dose that was used in the studies by Knecht et al. (2004) and Breitenstein, Flöel et al. (2006) had negative effects on memory performance on a word learning task. Participants had to remember as many words as possible from a list of 30 words that was shown to them three times. Based on EEG data recorded during the word learning task Linssen et al. (2014) argued that administering levodopa slowed down memory processes during the task as was shown by delayed latencies of ERP components (P3b and P600) during the encoding phase of the word learning task. Nevertheless, behavioural data showed that performance on the word learning tasks, as well as two working memory tasks and an associate learning task were not influenced in a positive or negative way by the drug administration.

In sum, although there are some indications that on a neurobiological level increased DA levels in the brain have a negative effect on memory formation, on a behavioural level, negative effects are absent and in some studies even positive effects on memory performance were found.

Explaining the Diverging Effects of Increased DA on Cognitive Performance

Linssen et al. (2014) used the inverted U-shape theory as a possible explanation for not finding effects of pharmacologically increasing DA levels in the brain on (working) memory performance of healthy adults. According to this theory, the relation between DA levels in the brain and attention and memory formation follows an inverted U-shape (Vijayraghavan et al., 2007), that is, that both 'too-high' and 'too-low' levels can hinder cognitive performance. However, this theory does not explain the positive effects of pharmacologically increasing DA on memory performance that have been found in other studies with healthy adults (e.g., Breitenstein, Flöel et al., 2006; Knecht et al., 2004), who are expected to have optimal or close to optimal DA levels. As a consequence, a direct test for the inverted U-shape theory is needed. Therefore, in the present study we test the effects of increased levels of DA in a subgroup of people who are expected to have a well-functioning dopaminergic system, i.e., optimal DA levels in the brain, and in a subgroup of people with reduced DA levels in the brain.

One gene that is found to be related to both levels of DA in the brain and attentional control, is the dopamine D4 receptor (DRD4) gene (Bonvicini et al., 2020). People who are carrier of the DRD4 7-repeat allele (DRD4-7R), sometimes referred to as 'the long variant', show a less efficient DA transmission, resulting in lower levels of DA in the brain (Ariza et al., 2012) than people carrying other variants of the allele. Carrying the DRD4-7R allele also has been shown to be a risk factor for ADHD, a disorder marked by difficulties in attentional control (see e.g., Bonvicini et al., 2020). In line with this reasoning, people carrying the DRD4-7R may benefit more from increased levels of DA in the brain than people who carry other polymorphisms of the DRD4 gene.

Present Study

The aim of the present study is to investigate the effects of increased levels of DA on attentional control during reading and reading comprehension. To achieve this aim, we pharmacologically manipulated the DA levels in the brain of healthy female university students using a similar dosage of levodopa as was used in previous studies (e.g., Breitenstein, Flöel et al., 2006; Knecht et al., 2004; Linssen et al., 2014). To the best of our knowledge, the present study is the first one testing the effects of pharmacologically manipulating DA in the case of reading comprehension. Additionally, our research expands the current literature by directly testing the inverted U-shape theory. Because the effects of increased DA may differ as a consequence of differences in baseline levels of DA in the brain, we investigated the effect of increased DA in two subgroups that are expected to

differ in baseline levels of DA in the brain: students who were carrier of the DRD4-7R allele and students who were not.

The present study employs a placebo-controlled double blind within-subjects experiment, in which healthy female students completed a reading task in one of two conditions (levodopa or placebo), after which their reading comprehension was measured. Based on previous research on DA and attentional control (see e.g., Boulougouris & Tsaltas, 2008; Nieoullon, 2002; Westbrook & Braver, 2016), we expect that administering levodopa will influence attentional control during reading. Additionally, in line with previous studies on the effects of administering levodopa on memory formation and word learning tasks (see Breitenstein, Flöel et al., 2006; Knecht et al., 2004; Linssen et al., 2014), we also expected administering levodopa to influence reading comprehension. In line with the inverted U-shape theory (Boulougouris & Tsaltas, 2008; Cools & D'Esposito, 2011; Vijayraghavan et al., 2007) and the fact that the DRD4-7R allele is related to reduced levels of DA (Ariza et al., 2012), we expected, on the one hand, that positive effects of levodopa would be particularly prominent in students carrying the DRD4-7R allele (i.e., less optimal DA levels), and on the other hand that increases in DA levels would result in a decrease in attentional control during reading and reading performance in the subgroup of students not carrying the DRD4-7R allele.

The present study takes a multimethod approach to measure attentional control during reading by measuring attentional control on both a biophysiological level and behavioural level. Recent research has shown that EEG data, specifically the frontal theta/beta ratio (TBR) might provide a biophysiological maker of attentional control during reading (Swart et al., 2020). In line with previous research on the relation between attentional control, fluctuations in attentional control, and (fluctuations in) frontal TBR in other cognitive tasks (e.g., van Son et al., 2019a), the study of Swart et al (2020) showed that both the average frontal TBR and fluctuations in frontal TBR are related to attentional control and fluctuations in attentional control. We take a similar multi-method approach to gain a thorough understanding of the effect of increased DA on reading comprehension, in the present study we investigate comprehension on both text-level and word-level. For text-level comprehension we combined two tasks, a summary writing task and reading comprehension questions. For word-level comprehension, we take both the breadth (i.e., the number of words participants learn after reading) and depth (i.e., knowledge on both word form and semantics; see e.g., Nation, 2020) of word-level comprehension into account by combining four tasks that each tap different levels of knowledge about the words in the text, ranging from questions on word form level to questions on passive and active semantic knowledge of a word.

