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Neuroplasticity of selective attention: Research foundations and preliminary evidence for a gene by intervention interaction

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This article reviews the trajectory of our research program on selective attention, which has moved from basic research on the neural processes underlying selective attention to translational studies using selective attention as a neurobiological target for evidence-based interventions. We use this background to present a promising preliminary investigation of how genetic and experiential factors interact during development (i.e., gene × intervention interactions). Our findings provide evidence on how exposure to a family-based training can modify the associations between genotype (5-HTTLPR) and the neural mechanisms of selective attention in preschool children from lower socioeconomic status backgrounds.

neuroplasticity | selective attention | gene × intervention | ERPs

Over the past four decades, the Brain Development Lab has engaged in a systemic program of research to understand the development and plasticity of different subsystems within vision, audition, sensory integration, language, and attention (e.g., refs. 1–5). By "plasticity," we refer to the capacity for subsystems to be changed by variations in the environment, ranging from complete sensory deprivation (e.g., as resulting from congenital deafness or blindness) to exposure to short-term education experiences (e.g., refs. 5–8). Our research program has had a particular focus on the development and plasticity of selective attention, or the ability to select and preferentially process specific information in the environment while simultaneously suppressing the processing of irrelevant, competing distractors. We have emphasized selective attention because it is a skill that has the potential to impact functioning across a range of domains. In this respect, we consider selective attention to act as a "force multiplier" that can have broad-reaching impacts on different aspects of cognition. In support of this, performance on selective attention tasks has been linked both to academic skills in general (9–12) and to specific cognitive abilities, including speech segmentation, working memory, and nonverbal intelligence (13–17). Here, we briefly review the trajectory of our research program on selective attention, which has moved from basic research on the neural processes underlying selective attention to translational research studies using selective attention as a neurobiological target for evidence-based intervention. We use this background to present a promising preliminary investigation of how genetic and experiential factors interact during development (i.e., gene × intervention interactions) in preschool children from lower socioeconomic status (SES) backgrounds.

Methodologically, our research on selective attention relies heavily on the use of event-related brain potentials (ERPs). ERPs are a powerful methodology with exquisite temporal resolution, allowing the identification of the stages of processing influenced by selective attention. Our research builds on a classic paradigm, first pioneered by Hillyard et al. (18) in 1973, in which ERPs are recorded to competing streams of stimuli presented simultaneously, with participants instructed to attend selectively to one stream. By comparing ERPs with probe stimuli in the attended versus unattended stream(s), the effects of selective attention on neural processing can be identified. Importantly, because stimuli are presented concurrently, with only the direction of attention manipulated while keeping arousal and task demands constant, this paradigm provides a relatively pure index of the effects of selective attention on neural processing. Across a range of studies using variations of this classic paradigm, and whether attention is directed to a particular location or stimulus attribute, it has been demonstrated that in adults the processing of attended information is enhanced (or, conversely, processing of unattended information is suppressed) by 100 ms of stimulus presentation (for reviews, see refs. 19, 20). This suggests that attentional modulation acts on early stages of processing, an effect we have likened to a volume control knob, where selective attention can be endogenously deployed to modulate neural responses to particular stimuli or stimulus attributes.

Initially, our research on selective attention examined changes in these neural mechanisms among special populations with atypical sensory experience resulting from congenital deafness or blindness (2, 5, 21). In these cases, selective attention in the remaining modalities was enhanced, showing larger modulations

Significance

Selective attention is the ability to select and preferentially process specific information while simultaneously suppressing the processing of irrelevant, competing distractors. It is a fundamental ability linked to various cognitive skills and academic achievement. We describe the foundations and history of our research program, which spans from basic research on neural mechanisms and neuroplasticity of selective attention to translational research aimed at designing interventions to improve selective attention. We also present preliminary evidence for gene × intervention interactions in neural mechanisms of selective attention in children from lower socioeconomic status backgrounds. This program of research demonstrates the marked malleability of neural systems for selective attention and highlights the potential for changes in selective attention as a function of intervention.

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of neural activity, particularly when attention was directed to peripheral, as opposed to central, visual or auditory locations. These studies indicated that a lifetime of atypical sensory experience could lead to compensatory changes in selective attention in the remaining modalities. However, across a range of outcomes showing compensatory changes, including peripheral motion detection (1), we began to observe evidence suggesting that plasticity is best characterized as a double-edged sword. That is, whereas compensatory enhancements were observed in some populations, other literatures suggested parallel deficits in these same malleable systems among other special populations (for a review, see ref. 22). However, different experimental paradigms were used across these diverse lines of research, making it difficult to address this possibility conclusively using the existing literature. Thus, as a stronger test of the two sides of plasticity, we examined peripheral motion processing using the same experimental paradigm and found both enhancements in adults with congenital deafness and deficits among adults with a history of developmental dyslexia (23). This suggested that the neural systems showing enhancements following sensory deprivation, perhaps including selective attention, might be vulnerable during development in some populations of children. However, to address this question, a child-friendly ERP paradigm was needed.

To study the neural systems of selective attention developmentally, our research team adapted the classic Hillyard selective attention ERP paradigm for use with children (24, 25). The details of this paradigm are important, as it has now been used across multiple studies and is also used in the research presented here. In the child-friendly version of the ERP selective attention paradigm, we focused on selective auditory attention. To manipulate selective attention, we presented two competing streams of auditory narratives (recordings of children's stories) and instructed participants to attend to one of the two narratives. These narratives were presented from separate speakers located 90° to the left or right of the participant, with one narrative read by a female narrator and the other by a male narrator. ERPs were recorded not to the stories themselves but rather to identical auditory probe sounds superimposed on both the attended and the unattended story. Because attention was directed to a particular spatial location, any enhancement of information from that channel would result in larger-amplitude ERPs to probe sounds embedded in the attended relative to unattended channel. This attention effect was observed robustly in adults, who showed typical attention effects beginning at about 100 ms of auditory processing (24, 25). Remarkably, similar amplitude enhancement was observed in children as young as 3 y of age (25).

In adults, the selective attention effect on auditory processing is generally observed as an increased negativity in amplitude for the attended versus unattended stream, often referred to as the "negative difference wave" (26). However, in studies using the dichotic listening paradigm described above, the selective attention effect has been observed as positive in amplitude in early childhood, mimicking the morphology of the auditory ERPs that are positive in amplitude for the probes in both the attended and the unattended stories in young children. As discussed in previous studies (24, 25, 27), we argue that this difference in morphology mainly stems from the maturation of the auditory cortex and that the selective attention effect that emerges around 100 ms in children reflects a developing early selection and sensory gain mechanism.

