What works for whom? Differential genetic effects of early literacy interventions in kindergarten

Plak, R.D.

Chapter 3

Brief Computer Interventions Enhance Emergent Academic Skills in Susceptible Children: A Gene-by-Environment Experiment

Published as:

Plak, R.D., Merkelbach, I., Kegel, C.A.T., Van IJzendoorn, M.H., & Bus, A.G. (2016). Brief computer interventions enhance emergent academic skills in susceptible children: A gene-byenvironment experiment. *Learning and Instruction*, 45, 1-8. doi;10.1016/j.learninstruc.2016.06.002

ABSTRACT

In this study we examined the potential of technology-enhanced educational programs for young children lagging behind in emergent literacy skills. Differential effects of technology-enhanced educational programs (*Living Letters* and *Living Books*) for poor performers were tested in a randomized controlled trial. Our previous study showed that children with a dopamine-related genetic polymorphism - DRD4 7-repeat - are more susceptible to their learning environment than children without this polymorphism, serving as a proxy for the dopamine-system related genetic pathway. In the current study, we aimed to replicate and extend these results in a sample of 583 kindergarteners from 136 schools. As predicted by the genetic differential susceptibility theory, carriers of the DRD4 7-repeat allele profited significantly from *Living Books* (d = .75), whereas non-carriers did not benefit (d = .02). *Living Letters* did not show a Gene x Environment interaction. We discuss why carriers of DRD4 7-repeat allele particularly benefit from *Living Books*.

Keywords: Early literacy intervention, Dopamine D4 receptor gene, Educational computer programs, Technology-enhanced picture storybooks, Differential susceptibility, Gene X Environment interaction

INTRODUCTION

In this study we examined the potential of educational computer programs for young children lagging behind in emergent academic skills and therefore at risk for learning problems in primary education. Building on the Simple View of Reading, Bowyer-Crane et al. (2008) proposed a two-dimensional model of early reading interventions with phonological skills positioned on one dimension, and non-phonological skills (e.g., semantics and syntax) positioned on the other. We explored the efficacy of both types of programs in kindergarten age: *Living Letters* to prevent the risk of word-level decoding difficulties, and *Living Books* to prevent the risk of reading comprehension difficulties associated with deficits in non-phonological language skills.

Average effects of technology-enhanced educational programs for young children are unfortunately rather disappointing unless subsamples are formed (e.g. Saine, Lerkkanen, Ahonen, Tolvanen, & Lyytinen, 2011). We argue that the average effects do not reflect true effects that are hidden in a subgroup of children who are more susceptible to environmental experiences, such as child rearing and school environment. Children who are thought to be susceptible to environmental factors not only catch up and perform at a level similar to other children, but they actually outperform their nonsusceptible peers. It appears from child development research that children with specific genetic or temperamental characteristics are more susceptible to the quality of the environment than others, and are at risk of a delayed development in comparison with their peers when they grow up in less stimulating families or other child rearing contexts (e.g., Ellis, Boyce, Belsky, Bakermans-Kranenburg, & Van IJzendoorn, 2011). These susceptible children easily catch up and even outperform their peers in an optimal environment. This is the For Better and For Worse principle of the Differential Susceptibility Theory (Belsky, Bakermans-Kranenburg, & Van IJzendoorn, 2007; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & Van IJzendoorn, 2011).

In the popular press, susceptible children have been compared to orchids - these flowers only bloom when temperature and humidity are optimal - in contrast to less susceptible species, like dandelions, which grow irrespective of the quality of the environment (Dobbs, 2009). This Differential Susceptibility Model challenges the traditional Diathesis Stress Model in which the idea is promoted that children with specific characteristics are more vulnerable to adversities or negative experiences and that others are less affected by the same experiences (Belsky & Pluess, 2013; Belsky, Bakermans-Kranenburg, & IJzendoorn, 2007). Boyce and Ellis (2005) stated that the Differential Susceptibility Model is fundamentally different from the Diathesis Stress Model in that individuals not only vary in the extent to which they are susceptible to negative experiences but also their malleability; individuals who are more malleable

are thought to be more susceptible to negative and positive experiences (Belsky et al., 2007). Children, who due to specific characteristics are thought to be less susceptible, are less influenced by negative or positive environmental factors.

Correlational and experimental studies showed that children with a specific dopamine-related genetic polymorphism - dopamine D4 receptor gene, with the polymorphism DRD4 7-repeat - are thought to be more susceptible to their environment than children without this polymorphism (Bakermans-Kranenburg & Van IJzendoorn, 2006, 2011, 2015). For example, in a randomized parent training experiment, carriers of the 7-repeat variant showed less externalizing behavior when their parents were coached to enhance their sensitive caregiving, whereas with the same coaching non-carriers did not make progress (Bakermans-Kranenburg & Van IJzendoorn, 2008). Children with the 7-repeat allele of the DRD4 gene (the long variant of the DRD4 gene) have a lower dopamine reception efficiency - caused by diminished anticipatory cell firing - which is associated with reduced attentional and reward mechanisms (Robbins & Everitt, 1999). It is hypothesized that these children are more sensitive to an environment that helps to structure their activities and is supportive of reward and attentional mechanisms (Bakermans-Kranenburg and Van IJzendoorn, 2015). A crowded noisy classroom can therefore be regarded as a negative learning environment for children with the DRD4 7-repeat allele. Due to reduced attentional mechanisms, they are at risk of wandering off and failing to use the learning opportunity.