Methods

Research Design

The experiment had a randomized, double-blind placebo-controlled within-subjects design. A total of 80 participants were submitted to two experimental conditions (levodopa and placebo) at two separate lab sessions. In the levodopa condition, participants were administered Sinemet125 (containing 100mg levodopa and 25mg carbidopa) at the beginning of the lab session, in the placebo condition participants took a placebo capsule. All medication was produced in identical capsules. To ensure that the study design was double-blind, randomization of the order of treatments (levodopa or placebo) and the order of texts that were read in both experimental sessions (text A and text B) was carried out by the university hospital pharmacy, resulting in four different combinations of the order of treatment condition and text. Before starting the research, its design and methodology were approved by the Education and Child Studies ethics committee of Leiden University (project ID: ECPW-2014/077) and the medical ethics committee of the Leiden University Medical Centre (project ID: NL49379.058.14).

Participants

An initial sample of 200 Dutch female undergraduate students were recruited via advertisements placed in university buildings and student houses and on social media. The total number of recruited students was based on the world-wide average prevalence of the DRD4 7-repeat genotype (20.7%; e.g., Chang et al., 1996). In order to end up with 40 participants with the DRD4 7-repeat allele, approximately five times as much participants had to be recruited. Because of gender differences in DA levels in the brain between men and women (see e.g., Munro et al., 2006) and the large proportion of female students within the faculty, it was decided to include only female participants. Participants had to be 18 years or older and right-handed. Students with dyslexia, medical illnesses indicating a risk in using haloperidol (e.g., cardiac illness, depression, thyroid disorders, or glaucoma), or known drug allergies, and students who were pregnant or lactating were excluded from participation in the study. Students also were excluded if they were using medication (other than contraceptives) or drugs in the two weeks prior to the experiment. After genotyping, 80 students (M_{age} 21.38 years, SD = 1,84; 40 participants carrying the DRD4-7r allele, and 40 participants who did not) were selected to participate in the experimental sessions.

Procedures

Buccal swabs were collected from all participants. DNA was isolated and variable number of tandem repeats (VNTR) genotyping was performed for the DRD4-gene by an external genomics company. Based on these results, participants were grouped in two subgroups: one group of participants carrying at least one DRD4 7-repeat allele (DRD4 7+) and one group carrying two shorter alleles (DRD4 7-). Each student that was selected after genotyping participated in two lab sessions on two separate days. Students were not informed about the individual results of the genotyping, so they were unaware of the genotype they carried.

At the beginning of the lab sessions, participants received capsules containing either Sinemet125 (release time of the ingredients is approximately 30 minutes; IBM Micromedex) or the placebo and took the capsules orally. The experiment was double-blind, which means that neither the participant, nor the experimenter knew whether Sinemet125 or the placebo was given to the participant. Except for one participant reporting nausea in the placebo condition, no side effects of the medication were reported by the participants. Immediately after administering the capsules during the first session, measures of executive functioning, attentional control, reading motivation and language skills were administered to control for comparability on these factors across the DRD4+ and DRD4- groups (for details on the measurement instruments for these background variables, see Appendix A).

Forty-five to sixty minutes after administration, the participant read a narrative text of approximately 4000 words. Participants read one of two passages from a Dutch translation of the novel *A Clockwork Orange* (Burgess, translated by Damsma & Miedema, 2012) that were selected for the present study. The passages were taken from two separate chapters of the book and were understandable without knowing the rest of the storyline. Events in the two chapters did not necessarily have to take place in the order in which the events actually appeared in the book, making counterbalancing of the order of the two texts possible. Text A consisted of 4049 words divided among 16 pages, and text B consisted of 4098 words divided among 17 pages. The texts respectively included 201 (text A, 5.0% of the total number of words) and 188 (text B, 4.6% of the total number of words) nonsense words from the fictional Nadsat language that was spoken by some of the characters in the novel.

Attentional control during reading was measured using the average frontal theta/beta-ratio (TBR) during reading and the *SD* in frontal TBR among the text pages (see Swart et al., 2020) and by a retrospective self-report that was administered directly after reading. Frontal TBR was extracted from the EEG-recording during reading. Immediately after reading the text, participants were provided with a paper version of the text and

were asked to mark moments in the text where they remembered being distracted from the text.

After self-reporting their attentional control during reading, participants were asked to write a summary of max. 5000 characters about the story they had just read and to answer open comprehension questions about the text (28 for text A and 24 for text B). Subsequently, participants completed four tasks concerning word-level comprehension.