Although the underlying ERP morphology differed in children and adults, in all age groups selective attention served to increase the amplitude of neural processing for stimuli in the attended channel by 100 ms after stimulus onset. Using this adapted paradigm, we have continued to trace normative developmental changes in the effects of selective attention through adolescence and into adulthood (27).

With this child-friendly paradigm, we were also able to examine vulnerability in selective attention during development. This line of research initially focused on children with atypical development, and we observed reduced effects of selective attention on neural processing both in children with specific language impairment (28) and in those with poor preliteracy skills (8). At the same time, we were able to show that children with specific language impairment or with poor early literacy skills, as well as typically developing children, showed increases in the effects of selective attention on neural processing following intensive academic training lasting 6–12 wk (8, 29). These lines of research represented a major expansion of the study of selective attention, revealing not only the vulnerabilities of selective attention during development but also the capacity for these systems to be modified in response to training.

Our more recent research has expanded this approach to study the neuroplasticity of selective attention in children growing up in lower SES environments. Here, our research moved from the study of clinical populations to a larger segment of the population that is at risk, by virtue of growing up in lower SES environments, for a wide range of adverse outcomes in childhood and into adulthood (30–33). Approaching neuroplasticity as a double-edged sword, this line of research has examined both the vulnerability and enhanceability of neural mechanisms of selective attention in children from lower SES backgrounds. In this context, we defined vulnerability as susceptibility to be influenced by risk factors associated with lower SES environments and defined enhanceability as the capacity to be modified in response to favorable changes in the environment, such as targeted training programs. With respect to selective attention among children growing up in different SES backgrounds, it has now been reported in both our own research and that of others that the neural mechanisms of selective attention are vulnerable in children from lower SES backgrounds (34–36). Whereas children from higher SES backgrounds show robust modulation of neural activity when selective attention is deployed, these effects are markedly reduced or absent in children from lower SES backgrounds. Further, in comparison with children from higher SES backgrounds, young children from lower SES backgrounds display both a maturational delay and divergent developmental pattern in neural mechanisms of selective attention (37). Despite these overall group differences, we also documented notable individual differences among children from lower SES backgrounds in the vulnerability of selective attention, and we linked greater effects of selective attention on neural processing to higher nonverbal intelligence (17).

In an extension of this research, we recently started to investigate the associations between genetic polymorphisms and individual differences in vulnerability of selective attention (38). As an initial step, we focused on a genetic polymorphism of the serotonergic system. Serotonin plays an important role in the development, functioning, and neuroplasticity of the frontal cortex in the mammalian brain (39). Given the structural and functional connections between serotonergic systems and the prefrontal cortex (39–41) and the critical role the prefrontal cortex plays as a source of attentional control (42, 43), we hypothesized that genetic variability in this system would be linked to individual differences in selective attention. In support of this, we found an association between allelic variations of the serotonin transporter-linked polymorphic region (5-HTTLPR) of the serotonin transporter gene *SLC6A4* and individual differences in the effects of attention on neural processing in children from lower SES backgrounds (38). Specifically, we found that children who carry at least one copy of the short allele of 5-HTTLPR exhibited more robust effects of selective attention on neural processing than children who are homozygous for the long allele (i.e., long homozygotes). In contrast, we did not observe any differences between children carrying one versus two copies of the short allele. These findings implied that being homozygous for the long allele of 5-HTTLPR may

denote a risk factor for neural mechanisms of selective attention in preschool-age children from lower SES backgrounds, although the precise mechanisms underlying this difference remain to be determined.

Together, these studies identified selective attention as a putative neurobiological target for interventions aimed at children growing up in lower SES backgrounds, which could also identify the role of environmental processes in shaping attention development in these same children. To investigate this, we began a long and productive partnership with Head Start of Lane County in our community. Head Start is a federally funded preschool program supporting children primarily from families living in poverty. In a randomized controlled trial study, we documented that neural mechanisms of selective attention can be enhanced in children from lower SES backgrounds following a family-based training program (7). Briefly, this 8-wk program, Parents and Children Making Connections - Highlighting Attention (PCMC-A), was designed to improve brain systems that support selective attention in preschool children using a two-generation approach that simultaneously targeted both children and parents. The child component of the program was designed to increase self-regulation of attention and emotional states with a focus on attention-training exercises. The parent component focused on improving parenting practices by targeting family stress regulation, contingency-based discipline, parental responsiveness, and language use and promoting child attention at home through links to child training exercises. The randomized, controlled trial study included both an active control and a passive control group. The active control group received a comparison program that primarily focused on child classroom training, with greatly reduced parent involvement, and the passive control group received Head Start services as usual with no additional training. In the relatively short time frame of 8 wk, children randomly assigned to PCMC-A showed enhancements in neural mechanisms of selective attention, along with improvements in standardized measures of nonverbal intelligence and language and parent reports of child behavior. Importantly, these enhancements in selective attention were observed relative to both the active and passive control groups, demonstrating both the enhanceability of selective attention as well as the potential of simultaneously training attention in children while working with their parents and engaging the home environment.

By suggesting that both genetic and environmental factors combine to explain variability in brain function for selective attention in children from lower SES backgrounds, these lines of research led to a broader question: To what extent might environmental experiences interact with or serve to alter genetic associations with brain function? Advances in molecular genetics now permit the investigation of interactions between gene polymorphisms and specific environmental factors, i.e., gene × environment interactions (44–47). Although the majority of the studies assessing gene × environment interactions are correlational in design (i.e., they rely on naturally occurring variation in environments), a growing body of work uses randomized, controlled trial studies to experimentally manipulate environmental factors (48–51). Such experimental gene × environment studies provide distinct advantages over correlational studies by directly manipulating the environment in a causal manner. This reduces the risk that results will be contaminated by gene–environment correlations (rGE) and also by inadequate assessment and characterization of the environment (50, 51). Most importantly, a gene × intervention design provides causal evidence that genotype associations can be moderated by changes in the environment.

Previous gene × intervention studies mainly focused on precursors and markers of developmental psychopathology (52–57). In this context, particular attention was paid to the investigation of interactions between specific candidate genes and interventions on problem behaviors, in particular on externalizing behavior problems from toddlerhood through adolescence (52, 53, 55, 58) and the use of substances such as tobacco and alcohol in adolescence (54, 56, 59–61). Together, these studies showed that gene × intervention findings may depend on a multitude of factors, such as the candidate genes in question, types of interventions, age period of inquiry, and the characteristics of intervention and control samples.