Educational computer programs may be especially helpful for supporting these children's learning processes especially when they do not just offer practice but also provide scaffolding during learning, thus helping them to stay task-focused (Kegel & Bus, 2012). *Living Letters* - a program promoting alphabetic knowledge - includes a tutor, one of the characters in the games, who responds to all attempts children make to solve the tasks. If children do not start solving a problem or their first attempt fails, the tutor encourages the child to try. After the second failure, the tutor provides a cue for finding a solution and after the third failure, the tutor models and explains the correct solution. Because of the scaffolding, children may be able to solve tasks that are just above the level that they normally can solve on their own (e.g., Kegel & Bus, 2012). *Living Books* is a technology-enhanced book reading program composed of eight different stories each repeated twice. The animated pictures, sounds, and music appearing simultaneous with the story text help to make sense of the story and the story text and thus enable the child to understand story events and language even when the oral text is difficult for the child (Bus, Takacs, & Kegel, 2015). This format stimulates building combined verbal and nonverbal representations, also referred to as multimedia learning (Mayer, 2005). If the music is congruent to the narration, it facilitates story comprehension and learning words from the narration (Takacs, Swart, & Bus, 2015). Furthermore, additions to the story, like movie-like presentations and background music, are engaging and may therefore be helpful in staying focused

while hearing the story.

In particular, carriers of the 7-repeat allele of the DRD4 gene that has been associated with ADHD (Maher, Marazita, Ferrel, & Vanykukov, 2002) may benefit from these computer programs. Lower dopamine reception efficiency may result in being less attentive during the learning process when the learning environment is not sufficiently structured and supportive (Kegel & Bus, 2012). Because carriers of the 7-repeat variant of the DRD4 gene might be less able to focus on a task in a somewhat chaotic environment, such as in regular classrooms, and therefore are often distracted from core learning processes, they may be dependent on special tailored programs that help them to focus. Even when part of the tailored programs have overlap with the regular curriculum, carriers of the DRD4 7- repeat allele may benefit from additional educational computer programs. *Living Letters* might be very helpful to them because it includes an Intelligent Tutoring System providing consistent feedback to all of the children's responses. *Living Books* retains and guides attention with the help of a movielike presentation. It may be that children with attentional problems benefit from the movie-like presentation in the *Living Books*. Acevedo-Polakovich, Pugzles Lorch, and Richard (2007) showed that children with ADHD enjoy watching television more and have greater involvement in television-related activities when compared to typically developing children. We expected therefore to find a cross-over Gene Environment interaction, showing that carriers of the 7-repeat allele of the DRD4 gene may profit most from both computer programs and even outperform their less susceptible peers without this DRD4 7-repeat allele.

Results so far were mixed. A study by Kegel, Bus, and Van IJzendoorn (2011) was the first experiment in which genetic differential susceptibility for *Living Letters* was tested. From this study, which included typical four-year-olds, it appeared that in particular children with the 7-repeat allele of the DRD4 gene were susceptible to the educational computer intervention *Living Letters*. Carriers of the 7-repeat allele fell behind in early literacy skills in comparison to their peers without the extra input of *Living Letters*, but outperformed their peers when they did work with *Living Letters*. Plak, Kegel, and Bus (2015) tested both the educational computer programs, *Living Letters* and *Living Books*, in a group of five-year-olds delayed in early literacy skills. They could not replicate the differential effects for *Living Letters* but did find differential effects of *Living Books*. Non-carriers of the 7-repeat allele did not benefit from *Living Books* but carriers did substantially. Teachers suggested that *Living Letters* was too easy and too boring for five-year-olds, which might explain results so far. In the current study, we therefore complicated the program by dropping the easiest games.

Current study

In a large countrywide randomized controlled trial, we provided 5-year-olds, just before their transition from kindergarten to first grade, with the computer programs that trained important precursors for learning to read in first grade.We targeted children from 136 different schools whose early literacy skills were delayed or rather low according to their teacher and their scores on a national standardized literacy test. In total, 583 5-year old kindergarten children were randomly assigned to one of two early literacy computer programs, *Living Letters*, *Living Books*, or a control condition, *Clever Together* that practiced visual-spatial skills. They practiced with *Living Letters*, *Living Books* and *Clever Together* for a brief period, ranging between 160 and 220 min and over the course of about 12 weeks. The researchers assigned the children randomly to one of the three programs and provided online access but were not involved in the implementation or testing. A standardized test for literacy administered by teachers in January and June in the senior kindergarten year provided pre- and posttest scores. We tested (1) main effects of literacy programs on the standardized literacy test, (2) whether there was evidence for a Gene x Environment interaction and carriers of the 7-repeat DRD4 gene outperformed non-carriers, and (3) conducted a metaanalysis to examine whether the outcomes of the randomized GxE experiment reported in this study match the outcomes of previous experiments using the same programs and measures.