Measurement Instruments

Frontal TBR During Reading

EEG data were recorded during a baseline period (three minutes eyes-closed and three minutes eyes-open) and during reading. We used 129-channel hydrocel Geodesic sensor nets and electrodes, which were placed according to the 10-20 system amplified by a NetAmps300 amplifier at a digitization rate of 500Hz (Electrical Geodesics Inc.). Impedances were kept below 50 kΩ. Raw data were further processed offline using Brain Vision Analyzer 2.0 software (Brain Products). Data were low-pass filtered at 100 Hz (-3 dB, 48 dB/oct) and high-pass filtered at 0.3 Hz (99.9% pass-band gain, 0.1% stop-band gain, 1.5 Hz roll-off) with a notch-filter of 50 Hz to eliminate electrical noise. Subsequently, EEG data were referenced to the average activity in all channels and ocular correction was performed using Gratton & Coles' procedure (Gratton et al., 1983). To retain as much artefact-free data as possible, raw EEG data were segmented in 2 second segments with an overlap of 5%. Segments containing artefacts (defined as: voltage steps exceeding 50 μV/ms, differences in values above 100 μV within an interval of 200 ms, amplitudes lower than -70 μV or higher than 70 μV or segments containing less than 0.5 μV activity in intervals of 100 ms intervals) were excluded from further analyses. In addition, noisy channels were replaced by average activity of the closest electrodes. After segmenting the data and correcting for artefacts, power densities in the theta (4-7 Hz) and beta (13-30 Hz) frequency bands were calculated by performing a fast Fourier transformation (resolution 0.25 Hz, hamming window 10%).

Frontal TBR was calculated for each text page, based on the average power density of three frontal electrodes (F3, Fz, and F4, represented by electrode numbers 24, 11, and 124 respectively; Putman et al., 2014; Swart et al., 2020). Because of non-normality, power density values within each frequency band were log-normalized before calculating the ratios. The average frontal TBR during reading was calculated by averaging frontal TBR for all text pages within each text. Higher ratios reflected lower attentional control during reading and lower scores reflected better attentional control during reading (see e.g., Putman et al., 2014; van Son et al., 2019a). The *SD* among the average frontal

TBRs for each text page within each text was calculated as an indicator for fluctuations in frontal TBR during reading.

Self-Reports of Attentional Control During Reading

For each moment in the text that a participant marked as being distracted, the experimenter asked the participant what she was thinking at that moment. All self-reports were scored by an undergraduate student and the first author to distinguish comments that reflected constructing meaning from the text during reading (e.g., "When I read this sentence, I thought back to a scene at the beginning of the text") vs. comments that reflected being distracted during reading (e.g., "At this part of the text I was not paying attention to the text anymore, but I was thinking about what I would buy for dinner after finishing the experiment"). The total number of marked moments in the text that reflected moments of distraction was used as an indication for attentional control during reading. Disagreements in scoring were resolved through discussion until consensus was reached. Inter-coder reliability was ICC = .96 ($p < .001$) for self-reports of attentional control during text A and ICC = 1.00 ($p < .001$) for self-reports on attentional control during text B.

Summary Task

Participants' summaries were scored for the number of main elements in the text that were included in the summary. Main elements in the texts were selected based on the Event-Indexing Model (Zwaan et al., 1995) and, in line with the model, included information on time, space, protagonists, causality, and intentionality of story events. The percentage of the correctly mentioned elements for each text was calculated. All summaries were scored by two trained undergraduate students. Inter-coder reliability was ICC = 1.00 ($p <.001$) for the summaries of text A and ICC = 1.00 ($p <.001$) for the summaries of text B. Disagreements in scoring were resolved through discussion until consensus was reached.

Text-Level Comprehension Questions

Correct answers to the open comprehension questions about the content of the text (27 for text A and 24 for text B) were awarded one point. If an answer contained two components (e.g., two reasons why the main character in the story did not want to go to school), participants could receive half a point for mentioning one of the two components. A proportion of the correct answers from the maximum scores was calculated for each

text. All answers were scored by two trained undergraduate students. Inter-coder reliability was ICC = .98 (p <.001) for the questions of text A and ICC = .96 (p <.001) for the questions of text B. Disagreements in scoring were resolved through discussion until consensus was reached.

Word-Level Comprehension Questions

Participants completed four tasks concerning 30 of the nonsense words from the fictional Nadsat language that was spoken by some of the characters in the novel. All four tasks concerned the same 30 nonsense words per text. First, participants were asked to fill in a nonsense word that they remembered from the text that would fit in one of the 30 new sentences that did not appear in the text (sentence task). Second, participants were shown a list of the 30 nonsense words and were asked to fill in one or two missing letters in each word (spelling questions). Third, participants were shown the 30 nonsense words and were asked to fill in the meaning of the 30 nonsense words (open word meaning questions). Fourth, for each word the participants had to choose the correct Dutch meaning of the nonsense words out of three alternatives (MC word meaning questions). A total score (max. 30 points) was calculated for each task based on the number of correct answers. All answers were scored by two trained undergraduate students. Inter-coder reliability for all word-level comprehension tasks was on average ICC = .98 (range: .93 – 1.00, all p's < .001). Disagreements in scoring were resolved through discussion until consensus was reached.