In the present study, we extended the application of this powerful approach in a preliminary investigation of gene × intervention interactions and neural mechanisms of selective attention in preschoolers from lower SES backgrounds. We examined whether our family-based intervention, previously demonstrated to result in enhancements of the effects of attention on neural processing (7), would moderate the associations between the 5-HTTLPR polymorphism and selective attention in preschool children from lower SES backgrounds. Participants were 71 preschoolers for whom we also had 5-HTTLPR genetic data and who had been randomly assigned to receive either PCMC-A or Head Start services as usual (HS-alone). This sample included both a subset from our previous study (7) who also agreed to provide genetic samples ($n = 57$) and children who participated in subsequent intervention studies using the same training program and provided genetic samples ($n = 14$). We categorized children either as 5-HTTLPR short-allele carriers (children who carry at least one copy of the short allele) or long homozygotes (children who carry two long alleles). To assess the neural mechanisms of selective attention, we used the child-friendly ERP dichotic listening paradigm described above. Effects of selective attention were measured by comparing the mean amplitude of ERPs evoked by the identical probes embedded in the attended versus unattended stories. ERPs were acquired before and after the 8-wk intervention (or HS-alone) period. This permitted an evaluation of the extent to which the effects of the family-based training program moderated the association between 5-HTTLPR and neural mechanisms of selective auditory attention.

Results

Following categorization of children into groups based on both their 5-HTTLPR genotype (short-allele carriers vs. long homozygotes) and experimental condition (PCMC-A vs. HS-alone, by random assignment), 71 children were identified as falling into one of four groups: long homozygotes in the training group ($n = 12$), long homozygotes in the control group ($n = 10$), short-allele carriers in the training group ($n = 25$), and short-allele carriers in the control group ($n = 24$). [There were too few short-homozygous children in each group to permit further subdivision of the short-allele carriers (PCMC-A $n = 6$, HS-alone $n = 4$). However, in our previous research we did not find any differences in ERPs of selective attention between children who carried one versus two copies of the short allele.] Descriptive statistics for study variables are presented in Table S1. Preliminary analyses showed no differences across groups in age, SES, or gender distribution (Ps > 0.16). At pretest, there were no main effects of or interactions between genotype and training on accuracy for the comprehension questions answered during the ERP task (Ps > 0.36). Controlling for pretest accuracy, at posttest there were also no main effects of or interactions between genotype and training on comprehension accuracy (Ps > 0.11).

The mean amplitudes of ERPs were measured between 100–200 ms poststimulus onset, collapsed across the linguistic and nonlinguistic probe types, consistent with previous studies using this paradigm with young children from lower SES backgrounds (7, 17, 35, 36). The effect of selective attention on neural processing was operationalized as the mean amplitude difference between the ERPs to the probes in the attended versus unattended stories (attended minus unattended).

Exploratory data analyses were conducted to detect outliers in ERP indices of selective attention within any of the four groups (±3 SD). These analyses revealed no outliers in ERP mean

amplitudes either at pretest or posttest. Fig. 1 presents the grand average ERPs from a representative fronto-central channel (FC5) on the left hemisphere for the four groups. The upper row presents the data at pretest, and the lower row presents the data at posttest. Figs. S1–S8 present the grand average ERPs from all electrodes for the four groups at pretest and posttest.

The first analysis examined pretest data only to confirm differences in the effect of selective attention on neural processing between the two genotype groups, as reported previously (38), but not between the two training groups. This analysis included two between-subjects factors (group: PCMC-A, HS-alone; genotype: long homozygotes, short-allele carriers) and one within-subject factor (electrode location: anterior, central, posterior). This analysis, similar to our analysis with a larger dataset (38), confirmed a significant effect of genotype on ERP mean amplitudes of selective attention [$F(1, 67) = 11.57$, $P = 0.001$, partial $\eta^2 = 0.15$], such that long homozygotes had reduced ERP mean amplitudes of selective attention compared with short-allele carriers, $d = 0.89$. As expected in a random-assignment design, this analysis also confirmed that there was no main effect of training group at pretest, $F(1, 67) = 0.24$, $P = 0.63$, partial $\eta^2 < 0.01$, nor was there a significant interaction between genotype and training, $F(1, 67) = 0.002$, $P = 0.97$, partial $\eta^2 < 0.01$, indicating that the groups were well-matched at pretest. There was a main effect of electrode location [$F(2, 134) = 5.52$, $P = 0.01$, partial $\eta^2 = 0.08$] such that the neural indices of selective attention were larger over the anterior and central electrodes than over the posterior electrodes. There were no interactions with electrode locations, Ps > 0.74.

The second set of analyses examined the posttest ERP data. To control for pretest ERPs, unstandardized residuals were calculated for each electrode cluster (anterior, central, posterior) by regressing the posttest ERP amplitudes on the pretest ERP amplitudes. These unstandardized residuals were used as the posttest dependent variable in a mixed model ANOVA including the following factors: group (PCMC-A, HS-alone) × genotype (long homozygotes, short-allele carriers) × electrode location (anterior, central, posterior). Controlling for pretest ERPs, this analysis indicated a significant main effect of training on ERPs, $F(1, 67) = 4.26$, $P = 0.04$, partial $\eta^2 = 0.06$, with children in the PCMC-A training group having larger posttest ERP indices of selective attention than children in the HS-alone group, $d = 0.27$. In contrast to the pretest analyses, at posttest there was no longer a significant main effect of genotype on ERPs, $F(1, 67) = 0.34$, $P = 0.56$, partial $\eta^2 < 0.01$. However, critical to the primary research question, at posttest there was a significant interaction between genotype and training, $F(1, 67) = 6.46$, $P = 0.01$, partial $\eta^2 = 0.09$, detailed below. There were no main effects of or interactions with electrode locations, Ps > 0.14.

To unpack the interaction between genotype and training on posttest ERP attention effects, step-down ANOVAs were conducted using the posttest unstandardized residuals. Within the HS-alone group, at posttest short-allele carriers exhibited larger ERP indices of selective attention than long homozygotes in this group, $F(1, 32) = 5.61$, $P = 0.02$, $d = 0.89$, similar to observations at pretest. There were no main effects of or interactions with electrode locations, Ps > 0.59. In contrast, among the PCMC-A training group, short-allele carriers and long homozygotes no longer showed differences in the effects on selective attention on ERPs, $F(1, 35) = 1.76$, $P = 0.19$, $d = 0.47$. There were no main effects of or interactions with electrode locations, Ps > 0.13.