METHOD

Design

In each class one child was assigned to *Clever Together*, the control condition, and at least one child to one of the literacyrelated programs, that is *Living Letters* or *Living Books*. Children in the *Living Books* condition were offered 8 sessions with 2 books per session and children in the *Clever Together* and *Living Letters* condition ranging between 8 and 11 sessions (due to a variable number of sessions depending on the number of errors children made). Each session took about 15 minutes and children practiced once aweek. Based on the data that were stored by the program, children completed on average 33.4 out of 34 *Living Letters* games (*SD* = 3.09) and they “read” on average 14.7 out of 16 books (*SD* = 2.1).

Buccal cell samples (samples from cells from a person’s cheek) were collected half way through the intervention period by trained research teammembers using a sterile swab designed for collecting buccal cells for DNA analysis (Omni Swabs, Whatman/GE Healthcare, UK). Collection took place at school. Given the large sample

and the stability of the percentage of carriers of the DRD4 gene, it was reasonable to assume that random assignment would result in a similar number of carriers of the 7-repeat allele of the DRD4 gene in each condition. Early literacy skills were tested before and after the intervention using the Central Institute for Test Development (Cito) Literacy Test for Kindergarten (CLT). In all schools this literacy test was administered group-wise in January and June (Lansink & Hemker, 2012).

Participants

A total of 136 schools participated in the experiment. From August 2013 to October 2013 information about the project was distributed via e-mail, mail, social media, and phone. In brochures and letters sent to the schools, it was emphasized that participation offered both a chance to provide extra guidance to pupils with literacy delays and an opportunity to experience how to implement technology-based programs in their teaching. Furthermore, after the intervention participating schools would receive free access to educational computer programs for kindergarten children for a period of three months (www.bereslim.nl).

Eligible children were selected between October 2013 and February 2014 by the kindergarten teachers in the 136 participating schools. Teachers were asked to select six pupils from their classroom achieving poorly in literacy. Pupils who were eligible were those, for instance, who were not yet able to write their proper name, to rhyme, to name a few letters, and to identify sounds in words. Preferably these children scored in the lowest ranges - between 0 and 59 - on the standardized literacy test CLT administered in January (Lansink & Hemker, 2012). If there were not enough children scoring below the 40th percentile, teachers also included children scoring midrange between the 40th and 60th percentile on the standardized literacy test. Dutch was required as the participants’ first language. When a parent refused consent, the teacher was asked to select another eligible pupil from his or her classroom.

Due to objection to genotyping, a condition for participation, parents often refused consent, resulting in less than six lowperforming participants per classroom (average number of participants per classroom: 2.94 children). From the 607 selected pupils, data were complete for 565 pupils. About half of these pupils showed a serious lag in literacy skills (*N* = 307), scoring below the 40th percentile according to national norms (Lansink & Hemker, 2012). The other half (*N* = 258) scored in the mid-range between the 40*th* and 60*th* percentile.

Procedure

Parents of eligible children received written information about the study explaining the scientific goals and the opportunity for their child to receive extra

coaching. Information about genotyping as part of the study was offered as well. Moreover, a website was available for additional information about the aim and the design of the study. Contact informationwas provided to allowparents to ask additional questions. Parents made frequent use of this opportunity. Genotypingwas a main reason for parents refusing consent for participation (roughly 25% of all children selected by the teachers) even though we guaranteed that buccal cells would be destroyed after genotyping had taken place and data would be stored anonymously.

Intervention programs

Living Letters. The intervention program *Living Letters* offers a framework that anchors instruction and practice in a personally motivating context of activities using children's own proper name (Van der Kooy-Hofland, Bus, & Roskos, 2012). The program adapts automatically to the child's proper namewhenavailable in the name database. If the name of the child is not available, the program uses 'mama' (mommy) - a word that is just as familiar to many young children. In all, there were 36 games from which 16 targeting name recognition, 6 games to recognize the first letter of the name, and 12 in which children are given the task of identifying pictures that start with or contain the first letter of the child's name. Feedback provided by a tutor followed every response by the child. When children answered a question incorrectly, feedback and clues were provided. After a maximum of three trials, the game ended on a positive note, irrespective of whether a correct response was given, whereupon a newgame started. Every time a child failed to fulfill an assignment, this assignment was repeated in the following two sessions. Therefore some children had more sessions than others.

Living Books, the second intervention program, was made up of eight age-appropriate digital animated storybooks. The animated pictures, sounds, and music support the meaning of the story text, which may stimulate the child's understanding of story events and language (Bus et al., 2015; Kamil, Intrator, & Kim, 2000). We assumed that when the oral narrative is accompanied by nonverbal information, and verbal and nonverbal information are simultaneously available, the narrative text would be understood and retained better than if conveyed by words alone (Bus et al., 2015). Multimedia offer optimal guidance in developing mental representations of the story and the language. Each reading of a book was interrupted four times for questions about the story and vocabulary. If the child's response was incorrect, the question was repeated maximally three times and feedback was adapted to the child's response, similar to *Living Letters*. Each book was presented twice and four questions were included in each session.