Results

Descriptive Results

The final sample consisted of 40 students with the DRD4 7+ genotype and 40 students with the DRD4 7- genotype. Students in the two groups did not differ in age, reading motivation, language skills, executive functioning or attentional control in daily life (see Table 1). Reading times did not differ between the levodopa condition (M = 18.02 minutes, SD = 4.34) and the placebo condition (M = 18.64 minutes, SD = 5.02, $t(78) = 1.60$, p = .11). Data on all outcome variables were complete for all participants, except for frontal TBR during reading, and the self-reports on attentional control. Missing data were due to technical issues. Frontal TBR data in the levodopa condition were missing for one participant in the DRD4 7+ group. Scores on the self-report on attentional control during reading were missing for two participants in the DRD4 7- group, one in the levodopa condition and one in the placebo condition. One participant had an outlying score (z > 3.29;

Tabachnik & Fidell, 2007) for frontal TBR in the levodopa condition, *SD* in frontal TBR in both conditions and on the self-report in both conditions. We excluded this participant from further analyses regarding attentional control. The scores on the sentence completion (word-level comprehension) subtest were highly skewed (standardized skewness placebo condition = 4.67, levodopa condition = 15.87). This subtest appeared to be too difficult for the participants. In the placebo condition 65.0% of the participants scored zero points on the test and in the levodopa condition, 72.5% of the participants scored zero points. The scores on this subtest were, therefore, not included in further analyses. Data for all outcome measures in both conditions, broken down by genotype subgroup, are shown in Table 2.

We performed the following repeated measures ANOVAs to test the effects of increasing DA levels (levodopa vs. placebo as a within subject factor) on attentional control and reading comprehension both with and without DRD4 genotype as a between-subjects factor. No main effects of DRD4 genotype or interaction effects involving DRD4 genotype were found (for the results, see Appendix B). We, therefore, report the results for the model that includes only the within-subjects factors condition (levodopa vs. placebo) and type of outcome measure (for attentional control: average frontal TBR, *SD* in frontal TBR and self-report; for reading comprehension: summary task, text-level comprehension questions, spelling questions, MC word meaning questions, and open word meaning questions).

The Effects of Dopamine on Attentional Control During Reading

In order to include the scores on the three attentional control measures (average frontal TBR during reading, *SD* in frontal TBR during reading, and self-reports) in one analysis, we decided in consultation with a stastical expert to calculate the proportion of each score of the maximum observed score for that attentional control measure to end up with similar scales for each measure. A repeated measures ANOVA with condition (levodopa vs. placebo) and type of attentional control measure (frontal TBR during reading, *SD* in frontal TBR during reading and self-reports of attentional control during reading) as within subject factors showed no main effect of condition (F (1,75) = 1.48, p = .23, η_p^2 = .02). Attentional control during reading did not differ between the levodopa condition and the placebo condition. The main effect of type of attentional control measure was significant (F(1,75) = 40.73, p < .001, η_p^2 = .35), showing that the proportional scores for the average frontal TBR during reading (M = .41, SD = .16), *SD* in frontal TBR during reading (M = .25, SD = .10), and scores for the self-reports (M = .22, SD = .15) varied. No interaction effect was found for condition and type of attentional control measure on attentional control during reading (F (1,75) = 1.27, p = .29, η_p^2 = .02).

The Effects of Dopamine on Reading Comprehension

A repeated measures MANOVA was performed with condition (levodopa vs. placebo) and type of reading comprehension measure (summary task, text-level comprehension questions, spelling questions, open word meaning questions, and MC word meaning questions) as within subject factors. Mauchly's test indicated that the assumption of sphericity had been violated for the main effect of type of outcome measure (χ^2 (9) = 116.95, $p < .001$) and the interaction effect of condition and type of outcome measure (χ^2 (9) = 110.45, $p < .001$). Therefore, degrees of freedom for these effects were corrected using Greenhouse-Geisser estimates of sphericity ($\varepsilon = .62$ for the main effect of condition and $\varepsilon = .57$ for the interaction effect of condition and type of outcome measure). There was a significant main effect of condition on reading comprehension ($F(1,79) = 11.55$, $p = .001$, $\eta_p^2 = .13$). Participants performed worse on reading comprehension in the levodopa condition than in the placebo condition. This effect was moderate. The main effect of type of reading comprehension measure was significant ($F(2.50,197.19) = 334.77$, $p < .001$, $\eta_p^2 = .81$), showing that the mean scores of participants varied among the comprehension tasks. In other words, participants perceived some tasks as more difficult than others, particularly the spelling task and the open word meaning questions (for means and *SD*s, see Table 3). No significant interaction effect of condition and type of outcome measure on reading comprehension was found ($F(2.27,179.51) = .93$, $p = .41$, $\eta_p^2 = .01$). Lepodova had a similar effect on the different comprehension measures.