Discussion

The present study expands on our prior research and heralds a promising line of inquiry that amalgamates cognitive neuroscience, genetics, and randomized controlled trial methods in investigations on the neuroplasticity of selective attention. Using the gene × intervention approach, we provide preliminary evidence on how exposure to a family-based intervention could moderate the effects of genotype on the neural mechanisms of selective attention in preschool children from lower SES backgrounds. Consistent with our previous research (38), in the present study we found that, before random assignment to intervention condition, children homozygous for the long allele showed more

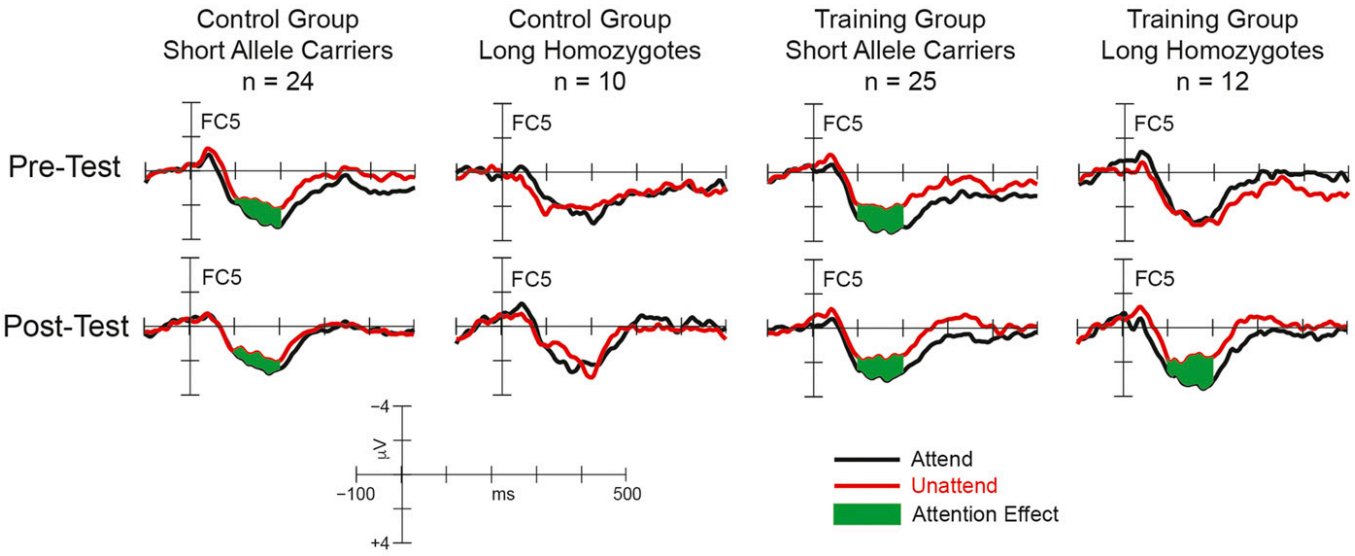

Fig. 1. ERPs from the selective auditory attention paradigm, averaged across all participants in each group, separately at pretest and at posttest at representative fronto-central electrode FC5. The selective attention effect was operationalized as the mean amplitude difference between ERPs elicited by the probes in the attended stories vs. ERPs elicited by the probes in the unattended stories, averaged across 24 electrode sites across the scalp. At pretest, long homozygotes showed more attenuated neural indices of selective attention than short-allele carriers in both the control and the training groups. At posttest, long homozygotes continued to show more attenuated neural indices of selective attention than short-allele carriers within the control group. However, among the children randomly assigned to the family-based training, long homozygotes no longer showed more attenuated neural indices of selective attention than their short-allele carrier peers.

attenuated neural indices of selective attention than children carrying at least one short allele. Also consistent with prior research (7), we found that after the training period children randomly assigned to the 8-wk family-based training showed larger effects of attention on neural processing than children randomly assigned to the control condition. Here, we extended prior work by demonstrating an interaction between genotype and training groups following the 8-wk intervention period. Specifically, we found that, within the control group, at posttest children homozygous for the long allele continued to show reduced effects of selective attention on neural processing relative to the short-allele carriers. In contrast, among children randomly assigned to the training group, following the 8-wk program children's neural indices of selective attention were no longer attenuated in the long homozygotes in comparison with their short-allele carrier peers. These results suggest that an effective training program could modify the links between 5-HTTLPR and neural mechanisms of selective attention in young children from lower SES backgrounds.

Results from the present study can be evaluated in the context of broader frameworks on the relationship between the 5-HTTLRP polymorphism and environmental characteristics. For example, one line of research argues that carriers of the short allele of 5-HTTLPR are differentially sensitive to environmental conditions relative to long homozygotes, showing greater vulnerability in the face of adversity and benefiting the most from supportive and enriching environments (62–65). This framework would predict that the short-allele carriers would outperform the long homozygotes after experiencing an effective family-based training program. Here, we did not find support for this prediction. One potential explanation is that our study focused on neural mechanisms of selective attention instead of on precursors or markers of developmental psychopathology. Traditionally, the short allele of 5-HTTLPR has been linked to unfavorable outcomes in the context of problem behaviors and psychopathology, especially in the face of adverse environmental conditions (66, 67). Not surprisingly, the extent to which short-allele carriers show differential susceptibility to environmental influences has been tested mainly for precursors and early markers of problem behaviors or psychopathology in children and adolescents (68–71). However, another line of research shows higher performance in short-allele carriers in cognitive abilities that are mediated by the prefrontal cortex, such as working memory, executive function, and decision-making (72–75). In line with such studies, we previously found that children from lower SES backgrounds who carry at least one short allele showed more enhanced effects of selective attention on neural processing (38). Given that the short-allele carriers in the present study already had more enhanced selective attention effects than long homozygotes at pretest, they might not have needed a boost in selective attention as much as children homozygous for the long allele. It is also plausible that being homozygous for the long allele confers differential sensitivity to training effects, at least in the context of neuroplasticity of selective attention. Although we did not find a significant difference between the long homozygotes and short-allele carriers in the training group at posttest, the effect size of this comparison was moderate, favoring the long homozygotes. Further investigations are warranted to determine whether such an effective training program helps long homozygote children either catch up with short-allele carriers or outperform them.