Clever Together supports basic concepts for mathematics like practicing cardinals and visual-spatial reasoning. It includes 40 games. As in *Living Letters* and *Living Books*, a tutor provides constructive, detailed feedback for every error and every correct response. Assignments were repeated in later sessions when children made errors.

Measures

Early literacy skills

Cito Literacy Test for Kindergarten Pupils (CLT) is a standardized literacy test for kindergarten pupils that is administered in almost every Dutch school class-wise in January and June of the senior kindergarten year. Because this test is administered at almost every school in the Netherlands, the CLT test was an obvious choice. The 60-item CLT assesses vocabulary, text comprehension, rhyming, hearing the first and last word, sound blending, writing conventions (e.g. reading from left to right), and prediction of book content based on the book cover (Lansink & Hemker, 2012). The Commissie Testaangelegenheden Nederland [Committee for Test Quality in the Netherlands] evaluated the CLT as adequate.

Genetic screening for DRD4 polymorphisms

A genotype is an assortment of characteristics inherited from the parents. The genetic information about those characteristics is stored in the DNA. Genotyping is the process of determining differences in the genetic make-up (genotype) of an individual by examining the individual's DNA sequence. Biological assays are used and compared to another individual's DNA sequence. The details are explained below. PCR Amplification. The region of interest of the DRD4 gene was amplified by PCR using the following primers: a FAM-labelled primer 50-GCGACTACGTGGTCTACTCG-30, and a reverse primer 50- AGGACCCTCATGGCCTTG-30. Typical PCR reactions contained between 10 and 100 ng genomic DNA template, 10 pmol of forward and reverse primer. PCR was carried out in the presence of 7.5% DMSO, 5x buffer supplied with the enzyme and with 1.25U of LongAmp Taq DNA Polymerase (NEB) in a total volume of 30 µl using the following cycling conditions: initial denaturation step of 10 min at 95 °C, followed by 27 cycles of 30sec 95 °C, 30sec 60 °C, 6sec 65 °C and a final extension step of 10 min 65 °C.

Analysis of PCR products for repeat number. One ml of PCR product was mixed with 0.3 µl LIZ-500 size standard (Applied Biosystems) and 11.7 µl formamide (Applied Biosystems) and run on a AB 3730 genetic analyser set up for fragment

analyses with 50 cm capillaries. Results were analysed using GeneMarker software (Softgenetics). The genetic variable was coded as 0 or 1 for absence or presence, respectively, of a 7-repeat allele at one or both alleles. Of the 593 participants, ten children could not be genotyped; 199 children (34%) were carriers of the 7-repeat of DRD4. The distribution of DRD4 polymorphisms was in Hardy-Weinberg equilibrium, $\chi 2$ (*df* = 1, *N* = 565) = .008, *p* = .93.

Data analysis

The posttest score of the CLT was regressed on the pretest CLT (scoring below the 40th percentile according to national norms vs. scoring midrange between the 40th and 60th percentile), *Living Letters* (contrast between the control condition *Clever Together* and *Living Letters*), *Living Books* (contrast between *Clever Together* and *Living Books*), DRD4 (7-repeat at one or both alleles vs. others), two and three-way interactions involving pretest CLT, interventions, and DRD4. Age, sex, and father's education were entered as covariates.

RESULTS

Characteristics of the sample

Table 1 presents data on children with delayed versus midrange pretest scores on the literacy test. Delayed participants had a mean age of 66.87 months (*SD* = 4.14) at pre-test, participants who scored midrange had a mean age of 67.87 months (*SD* = 4.66). Boys were overrepresented (62%) particularly in the delayed group. In the midrange group, numbers of boys and girls were equal. The mean score for father's education was 3.63 (*SD* = 1.37) on a scale ranging from 0 to 6, where 0 represents primary school and 6 represents university-level education.

Table 1: Characteristics in the conditions *Living Letters*, *Living Books*, and *Clever Together* of participants scoring below the 40th percentile (delayed) or between the 40th and 60th percentile (midrange) on the pretest

		Complete group	*Living Letters*	*Living Books*	*Clever Together*
	Male/Female	190/117	69/46	67/33	54/38
	Age months (*SD*)	66.87 (4.14)	67.17 (4.25)	66.53 (4.18)	66.87 (3.97)
	CLT pretest (*SD*)	53.40 (4.78)	53.18 (4.82)	53.91 (4.45)	53.12 (5.06)
Literacy delayed	CLT posttest (*SD*)	61.79 (7.55)	61.22 (7.11)	62.98 (8.03)	61.23 (7.49)
	Male/Female	129/129	50/43	43/51	36/35
	Age months (*SD*)	67.87 (4.66)	68.28 (4.72)	67.56 (4.79)	67.74 (4.44)
	CLT pretest (*SD*)	65.95 (6.80)	65.44 (5.53)	66.02 (6.01)	66.54 (9.00)
Midrange	CLT posttest (*SD*)	72.66 (9.58)	71.95 (9.07)	73.46 (10.92)	72.52 (8.27)

The percentage of children carrying the 7-repeat allele of DRD4 in the delayed and the midrange literacy level groups was respectively 37.5% and 31.8%, a non-significant difference, $\chi 2$ (*df* = 1, *N* = 565 = 2.00, *p* = .158. The number of children with a DRD4 7- repeat allele did not differ significantly across the three experimental conditions: *Living Letters* (37.0%), *Living Books* (33.0%), and *Clever Together* (34.4%), $\chi 2$ (*df* = 2, *N* = 565) = .744, *p* = .689.