Discussion

The aim of the present study was to gain insight into the neurobiological processes, particularly dopaminergic mechanisms, underlying attentional control during reading and reading comprehension by investigating the effects of pharmacologically increasing DA. To the best of our knowledge, the present study is the first study to investigate the effects of pharmacologically manipulating DA in the field of reading comprehension. In order to test the effects of increased DA in the brain, university students participated in a placebo-controlled within-subject experiment in which they were orally administered either levodopa, a precursor of DA in the brain, or a placebo before reading a text. In order to directly test the inverted U-shape theory concerning the effects of DA on cognitive performance (see Boulougouris & Tsaltas, 2008; Cools & D'Esposito, 2011; Vijayraghavan et al., 2007), two subgroups of students were included in the experiment: one group of students carrying the DRD4 7R allele and one group of students who did not. No differences in attentional control between the DRD4 7+ and the DRD4 7- groups were found at the start of the study. Also, a first set of analyses showed no main effects of DRD4 genotype or interaction effects of DRD4 genotype and condition or

type of outcome measure, neither for attentional control during reading nor for reading comprehension. As a consequence, DRD4 genotype was not included as a between-subjects factor in the core analyses of the present study. Results of the core analyses showed that increased levels of DA did not affect attentional control during reading in a positive or negative way, as measured on both a neurobiological and behavioural level. However, on a behavioural level, increased levels of DA influenced reading comprehension in a negative way. That is, students performed significantly worse on the comprehension tasks when reading a text in the levodopa condition than in the placebo condition. This effect was moderate.

DRD4 Genotype and the Inverted U-Shape Theory

In line with the inverted U-shape theory (see Boulougouris & Tsaltas, 2008; Cools & D'Esposito, 2011; Vijayraghavan et al., 2007), we expected that pharmacologically increasing DA would particularly enhance attentional control during reading and reading performance in adults carrying the DRD4-7R allele, which has shown to be related to a less efficient transmission of DA in the brain, resulting in lower levels of DA in the brain (Ariza et al., 2012). As a consequence, we expected that the levels of DA in the brain of this group of adults would be situated left from the top of the inverted U-shape and that, therefore, they would be more susceptible for the positive effects of administering levodopa. Contrary to what was expected, there were no differences in attentional control between the two groups at pretest and no interaction effects of DRD4 genotype and condition were found, suggesting that the students from the DRD4 7+ and DRD4 7- groups did not differ in DA levels at pretest.

It is possible that the reduced levels of DA in the brain that are related to the DRD4 7+ genotype are particularly problematic in younger children. Bonvicini et al. (2020) found the DRD4-7R allele to be a major risk factor for ADHD, but only for children. The association was not present for adults. Other studies also have shown that the relation between DRD4 genotype and ADHD symptoms decreases with age (Bonvicini et al., 2018). If all participants, both those who carry the DRD4 7R allele and those who do not, are on average already located near or at the top of the inverted U-shape model regarding the levels of DA in the brain, it would mean that pharmacologically increasing DA would have no effect or possibly even a negative effect on attentional control and reading comprehension.

The Effects of Dopamine and Attentional Control During Reading

Despite the key role of DA in attentional control processes that has been found in previous studies (see e.g., Boulougouris & Tsaltas, 2008; Nieoullon, 2002; Westbrook & Braver, 2016), increased levels of DA did not increase or decrease attentional control during reading as measured by the average frontal TBR during reading, fluctuations in frontal TBR during reading, and a retrospective self-report. A possible explanation for not finding an effect of increased DA on attentional control during reading might be the limited sensitivity of the average frontal TBR to fluctuations in attentional control while reading the text. Ups and downs in attentional control average out in the overall average frontal TBR for the whole text. As a consequence, no conclusions could be formed on the effect of DA on the amount of fluctuations in attentional control based on this attentional control outcome measure. Nevertheless, the average frontal TBR during reading might still be informative as a broad measure of attentional control during reading. Results from a previous study showed that the average frontal TBR was moderately to strongly related to attentional control in daily life and to text-level reading comprehension (Swart et al., 2020). However, although the texts used in both the current and the previous study came from the same chapters of the novel 'A Clockwork Orange', the texts in the present study were 1500 words longer than those used in the previous study, and participants took nearly twice as long to read the longer texts. Longer tasks might evoke more lapses of attention which may not be reflected in an average score of attentional control during reading (see Krimsky et al., 2017).

Whereas the average frontal TBR provides a broad measure of the average attentional control during reading, the self-report measure of attentional control included in the present study could be informative on the point of fluctuations in attentional control. However, we also did not find an effect of DA on attentional control for these outcome measures. Possibly, meta-awareness could have confounded the results for this measure. Self-awareness is required for reporting moments of distraction during reading. However, research has shown that readers are not always aware that they fail to control attention. Additionally, it is the lapses in attentional control that readers are not aware of that are most detrimental for memory formation (for a review see Smallwood & Schooler, 2015). Such lapses are obviously not reflected in a self-report measure. Nevertheless, the absence of an effect of increasing DA on self-reports of attentional control is in line with the results for fluctuations in frontal TBR found in the present study.

The Effects of Dopamine on Reading Comprehension

In line with previous studies on the effects of administering levodopa on memory formation and word learning tasks (see Breitenstein, Flöel et al., 2006; Knecht et al., 2004; Linssen et al., 2014), we expected administering levodopa to influence reading comprehension. In the present study we found that administering levodopa negatively influenced reading comprehension, i.e., the formation of a mental representation of a text. According to Linssen et al. (2014), on a neurological level, the encoding of information in long-term memory, which is crucial for the formation of a mental representation of a text, is slowed down as a consequence of administering levodopa. However, although Linssen et al. (2014) found negative effects of administering levodopa on memory formation on a neurological level but not on a behavioural level, in the present study we found negative effects on memory formation (i.e., the mental representation of the text) on a behavioural level (i.e., performance on the reading comprehension outcome measures) and no effect on a neurological level.