The precise neurobiological mechanisms through which the allelic variations of 5-HTTLPR relate to brain functioning remain to be determined (76). However, the role of serotonin in the prefrontal cortex may be critical to the neurobiological mechanisms linking the 5-HTTLPR genotypes and selective attention. The serotonergic system, which originates in the raphe nuclei, projects to a wide range of brain regions, including the frontal cortex (39). The prefrontal cortex in particular is densely populated with serotonin receptor and transporter sites (40, 41), and the serotonergic system contributes to the development, neuroplasticity, and functioning of the frontal cortex in the mammalian brain (39). As it is well documented that the prefrontal cortex is a critical component of the neural networks involved in selective attention (43, 77, 78), it is plausible that the associations between the serotonergic system and selective attention are mediated through the contributions of the serotonergic system to the structure and functioning of the prefrontal cortex. However, it is important to note that attention relies on a wide network of brain regions, including both the dorsal frontoparietal and the ventral frontoparietal networks (77, 79), and that selective attention modulates the processing of information in the sensory cortices (20, 78). Therefore, it is possible that there are neural pathways in addition to or in lieu of the prefrontal cortex through which the serotonergic system influences selective attention. Further investigations are crucial to elucidate the specific neural pathways through which serotonergic genotypes may relate to individual differences in the development and neuroplasticity of selective attention.

While we found differences in neural mechanisms of selective attention as a function of genotype and training, these findings did not extend to comprehension accuracy measured during the dichotic listening task. Neither at pretest nor at posttest were there main effects of genotype or interactions between genotype and training on comprehension accuracy. It is possible that there were genotype or training differences in behavior that we could not detect with our limited sample size. However, it is also possible that this behavioral measure was not sensitive enough to capture individual differences in selective attention. As noted in our previous studies (17, 35), we find our comprehension accuracy questions useful as they reinforce to children the goal of attending to a single story. Further, they provide a gross index that children included in the analysis were generally on task. However, these forced-choice questions about the attended stories do not provide a sensitive assay of children's selective attention. It is important to incorporate more sensitive behavioral measures of attention in future studies assessing genetic and experiential factors that contribute to the development and plasticity of selective attention.

Previous studies have linked enhanced neural mechanisms of selective attention to better performance in cognitive tasks, such as tasks of working memory and nonverbal intelligence (15, 17). Further, in prior research we demonstrated that our family-based training program, designed to enhance selective attention in preschool children, improved performance in standardized tests of cognition (7). Given the associations between serotonergic systems and selective attention reported here and the links between selective attention and other cognitive abilities, it is plausible that selective attention may act as a mediating mechanism through which the serotonergic systems in the brain are associated with performance in cognitive tasks. This pathway may explain the links between 5-HTTLPR genotypes and performance on executive functioning tasks (e.g., refs. 73, 75). Further, based on the genotype and training interactions we demonstrate in the present study, it is possible that effective training programs could moderate the links between 5-HTTLPR genotypes and cognitive abilities.

Our preliminary findings provide causal evidence that supportive environments can modify genetic associations with neural mechanisms of cognition in children from lower SES backgrounds. It has been argued that one of the advantages of gene × intervention studies is that they do not require the large sample sizes that would be needed in gene × environment studies in which the environment is not controlled (51). Consistent with this argument, the randomized, controlled design of our study and the sensitive electrophysiological measures allowed us to document significant gene × intervention effects in young children even with limited sample sizes. However, it is important to emphasize that our preliminary findings call for replication and extension studies to test

for similar interactions in larger and more diverse groups of children. Another key future direction will be investigations that provide more specificity with regard to how the moderation of genetic associations is mediated by specific training components. Further, how environmental factors, such as cumulative risk or enriching home environments, can moderate such genetic associations remain to be determined.

It will also be critical to investigate how 5-HTTLPR interacts with other candidate polymorphisms. Previous studies have reported gene × intervention effects for polymorphisms of various candidate genes, such as the dopamine D4 receptor (*DRD4*) gene (53, 54, 59, 80, 81), dopamine active transporter (*DAT1*) gene (57), and brain-derived neurotrophic factor (*BDNF*) gene (58, 82). As no single candidate gene can explain all the variability in any aspect of cognition or responsiveness to intervention, investigations of interactions between these polymorphisms are important to provide a more comprehensive account of the genetic underpinnings of the neuroplasticity of selective attention.

Although there is much more work be done, the general approach and findings reported here present a promising direction that builds on decades of basic research demonstrating the two sides of the plasticity of neural systems for selective attention. Results from this prior work have identified both genetic and environmental factors contributing to variability in these systems. We have also repeatedly observed that the neural systems for selective attention are modifiable in response to training, whether the training program is a child-focused academic intervention that centers on cognitive skill training (8, 29) or a family-based two-generation program that integrates training for both children and their parents (7). Importantly, the experimental work showing that the neural mechanisms of selective attention can be modified following training provides the strongest evidence for the malleability of these neural systems. For policymakers and advocates for children, these findings suggest that investments in evidence-based programs targeting highly modifiable systems during early childhood have great potential to improve outcomes for children at risk for delays in school readiness. Our gene × intervention findings imply that the genetic associations observed in prior research (38) are not static and can be modified with an efficient training program. However, we would like to emphasize that we consider these findings promising but preliminary and that future research is necessary to understand the interactions between genetic factors and training programs in relation to the plastic subsystems of the brain.

Despite the preliminary nature of this study, the present findings add to the literature on the plasticity of neural systems for selective attention. Critically, we wish to underscore that these emerging lines of inquiry are possible only with decades of prior research upon which to build. In our case, the pioneering work of Hillyard and colleagues in developing an elegant paradigm for measuring the effects of selective attention on neural processing built a critical foundation. Numerous researchers collaborating in the Brain Development Lab, who brought developmental and methodological expertise, then adapted these paradigms and created a highly engaging and empirically rigorous paradigm that has been very successful in studies of children (7, 17, 24, 25, 29). Only after this careful foundational work was it possible to examine patterns of vulnerabilities in special populations and the capacity for these systems to be modified through intervention.