Intervention efficacy

We tested whether or not it was necessary to allow the intercept to differ between schools and to have an interaction between intervention and school in the regression model (Twisk, 2006). The difference between the -2log likelihood of the model with a random intercept and the -2log likelihood of the model without a random intercept equaled 8.03. Following a chi-square distribution with one degree of freedom, this difference was highly significant. The difference between the -2log likelihood of the model with only a random intercept and the -2log likelihood of the model with both a random intercept and a random slope was not significant ($\chi 2$ = 1.41, *df* = 2). Therefore we applied multilevel analysis with a random intercept for schools (Luke, 2004). The intraclass correlation of.10 ([6.86/(6.86 + 62.85)], see Table 2) demonstrated that 10% of the differences in the CLT scores were attributable to school characteristics. Therefore multi-level analyses were applied to account for variation attributable to school-level characteristics using school as a random factor.

Neither the experimental conditions *Living Letters* (*Est* = -.04, *p* = .959) and *Living Books* (*Est* = .17, *p* = .838) nor DRD4 (*Est* = 1.00, *p* = .308) revealed main effects, in contrast to the dichotomized CLT pretest (*Est* = 10.88, *p* = .000). The dichotomized pretest did not show an interaction with DRD4 (*Est* = -2.16, *p* = .144). *Living Letters* (vs. control) did not show an interaction effect with the dichotomized CLT pretest (*Est*

= -1.21, p = .315) and DRD4 (*Est* = -1.82, p = .174) or a three-way interaction effect with the dichotomized CLT pretest and DRD4 (*Est* = 3.08, p = .133). *Living Books* (vs. control) did not show a two-way interaction effect with the dichotomized CLT pretest (*Est* = 1.75, p = .143), but there was a significant interaction with DRD4 (*Est* = 3.49, p = .015) and the three-way interaction including *Living Books* (vs. control), DRD4, and the dichotomized CLT pretest was found to be significant (*Est* = -6.57, p = .002).

Table 2*: Outcomes of multilevel analysis using posttest literacy skills (CLT) language as an outcome variable (N = 565)*

	Est. (*SE*)	95% CI	t	*p*	*df*
Intercept	46.71 (5.74)	35.44 - 57.98	8.141	.000	564.98
Background					
Age	.19 (.08)	.03 - .35	2.356	.019	565.00
Sex	.43 (.71)	-.96 - 1.82	.612	.541	549.68
Father's educational level	.54 (.26)	.03 - 1.05	2.084	.038	564.60
Main Effects					
CLT pretest	10.88 (.88)	9.16 -12.61	12.396	.000	562.88
Living Letters (vs. control)	-.04 (.84)	-1.69 - 1.60	-.051	.959	546.35
Living Books (vs. control)	.17 (.82)	-1.44 - 1.77	.205	.838	523.38
DRD4 variant	1.00 (.98)	-.93 - 2.93	1.021	.308	539.99
Interaction Effects					
CLT pretest X *Living Letters*	-1.21 (1.20)	-3.57 - 1.15	-1.005	.315	556.00
CLT pretest X *Living Books*	1.75 (1.19)	-.59 - 4.09	1.47	.143	535.41
CLT pretest X DRD4 variant	-2.16 (1.48)	-5.06 - .74	-1.462	.144	541.79
DRD4 variant X *Living Letters*	-1.82 (1.34)	-4.44 - .81	-1.36	.174	557.03
DRD4 variant X *Living Books*	3.49 (1.42)	.69 - 6.29	2.45	.015	555.00
CLT pretest X *Living Letters* X DRD4 variant	3.08 (2.05)	-.94 - 7.10	1.504	.133	553.83
CLT pretest X *Living Books* X DRD4 variant	-6.57 (2.07)	-10.64 - -2.50	-3.174	.002	543.92

Random Effects	Est. (*SE*)	Wald Z	p
Variance			
Level Child	62.85 (4.24)	14.820	.000
Level School	6.86 (3.16)	2.172	.030

As the results indicated that effects differed dependent on the starting level, analyses were repeated for delayed and midrange children separately. In the delayed

group (*N* = 307), there was neither a main effect for *Living Letters* (*Est* = .18, p = .804), *Living Books* (*Est* = .07, p = .924) or DRD4 (*Est* = 1.15, p = .176), but significant two-way interactions between *Living Letters* and DRD4 (*Est* = -2.29, p = .049 and between *Living Books* and DRD4 (*Est* = 3.76, p = .002). See Table 3 and Figure 1. There were no significant effects in the midrange group (*N* = 258).