If the negative effects of administering levodopa on reading comprehension would, in line with Linssen et al.'s (2014) reasoning, be the consequence of slower memory processing (i.e., on a neurological level), it would have taken readers more time to construct a mental representation of the text and they would have had to allocate more attentional resources to process the information in the text. This would then have resulted in longer reading times in the levodopa condition compared to the placebo condition. However, no differences in attentional control and reading times between the levodopa condition and the placebo condition were found in the present study.

A possible dopamine-related mechanism that could account for the negative effect of administering levodopa on reading comprehension is that participants in the present study experienced a flattened emotional responsiveness to information in the text during reading as a consequence of the pharmacological manipulation of DA. Pharmacological manipulation of DA levels using levodopa is aimed at increasing both tonic levels of DA (i.e., sustained background levels) and phasic levels (i.e., short-term activations) of DA in the brain (Breitenstein, Korsukewitz et al., 2006). However, Breitenstein, Korsukewitz et al. (2006) argued, based on an experiment with healthy adults in which they pharmacologically manipulated only tonic DA levels in the brain, that the dynamic combination of levels of phasic and tonic DA in the brain is a delicate balance (see also Linssen et al., 2014). Tonic increases in DA that are too large may lead to a reduction of phasic DA activity in healthy adults. As a consequence of pharmacologically increasing tonic DA, healthy adults in the experimental study of Breitenstein, Korsukewitz et al. (2006) showed flattened emotional responsivity and impaired learning, which was, according to Breitenstein, Korsukewitz et al. (2006) related to a decrease in phasic DA

activity. If participants in the present study experienced a comparable flattened emotional responsiveness to information in the text during reading, this could have led to less task engagement during reading. In line with the engagement perspective of reading (see Klauda & Guthrie, 2015), lowered engagement during reading could have led to a more superficial processing of the information in the text, resulting in a less coherent and complete mental representation of the text, hindering learning from text (van den Broek et al., 2005). Additionally, phasic DA appears to be particularly important for updating working memory knowledge (see Westbrook & Braver, 2016), which is a crucial process for reading comprehension (Palladino et al., 2001). If an excessive increase in tonic DA leads to reduced phasic DA activity, readers could have experienced difficulties in updating working memory in the levodopa condition, and, as a consequence, they could have had difficulties updating the mental representation of the text.

Another possible explanation for the negative effect of pharmacologically increasing DA on reading comprehension might be the difference in the reading task used in the present study compared to the word learning tasks used in previous research in which the effects of pharmacologically increasing DA on learning were tested (see Knecht et al., 2004, Breitenstein, Flöel et al, 2006; Linssen et al., 2014). In these studies, participants listened to single words being read to them. These tasks included much repetition, which could have caused boredom in participants, as was also argued by Knecht et al. (2004). In that case, pharmacologically increasing DA might have helped participants to perceive the task as more positive, i.e., less boring, because increased DA helps participants to interpret neutral stimuli as more positive or salient (Tripp & Wickens, 2008). In the case of reading comprehension, manipulating the experienced salience of information through pharmacologically increasing DA levels in the brain, which results in perceiving less salient information as salient and/or important, could have consequences for distinguishing main issues and side issues from the text. Participants' sensitivity to structural centrality of information in the text could have been hindered, which negatively influences reading comprehension (Kendeou et al., 2014).

Suggestions for Future Research

To further disentangle the dopamine-related mechanisms that might explain the effects of increased DA on attentional control and reading comprehension, future research should investigate the effects of increased DA on other cognitive processes that are related to attentional control and memory formation, such as working memory and goal-directed behaviour, that closely overlap with the neural correlates of attention (see e.g., Wass et al., 2012) and also rely on dopaminergic systems (see e.g., Cools & D'Esposito, 2011). A complementary approach in which these processes are measured in both the levodopa and

the placebo condition could provide further insight in the mechanisms underlying attentional control and reading comprehension. Additionally, the combination of physiological and behavioural measures could help to gain insight in both neurobiological and behavioural effects of DA. In the present study, the outcomes on both physiological and self-report measures of attentional control during reading point in the same direction, i.e., neither a positive nor a negative effect of increased DA on attentional control. However, in previous studies, effects of increased levels of DA on physiological measures and behavioural measures of cognitive processing varied (e.g., ERP latencies vs. learning accuracy and learning speed, see Linssen et al., 2014). Finally, the effects of the number of levodopa dosages should be investigated on both a psychophysiological and behavioural level, because the effects of pharmacologically increasing DA differs across time spans of the experimental learning tasks used in previous studies and the present one. In the study of Linssen et al. (2014), only a negative psychophysiological effect of administering levodopa was found, but no behavioural effects. In the present study, in which we also administered a single dose of levodopa, the results were contradictory. No psychophysiological effects were found, i.e., no difference in the average frontal TBR during reading, but negative effects were found on a behavioural level, i.e., impaired reading comprehension. In the studies that used a similar daily dose, but a longer five-day word-learning intervention (Breitenstein, Flöel et al., 2006; Knecht et al., 2004), positive effects were found on a behavioural level.