It is important to continue to build upon and extend these foundations, especially as studies of the neuroplasticity of selective attention begin to intersect with large and established literatures on parenting, stress, and child development. It is also promising to see evidence that genetic associations with neural systems are not static; indeed, genes are not destiny. These studies add specificity to efforts to understand the mechanisms by which early adversity impacts the developing brain in ways that can have lasting impacts across a wide range of outcomes. We look forward to the next 40 years of research in this area for the promise it represents to inform evidence-based approaches to support the healthy development of children, and particularly those who may be the most vulnerable.

Methods

Participants. All children were recruited in Oregon, from 12 preschool sites of Head Start, a program for families living at or below the poverty line. In the present study, we included only children for whom DNA was collected and ERP data were available for both pretest and posttest sessions. Based on parent reports, children with diagnosed behavioral or neurological problems [e.g., attention deficit/hyperactivity disorder (ADHD), specific language impairment, epilepsy] and children taking psychoactive medications were excluded from the present study. All children included in the ERP analyses were right-handed, monolingual, native English speakers. All children passed a hearing screening at 20 dB HL at 500, 1,000, 2,000, and 4,000 Hz in both the right and left ears.

The initial sample included 95 children for whom DNA data were available, who were randomly assigned to either the family-based training program or the control group, and from whom ERPs were collected at pre- and posttest periods. From this sample, we excluded children who had low ERP quality due to excessive EEG artifacts, fewer than 75 trials per condition, and/or less than 50% accuracy on the comprehension questions presented during the ERP tasks, consistent with the exclusion criteria used in previous research with this paradigm (17). By these criteria, 15 children were excluded for not meeting the criteria at pretest, and nine children were excluded for not meeting the criteria at posttest.

The final sample included 71 children (46 females) between the ages of 41 and 66 mo (mean age = 55 mo, SD = 6 mo). In this final sample, 70% of the children were white/Caucasian, 6% American Indian or Alaskan, 18% more than one ethnicity, 6% unknown or unreported. Of the final sample, 37 children (25 females) had been randomly assigned to the family-based training group, and 34 children (21 females) had been randomly assigned to the control group.

Informed consent was obtained from parents or other caregivers. In addition, verbal assent was obtained from child participants. DNA was collected at either pretest or posttest sessions. All families were paid for participation. Study procedures were approved by the University of Oregon Institutional Review Board.

PCMC-A. The family-based training program, Parents and Children Making Connections – Highlighting Attention, included both a child-directed component, and a parent-directed component, described in detail in ref. 7. Briefly, the child component of the training program included activities designed to increase self-regulation of attention and emotion states. In each session, children completed two to four small group activities (four to six children, two adults) selected from a set of 20 activities. Activities targeted specific aspects of attention, such as vigilance, selective attention, and task switching. Furthermore, activities permitted children to learn emotional vocabulary, to recognize emotional states of others, and to express and regulate emotional states. The child-directed portion of PCMC-A included eight 50-min child sessions held concurrently with the parenting sessions in a separate room.

The parent component of PCMC-A was adapted from the Linking the Interests of Families and Teachers (LIFT) curriculum developed at the Oregon Social Learning Center (83). In each session, an interventionist delivered parenting strategies in small-group format (the parents of four to six children). The sessions focused on family stress regulation with consistency and predictability, planning, and problem-solving strategies; contingency-based discipline; and parental responsiveness and language use with child. Furthermore, parents were provided with information on the attention activities their children participated in and received suggestions for home-based modifications to provide further practice. In addition to these small-group parent sessions, an interventionist made weekly support calls to confirm the correct implementation of home-practice activities, elucidate instruction points, and offer family-specific suggestions in response to parents' experiences. Parents attended eight weekly, 2-h classes that occurred in the evenings or on weekends. Family meals and childcare were provided.

Comparison Group (HS-Alone). The comparison group included children who attended their regular half-day Head Start classes over the 8-wk evaluation period. Within the Head Start curriculum, there are no specific attention-training components. Furthermore, although Head Start has a parent education component, there is no required parent-guidance curriculum, and

parents are contacted primarily to share information regarding Head Start policies and services available for families.

Genotyping. Buccal epithelial cells were collected with cotton swabs. For each child, two swabs were collected. Genotyping was conducted at the University of Oregon. Genomic DNA was isolated from the swabs, as described in ref. 38. In the present study, allele frequencies of 5-HTTLPR were 58% for the long (l) allele and 42% for the short (s) allele. According to the Hardy–Weinberg equilibrium, the expected distribution of 5-HTTLPR genotypes would be 34% for l/l ($n = 24$), 49% for s/l ($n = 35$), and 17% for s/s ($n = 12$). In our sample, genotype frequencies were 31% for l/l ($n = 22$), 55% for s/l ($n = 39$), and 14% for s/s ($n = 10$). χ^2 tests revealed no significant differences between the observed frequencies and the expected frequencies according to the Hardy–Weinberg equilibrium [χ^2 (2) = 0.96, $P = 0.62$].

Electrophysiological Assessment of Selective Auditory Attention. We recorded ERPs in a spatial selective auditory attention ERP paradigm described in previous studies with preschoolers from lower SES backgrounds (7, 17). The details of the data collection procedure, EEG recording, and analyses are provided in *SI Electrophysiological Assessment of Selective Auditory Attention*.

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Supporting Information

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SI SES

All children in the present study were considered to be from lower SES backgrounds by virtue of their eligibility for and participation in Head Start, a program for families living at or below the poverty line. An additional metric of SES was obtained from parents/caregivers via a short questionnaire about the education level and profession of the primary caregivers. The questionnaire was used to calculate an index of child SES background, which was coded by trained research assistants according to the Hollingshead Four Factor Index of Social Status.

SI Electrophysiological Assessment of Selective Auditory Attention

ERPs were recorded in a spatial selective auditory attention paradigm used in previous studies with preschoolers from lower SES backgrounds (7, 17). Briefly, 16 narrative stories were digitally recorded (16 bit, 22 kHz). A female narrator read half of the stories, and a male narrator read the other half, at a normal speaking rate in a child-directed manner. The 16 audio files were matched into eight pairs of stories, where a pair was created by matching stories of the same length but spoken by different narrators (male/female) and from different children's story series. One story was pasted into the right audio channel and the other to the left audio channel to create stereo files with pairs of stories that differed in narrator voice (male/female) and speaker location (left/right), with one story designated the "attended" and the other the "unattended" story. Each of the four possible narrator and story series appeared twice in the attended and twice in the unattended position. Each story file was 2.5–3.5 min in length. The stories were presented at an average of 60 dB sound pressure level (SPL) (A-weighted). Fifteen to twenty images were selected from the attended story and presented for 5–15 s at points relevant to the content of the story. To indicate the attended side, a small green arrow pointing to the left or right was superimposed at the bottom of each image.