Table 3: *Means and Standard Deviations for CLT post-test in the Delayed Group by Condition and DRD4 (N = 307)*

	Living Letters	*n*	*Living Books*	*n*	*Clever Together*	*n*
DRD4(7-)[b]						
Raw	61.42 (7.00)	65	61.45 (8.20)	69	61.72 (6.87)	58
Corrected[a]	61.49 (7.43)	65	61.59 (7.36)	69	61.42 (7.39)	58
DRD4(7+)[c]						
Raw	60.96 (7.30)	50	66.39 (6.54)	31	60.38 (8.48)	34
Corrected[a]	60.91 (7.37)	50	66.21 (7.37)	31	60.70 (7.40)	34
Total						
Raw	61.22 (7.11)	115	62.98 (8.03)	100	61.23 (7.49)	92
Corrected[a]	61.20 (7.42)	115	63.90 (7.98)	100	61.06 (7.61)	92

[a] Covariates appearing in the model are evaluated at the following values: gender = .38, age = 66.87, and educational level of the father = 3.61.
[b] non-susceptible.
[c] susceptible.

Of the children who received the *Living Books* intervention and were delayed at pretest and were carriers of the DRD4 7-repeat allele, 80.6% scored at least midrange on the posttest. For children assigned to the control condition this percentage did not exceed 55.6%.

Effect sizes

The overall effect size of *Living Books* in the delayed group (see Table 4), based on the corrected means and standard deviations, was rather small (Cohen's *d* = .36) in contrast to the effect in the sub-group of carriers of the DRD4 7-repeat allele (7+, Cohen's *d* = .75), which indicates a large effect. For the non-carriers of the DRD4 7-repeat allele (7-), the effect size was about zero (Cohen's *d* = .02). Results showed that only the group of carriers of the 7- repeat allele benefited from *Living Books*. *Living Letters* yielded a non-significant overall effect size (Cohen's *d* = .02), without differences between the carriers of the DRD4 7-repeat (Cohen's *d* = .03) and the non-carriers (Cohen's *d* = .01).

Table 4: *Effect Sizes and 95% Confidence Intervals for Living Letters and Living Books based on the means corrected for covariates*

Contrast	DRD4	*d*	95 % CI
Living Letters vs. Control	All	.018	-.256 - .292
	7-	.009	-.345 - .364
	7+	.028	-.407- . .464
Living Books vs. Control	All	.364	.078 - .649
	7-	.023	-.326 - .372
	7+	.746	.243 - 1.249

Figure 1:
Means and confidence intervals for CLT posttest corrected for father's education, age and gender for carriers of DRD4 (7-) and DRD4 (7+) scoring below the 40th percentile (delayed) on the pretest (N = 307).

Meta-analysis

To test the consistency of the current outcomes with results of prior experiments (Kegel et al., 2011; Plak et al., 2015), we conducted a meta-analysis. We included two prior experiments and the current study - in all 5 contrasts - encompassing *N* = 730 participants of which 272 were carriers of the 7-repeat allele of the DRD4 gene. The

studies revealed three contrasts between *Living Letters* and *Clever Together* and two between *Living Books* and *Clever Together*. For an overview of the contrasts included in this metaanalysis and the results, see Table 5.

Table 5: *Overview of Studies Included in the Meta-Analysis*

	Cohen's *d* overall [95%]	*n* Exp/ control	Cohen's *d* (7+) [95%]	*n* Exp/ control	Cohen's *d* (7-) [95%]	*n* Exp/ control
Kegel et al. *Living Letters*	.65 [.28, 1.02]	45/88	1.06 [.41, 1.72]	14/35	.35 [-.10, .79]	31/53
Plak et al. I *Living Letters*	.04 [-.33, .41]	97/40	-.03 [-.62, .57]	38/15[a]	.11 [-.36, .58]	59/25[a]
Plak et al. II *Living Letters*	.02 [-.32 - .36]	115/46[a]	.03 [-.52 - .58]	50/17[a]	.01 [-.43 - .45]	65/29[a]
Plak et al. I *Living Books*	.13 [-.24, .49]	103/40[a]	.39 [-.22, .99]	37/15	-.12 [-.58, .34]	66/25
Plak et al. II *Living Books*	.36 [.01 - .71]	100/46	.75 [.18 – 1.31]	31/17[a]	.02 [-.41 - .46]	69/29[a]

Notes. All values are weighted and based on the complete set unlike in earlier reports.
[a] In Plak et al., I and II, the experimental conditions (*Living Letters and Living Books*) were both compared with the same control condition. Therefore the number of children in the control condition was equally divided over the two contrasts.

Living Letters. Outcomes across three experiments are summarized in Figure 2. *Living Letters* revealed a non-significant effect both in the carriers of the 7-repeat allele (*d* = .33, 95% CI = -.131- .787, *p* = .162) and in the non-carriers (*d* = .14, 95% CI =-.260- .539, *p* = .494). The difference between carriers and non-carriers was not significant, Q(1) = .367, *p* = .545. The heterogeneous results of the three experiments showed a large effect in favor of the carriers of the 7-repeat allele in Kegel et al. (2011), a small effect in Plak et al. (2015) and a low effect in the current study.