Conclusions

In conclusion, the results of the present study, which is to the best of our knowledge the first one testing the effects of pharmacologically increasing DA on reading comprehension including participants who might be expected to differ in DA uptake in the brain as a consequence of their genotype, showed that increased levels of DA did not influence attentional control during reading as measured by the average frontal TBR during reading, fluctuations in frontal TBR during reading, and a retrospective self-report, but negatively influenced reading comprehension in healthy female university students. In other words, although the ability to attentively read and understand longer stretches of texts is crucial for success in academic, professional and personal life, pharmacologically optimizing reading comprehension and attentional control, is a complex issue that requires a more thorough understanding of the neurobiological processes and mechanisms underlying these complex skills. Because of diverging findings in the present study and previous studies regarding the effects of pharmacologically increasing DA on both a neurobiological and behavioural level of cognitive processes and the difference in duration and complexity of learning tasks, more research and replication studies are

needed to further unravel the dopamine-related mechanisms that could explain these effects.

Table 1

Descriptive Statistics for the Demographic Variables for Participants with the DRD4 7- Genotype (n = 40) and the DRD4 7+ Genotype (n = 40)

Variable	Genotype	Min.	Max.	*M*	*SD*	*t*(78)	*p*
Age (in years)	DRD4 7-	18	27	21.58	2.01	0.82	.41
	DRD4 7+	18	24	21.18	1.65		
Reading Motivation	DRD4 7-	-3.63	1.66	-0.11	1.05	-0.83	.41
	DRD4 7+	-2.20	2.03	0.11	0.95		
Language skills	DRD4 7-	-1.60	1.63	-0.03	0.93	-0.19	.85
	DRD4 7+	-1.78	3.53	0.03	1.08		
Executive functioning (BRIEF-A)	DRD4 7-	78	167	114.13	20.81	0.52	.60
	DRD4 7+	75	178	111.62	21.86		
Attentional Control (ACS)	DRD4 7-	31	76	53.30	9.01	-0.39	.70
	DRD4 7+	40	69	53.80	8.00		

Table 2

Descriptive Statistics for Outcome Measures in the Levodopa Condition and the Placebo Condition, Separated per Subgroup of Genotype (N = 80).

Outcome measure	Subgroups	Levodopa condition			Placebo condition		
		n	*M*	*SD*	*n*	*M*	*SD*
Average frontal TBR during reading	DRD4 7-	40	.40	.24	40	.40	.18
	DRD4 7+	39	.39	.16	40	.38	.17
	Total	79	.40	.20	80	.39	.17
SD in frontal TBR during reading	DRD4 7-	39	.09	.07	39	.08	.05
	DRD4 +	39	.10	.05	40	.09	.06
	Total	78	.09	.06	79	.09	.05
Self-reported attention during reading	DRD4 7-	39	3.23	3.07	39	3.33	2.85
	DRD4 7+	40	2.73	2.45	40	2.85	2.03
	Total	79	3.09	2.47	79	2.97	2.76
Summary task (% correct mentioned main events)	DRD4 7-	40	24.21	13.44	40	24.29	13.54
	DRD4 7+	40	25.18	13.93	40	26.66	12.79
	Total	80	24.70	13.61	80	25.47	13.14
Text-level comprehension questions (% correct)	DRD4 7-	40	33.73	19.47	40	37.66	19.32
	DRD4 7+	40	29.90	15.59	40	35.78	15.91
	Total	80	31.82	17.63	80	36.72	17.61

Outcome measure	Subgroups	Levodopa condition			Placebo condition		
		n	*M*	*SD*	*n*	*M*	*SD*
Spelling questions (% correct)	DRD4 7-	40	7.75	5.62	40	10.67	6.97
	DRD4 7+	40	8.92	5.91	40	10.33	8.80
	Total	80	8.33	5.76	80	10.50	7.89
MC word meaning questions (% correct)	DRD4 7-	40	45.08	9.31	40	45.67	12.43
	DRD4 7+	40	42.92	9.52	40	48.08	14.65
	Total	80	44.00	9.42	80	46.88	13.56
Open word meaning questions (% correct)	DRD4 7-	40	4.58	5.37	40	6.25	6.32
	DRD4 7+	40	5.00	5.99	40	6.58	8.08
	Total	80	4.79	5.66	80	6.42	7.21

Table 3

Estimated Marginal Means of the Main Effect of Type of Reading Comprehension Measure (N = 80).

Reading comprehension measure	*M*	*SE*
Summary task	25.08	1.23
Text-level comprehension questions	34.27	1.59
Spelling questions	9.42	0.62
MC word meaning questions	5.60	0.52
Open word meaning questions	45.43	1.00

Appendix A

Background Variables

Executive Functioning

Participants completed the Behavior Rating Inventory of Executive Function—Adult version (BRIEF-A; Scholte & Noens, 2011), a self-report questionnaire of 75 items designed to examine adult's executive functions in daily life. Participants rated the frequency of the described behaviours on a 3-point scale (1 = never, 2 = sometimes, 3 = often). Scores on the BRIEF-A range from 75 to 225, with a lower score reflecting better executive functioning. A total score was calculated for each participant. Internal consistency of the scale in the present study was Cronbach's α = .96.