Two probe stimuli were created by digitizing a token of the syllable /ba/ spoken by a female voice (different from the female narrator) to create linguistic probes and scrambling the order of the 4–6 ms segments of that token to create a nonlinguistic sound probe with similar acoustic characteristics. Both probes were 100 ms in length and were presented at 70 dB SPL. An equal number of linguistic and nonlinguistic probes were presented across the stories. Approximately 200 linguistic and 200 nonlinguistic probes ($n \sim 180$–206) were presented to each child. The probes were presented in a pseudorandom order at an interstimulus interval of 200, 500, or 1,000 ms in one of the two channels. Probes were never presented simultaneously in the attended and unattended channels.

Procedure. Before placement of the electrode cap, children were provided time to acclimate to their environment. Once the EEG cap was in place, children were seated in a comfortable chair in an electrically shielded, sound-attenuating booth. Two audio speakers were placed on either side of the participant (90° to the left and right of the chair). A computer monitor was positioned ∼145 cm in front of the child. Children were instructed not to move or lean from side to side, and a researcher sat next to the child at all times to monitor compliance and ask comprehension questions following each story (see below). Before the data were recorded, children received instructions about the task via a prerecorded introduction. They were instructed to attend to the story played from one speaker while ignoring the story presented on the other speaker. They were told that an arrow at the bottom of the screen would point to the speaker they should attend to and that the attended story would correspond to the pictures on the screen. Children were also familiarized with the probe sounds and told to ignore these sounds.

At the beginning of each story, participants were presented with a sound sample of the narrator to whom they should attend. They were instructed to listen carefully to the story from this narrator and ignore the other voice. Children attended to a total of four narratives selected from the four story sets, attending twice to the right side (R) and twice to the left side (L); the order was either RLLR or LRRL. All children were presented with two stories narrated by a female and two stories narrated by a male. A different set of four story pairs was used at pretest and posttest for each child, and the set used at pretest versus posttest was counterbalanced across participants. For the duration of the experiment, children were monitored by an intercom system and a video camera. Throughout the experiment, a trained research assistant accompanied the child in the booth. After each story, the experimenter asked the child three basic comprehension questions about the attended story. The comprehension questions were always about the attended story and had two alternatives. A response of "I don't know" was considered incorrect.

EEG Recording and Analysis. EEG was recorded at a sampling rate of 512 Hz from 32 Ag-AgCl electrodes attached to an electrode cap and arranged according to the 10/20 system. Recordings were made using the Active-Two system (Biosemi). Additional electrodes were placed on the left and right mastoid, at the outer canthi of both eyes, and below the right eye. Scalp signals were recorded relative to the Common Mode Sense (CMS) active electrode and then rereferenced off-line to the algebraic average of the left and right mastoids. Left and right horizontal eye channels were rereferenced to one another.

ERP analyses were carried out using EEGLAB (84) and ERPLAB (85). Data were down-sampled to 256 Hz and bandpass filtered from 0.1 to 40 Hz. The EEG data were epoched off-line between 100 ms before and 500 ms after stimulus onset, using the first 100 ms as the prestimulus–onset baseline. Artifact rejection was conducted via a multistep procedure. First, automatic artifact rejection was conducted with the following parameters: a 200-ms window, moving at 50-ms increments with peak-to-peak rejection criteria of 100 μV for the eye channels and 200 μV for all other channels. Then, trained research assistants performed visual inspection of the epoched EEG data. If the automatic rejection parameters were insufficient for a participant (indicated by either clean trials being incorrectly rejected or by blinks and saccades failing to be correctly rejected), the rejection parameters were adjusted individually. Then, a subsequent artifact rejection step was performed to exclude additional epochs containing eye movements and muscle artifacts.

We measured the mean amplitudes of ERPs between 100 and 200 ms poststimulus onset, collapsed across the linguistic and nonlinguistic conditions, consistent with previous studies using this paradigm with young children from lower SES backgrounds (7, 17, 35, 36). We operationalized the ERP attention effect as the mean amplitude difference between the ERPs to the probes in the attended versus unattended stories (attended minus unattended). Twenty-four electrodes were included in the analyses, grouped into three rows of eight electrodes as follows: anterior: F7/8, F3/4, FT7/8, FC5/6; central: T7/8, C5/6, CP5/6, C3/4; posterior: P7/8, P3/4, PO3/4, O1/2. For ANOVAs, partial η^2 was used to measure effect sizes. For pairwise comparisons, effect sizes were computed with Cohen's d.