Living Books. Outcomes across two experiments are summarized in Figure 2. Carriers of the 7-repeat allele were strongly affected by *Living Books* (*d* = .59, 95%

CI = .157- 1.105, p = .007) whereas non-carriers were not (d = -.05, 95% CI = -.363 - .267, p = .767). The difference between carriers and non-carriers was significant, Q(1) = 5.454, p = .020.

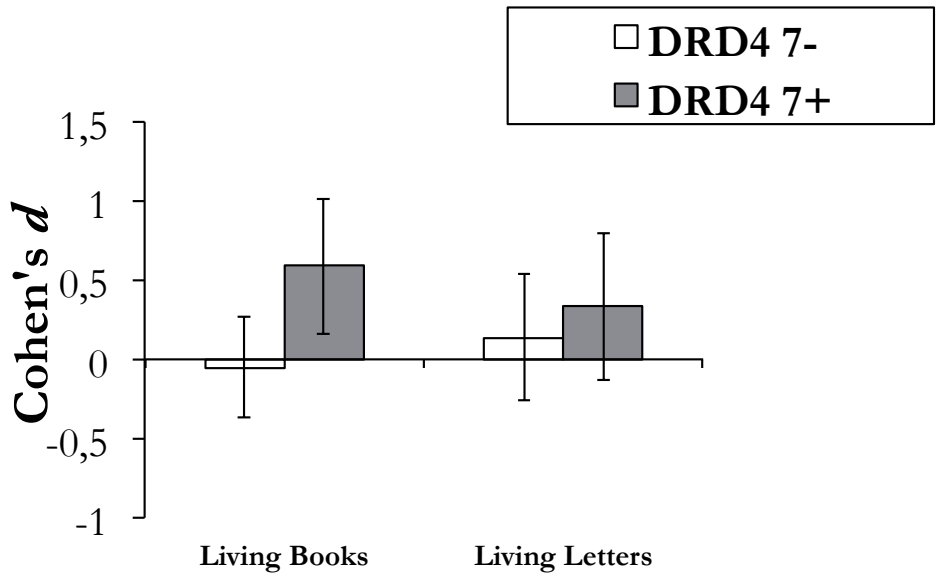

Figure 2:
Cohen's d for DRD4 (7-) and DRD4 (7+) scoring in the lowest ranges of literacy tests (N = 730) for *Living Books* and *Living Letters* across five experiments.

DISCUSSION

In the current randomized controlled trial including 565 five year- olds, we showed that two digitized programs, *Living Letters* and *Living Books* - both providing support in solving age-appropriate literacy-related tasks - failed to show effects across all subjects and programs. A subsample - slightly more than 30% of all kindergarten children - did benefit from *Living Books* as was demonstrated by a significant Gene x Environment interaction that fits the Differential Susceptibility Model (Belsky et al., 2007; Belsky & Pluess, 2009, 2013; Ellis et al., 2011; Van IJzendoorn & Bakermans-Kranenburg, 2012). As predicted by the genetic differential susceptibility hypothesis, we showed that carriers of the DRD4 7-repeat allele profited significantly from *Living Books*, whereas non-carriers did not benefit. *Living Letters*, by contrast, did not reveal a Gene x Environment interaction in the current randomized controlled trial: Carriers of the 7-repeat allele did not significantly benefit from the guidance that was offered by this program, similar to a previous trial with same age children (Plak et al., 2015) but

in contrast to a previous trial with younger children (Kegel & Bus, 2012).

Living Books guided the comprehension of the story by providing nonverbal information (animated pictures, music and sound effects) closely matched with the narration (Bus et al., 2015). This book reading intervention thus narrows the gap in language and literacy skills for poor performers who - as carriers of the DRD4 7-repeat allele - are known to be particularly susceptible to qualities of their learning environment. We hypothesize that particularly due to the multimedia in *Living Books*, including movie-like representations, sound and music, these susceptible children are more successful in understanding a story. Children with the 7-repeatallele may fail to benefit from storybook reading in a regular classroom environment because they are easily flooded with irrelevant perceptual and auditory stimuli. Just as is found in children with ADHD (see Schecklmann et al., 2008), carriers of the 7- repeat allele may become less susceptible to stimuli that are irrelevant to the task, due to numerous sources of sensory information each of which demands high levels of attention. It is even imaginable that the high attentional load of the books may result in a state of inattentional blindness and deafness (Molloy, Griffiths, Chait, & Lavie, 2015), which is known to make children insensitive to irrelevant stimuli from their surroundings, for example a crowded classroom. They may, so to speak, become hyper-focused on tasks that put a load on visual and auditory perception, resulting in outperforming their peers who are not carriers of the 7-repeat allele.

For children scoring midrange, *Living Books* may not be challenging enough since difficult words used in the stories are known by most children in kindergarten (Schaerlaekens, Kohnstamm, & Lejaegere, 1999). It is possible that children scoring midrange, who are carriers of the DRD4 7-repeat allele, would benefit from a more advanced version of *Living Books* including books with more difficult words and storylines.