Attentional Control

Participants completed a Dutch translation of the Attentional Control Scale (ACS; Derryberry & Reed, 2002). Participants rated twenty statements about attention and concentration in daily life on a four-point Likert-scale (e.g., 'It's very hard for me to concentrate on a difficult task when there are noises around', 'It is easy for me to switch between two different tasks' and 'After being disrupted or distracted, it is easy for me to shift my attention away from the distractor'). Scores on the ACS range from 20 to 80 points, with a higher score reflecting better attentional control in daily life. A sum score for all items was calculated for each participant. Internal consistency was Cronbach's α = .85.

Reading Motivation

Participants completed a researcher-constructed reading motivation survey. The survey consisted of three subscales: engagement in reading related activities (13 items, e.g., 'If I like a book of a certain author I will read more books of the same author', 'I am a member of a book club', 'I regularly go to a book store to see if there are nice books'; Cronbach's α = .71), attitude towards reading for pleasure (21 items, e.g., 'Reading a book for pleasure is amusing', 'Reading a book for pleasure is boring'; Cronbach's α = .82), and reading in spare time (12 items, e.g., 'Reading a book costs me too much of my spare time', 'I only read if I have to', 'I always read before I go to sleep'; Cronbach's α = .81). Items were based on and extensions of the *Reading Attitude Scale* (Aarnoutse & Konings, 2013), the 'Reading Involvement' and 'Social Reasons for Reading' subscales of the *Motivations for Reading Questionnaire* (MRQ; Wigfield & Guthrie, 1997), the 'Value of Reading' subscale of the *Motivation to Read Profile* (MRP; Gambrell et al., 1996), and the *Self-Regulation*

Questionnaire-Reading Motivation (de Naeghel et al., 2012). Participants rated their agreement with statements on a 5-point Likert-scale, with higher scores indicating higher agreement. Negative statements were recoded so that higher scores on statements reflected a more positive attitude or more motivation. Principal components analysis applied to the three subscales resulted in one component, containing component loadings ranging from .77 to .88, explaining 70.1% of the variance. Higher aggregate scores reflected higher reading motivation.

Language Skills

Participants completed a researcher-constructed language test, containing four subtests: spelling, grammar, vocabulary and syntax. For the spelling subtest, participants had to complete the spelling for 40 words in which one or two letters were missing. In the grammar subtest (15 items), participants had to choose the right form of a verb, noun, or pronoun from two options. For both the spelling and the grammar subtest, one point was awarded for each correct answer. For the vocabulary subtest, participants had to determine whether words were real words or nonsense words from a list of 68 words containing 51 real words and 17 nonsense words. A total score was calculated by adding all correctly recognized real words minus the nonsense words that were incorrectly categorized as real word. Finally, participants had to complete twenty MC-questions about the form and meaning of several sentences. One point was awarded for each correct answer. Principal components analysis applied to the four subtests resulted in one component containing component loadings ranging from .68 to .76, explaining 51.5% of the variance. Higher aggregate scores reflected better language skills.

Appendix B

Table S1

Repeated Measures ANOVA Statistics for the Effect of DA on Attentional Control Including Main and Interaction Effects of the DRD4 Genotype (n = 76).

Effects	ANOVA statistics		
	$F(1,74)$	p	η_p^2
Main effects			
Condition	1.56	.22	.021
DRD4 genotype	.02	.88	.000
Type of attentional control measure	40.39	<.001	.353
Two-way interactions			
Condition * DRD4 genotype	1.14	.29	.015
Type of attentional control measure * DRD4 genotype	.44	.65	.006
Condition * Type of attentional control measure	1.26	.29	.017
Three-way interaction			
Condition * DRD4 genotype * Type of attentional control measure	.43	.65	.006

Table S2

Repeated Measures ANOVA Statistics for the Effect of DA on Reading Comprehension Including Main and Interaction Effects of the DRD4 Genotype (n = 80).

Effects	ANOVA statistics			
	F	*df*	*p*	η_p^2
Main effects				
Condition	11.52	1,78	.001	.129
DRD4 genotype	.001	1,78	.97	.000
Type of reading comprehension measure	334.09	2.49, 194.06	< .001	.811
Two-way interactions				
Condition * DRD4 genotype	.76	1,78	.39	.010
Type of reading comprehension measure * DRD4 genotype	.84	2.49, 194.06	.46	.011
Condition * Type of reading comprehension measure	.93	2.26, 176.02	.41	.012
Three-way interaction				
Condition * DRD4 genotype * Type of reading comprehension measure	.50	2.26, 176.02	.63	.006

Note. Mauchly's test indicated that the assumption of sphericity had been violated for the main effect of type of reading comprehension measure (χ^2 (9) = 115.11, p < .001) and the interaction effect of condition and type of reading comprehension measure (χ^2 (9) = 111.02, p < .001). Therefore, degrees of freedom for these effects were corrected using Greenhouse-Geisser estimates of sphericity (ε = .62 for the main effect of condition and ε = .56 for the interaction effect of condition and type of reading comprehension measure).