There were no effects of *Living Letters*, even in the delayed group. As teachers in the Plak et al. (2015) study had complained that *Living Letters* was too tedious, we made a reduction in the easy games that mainly focused on familiarizing with the proper name. The rest of the program - learning the name of the first letter of the proper name and identifying the sound of this letter in words - remained unaltered. Despite this change, the program may not have corresponded to the level of five-year-olds even though they were delayed in literacy skills. On the other hand, *Living Letters* may not meet the criteria of a task that can keep children's attention with the 7-repeat allele focused. Even though *Living Letters* has various sources of sensory information, the pace of the program may be too slow: the push and pull between watching the general introduction, listening to specific instructions, and fulfilling the assignments may make it hard for the 7-repeat carriers to become totally engrossed in *Living Letters*.

Overall effects for carriers of the 7-repeat allele - meta analysis

To compare the results of the current randomized controlled trial with previous findings in studies that share a common design and instrumentation, we conducted a meta-analysis to show the consistency in outcomes of experiments so far, in line with guidelines of the New Statistics idea (Cumming, 2014). *Living Letters* showed an effect size of d = .33 for carriers of the 7-repeat allele, but results were not homogeneous ranging from d = 1.06 in Kegel et al.'s study to d = .03 in the current study. Younger children seem to benefit more than older children even when the older group only includes delayed children. *Living Books*, in contrast, revealed a homogeneous effect size of d = .59 for delayed carriers of the 7- repeat allele. The effect sizes for delayed non-carriers of the 7- repeat allele range from very small to non-existing. The current research result supports the results of previous studies on differential susceptibility. That is those children who are thought to be susceptible and are carriers of the 7-repeat allele benefit from this technology-enhanced educational program, while their presumably less-susceptible peers, non-carriers of the 7-repeat allele, do not.

In conclusion, it seems most plausible that *Living Letters* does not seem to fit the needs of literacy-delayed children, susceptible or non-susceptible. Please note that this does not exclude this program matching the needs of other subgroups not included in the current study (Merkelbach, Plak, van der Kooy-Hofland, Kegel, & Bus, under review). However, the program *Living Books* does support learning in carriers of the long variant of DRD4. These children may be particularly susceptible to *Living Books* because they have attentional problems: the animated stories are so engaging that they elicit a state of inattentional deafness to irrelevant stimuli from the environment (for example a noisy classroom). This may explain why carriers of the long variant benefit more from *Living Books* than they normally do from book reading while the program is not particularly effective for other children.

Limitations

We studied the role of one gene as a marker of differential susceptibility and more research is needed to obtain a good understanding of how the DRD4 gene interacts with other dopamine genes and the dopaminergic system in general. A single gene cannot, of course, be the exclusive cause of neurotransmitter levels in the brain and be responsible for a specific type of learning behavior (Kegel & Bus, 2012). The current findings suggest that the single dopamine-related gene DRD4 functions as a marker for differential susceptibility because it is a proxy for the dopaminergic system. The mechanisms that explain how the dopaminergic system interacts with the program are still unknown and need further research. A second limitation was that the qualities of *Living Letters* were

insufficient to promote learning in the group of delayed learners. A strong element of this study is the number of participants. Taking into account that the current study is not correlational but a randomized controlled trial, the scale of this GxE study is substantial and well-powered (Van IJzendoorn et al., 2011). Longterm effects in the field of reading instruction are needed to show that the programs are indispensable and for whom.

Implications

We can conclude from the results of our study that brief educational computer programs can be effective specifically for a group of delayed presumably susceptible children: carriers of the DRD4 7-repeat allele. Without an additional literacy program, they lag behind in literacy skills, but they outperform their peers when they receive additional optimal instruction in a positive learning environment provided by a computer program. For their less susceptible peers, non-carriers of the 7-repeat allele, the brief additional programs have no effect probably because these children do not experience problems with on-task behavior. It is also possible that the non-carriers of the 7-repeat allele are in need of a more prolonged and intensive version of additional programs.

While the findings for *Living Letters* are mixed across experiments, *Living Books* yielded consistent positive effects. *Living Books* promotes basic language and literacy skills - comprehension and vocabulary - and may therefore best fit the needs of children lagging behind in an early stage of learning to read. The program *Living Letters* that targets basic alphabetic skills may not fit the needs of the most delayed group five-year-olds. We hypothesize that for the purpose of learning literacy skills, educational computer programs can even be more helpful than scaffolding by an adult (Takacs et al., 2015). Carriers of the 7-repeat allele can be considered as vulnerable since in a negative learning environment they may not thrive. A noisy and crowded classroom without personalized positive feedback by the teacher can be characterized as such a learning environment.

Carriers of the 7-repeat allele show their full potential when placed in a learning environment that helps them to engage in the task. Thus, the academic success of these presumably susceptible children can be enhanced if their susceptibility to the environment, for better and for worse, is acknowledged. When children, who are carriers of the 7-repeat allele, are offered a more suitable learning environment, they easily catch up with and even outperform their peers.

ACKNOWLEDGEMENTS

This study was supported by a grant from the Dutch organization Kennisnet to Adriana G. Bus.

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