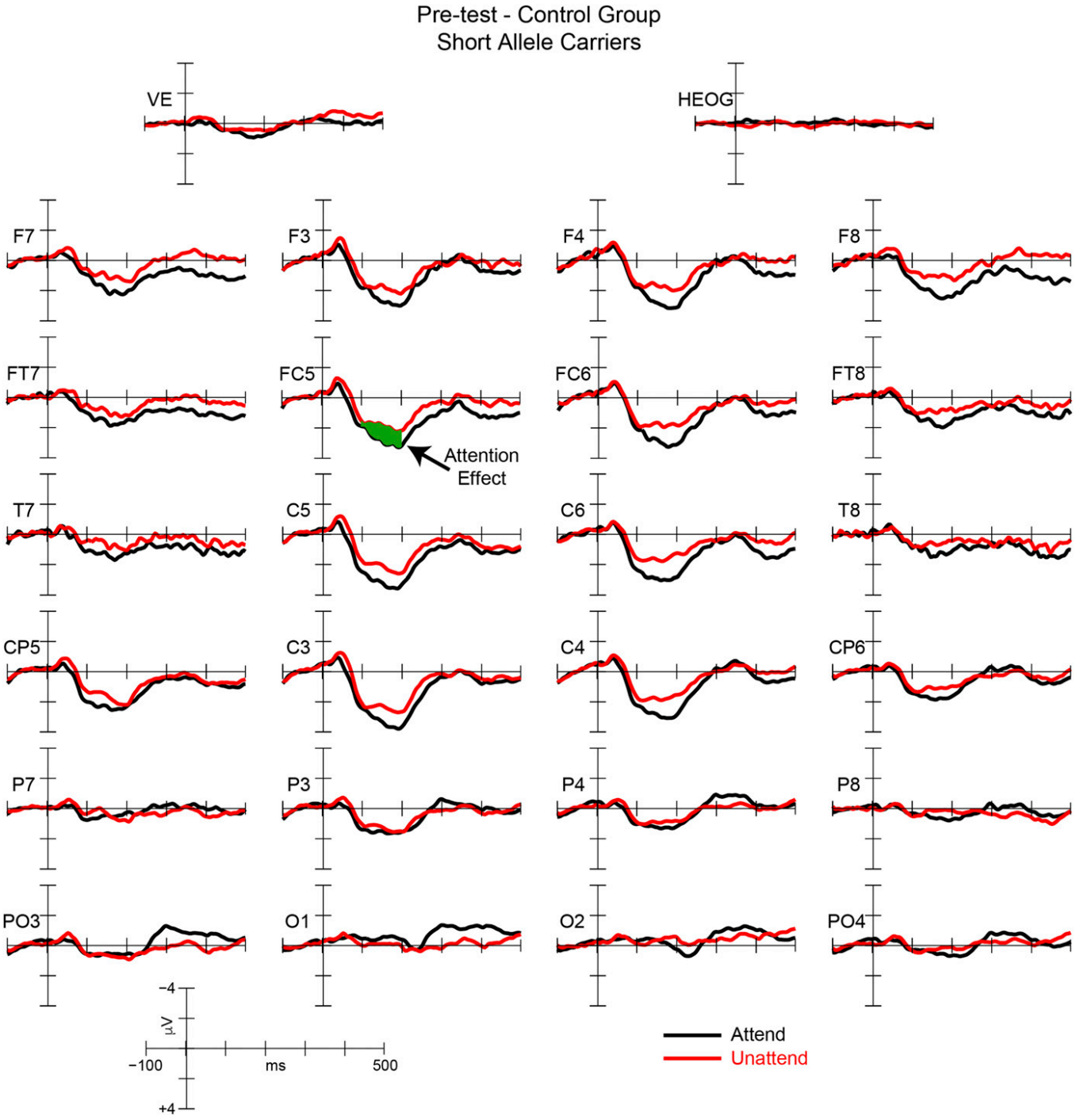

Fig. S1. Pretest grand-average ERP waveforms for short-allele carriers in the control group. This and all subsequent grand-average figures show ERPs elicited by the probes in the attended (black) vs. unattended (red) stories. In all grand-average figures, negative is plotted upward.

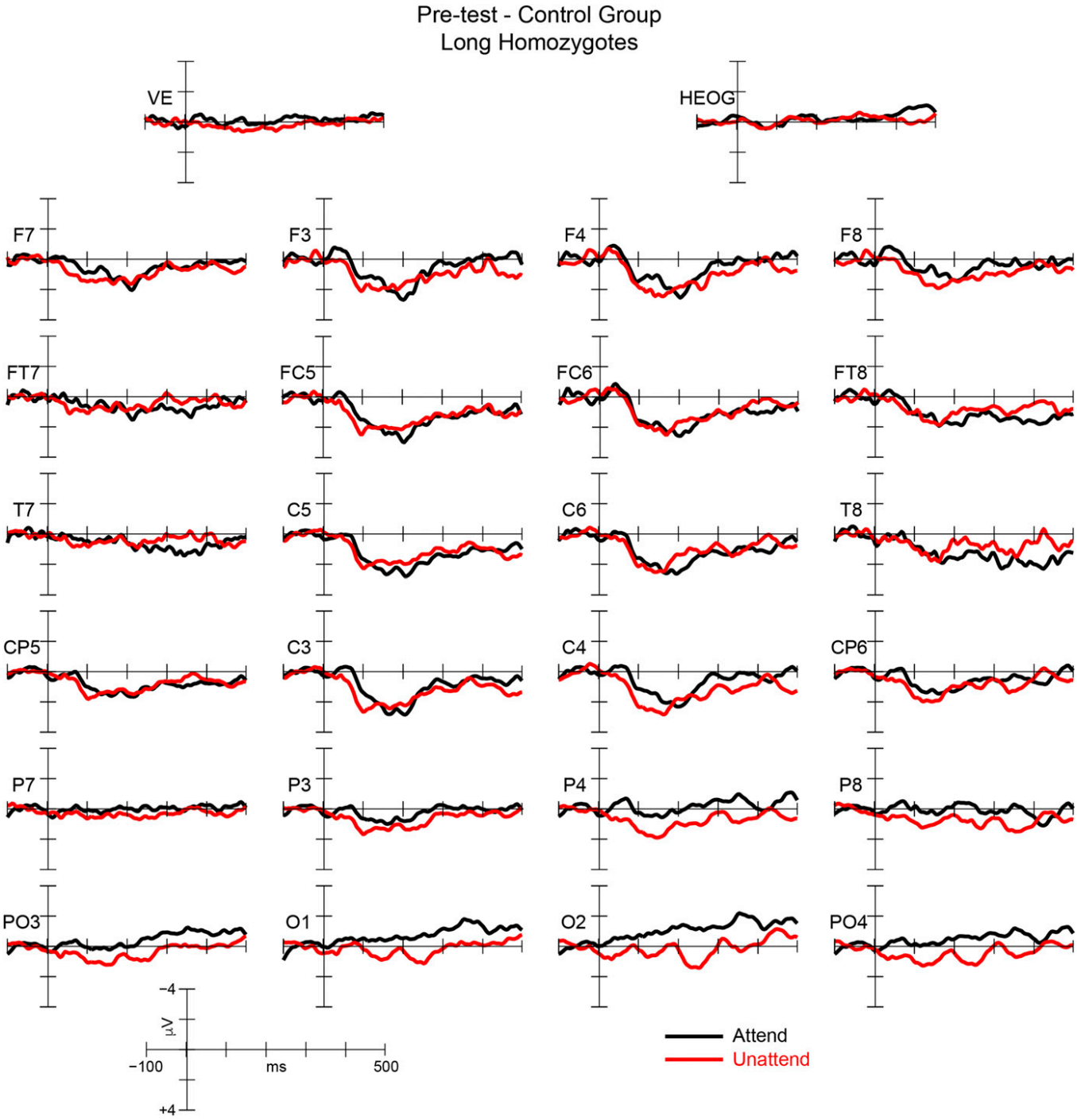

Fig. S2. Pretest grand-average ERP waveforms for long homozygotes in the control group.

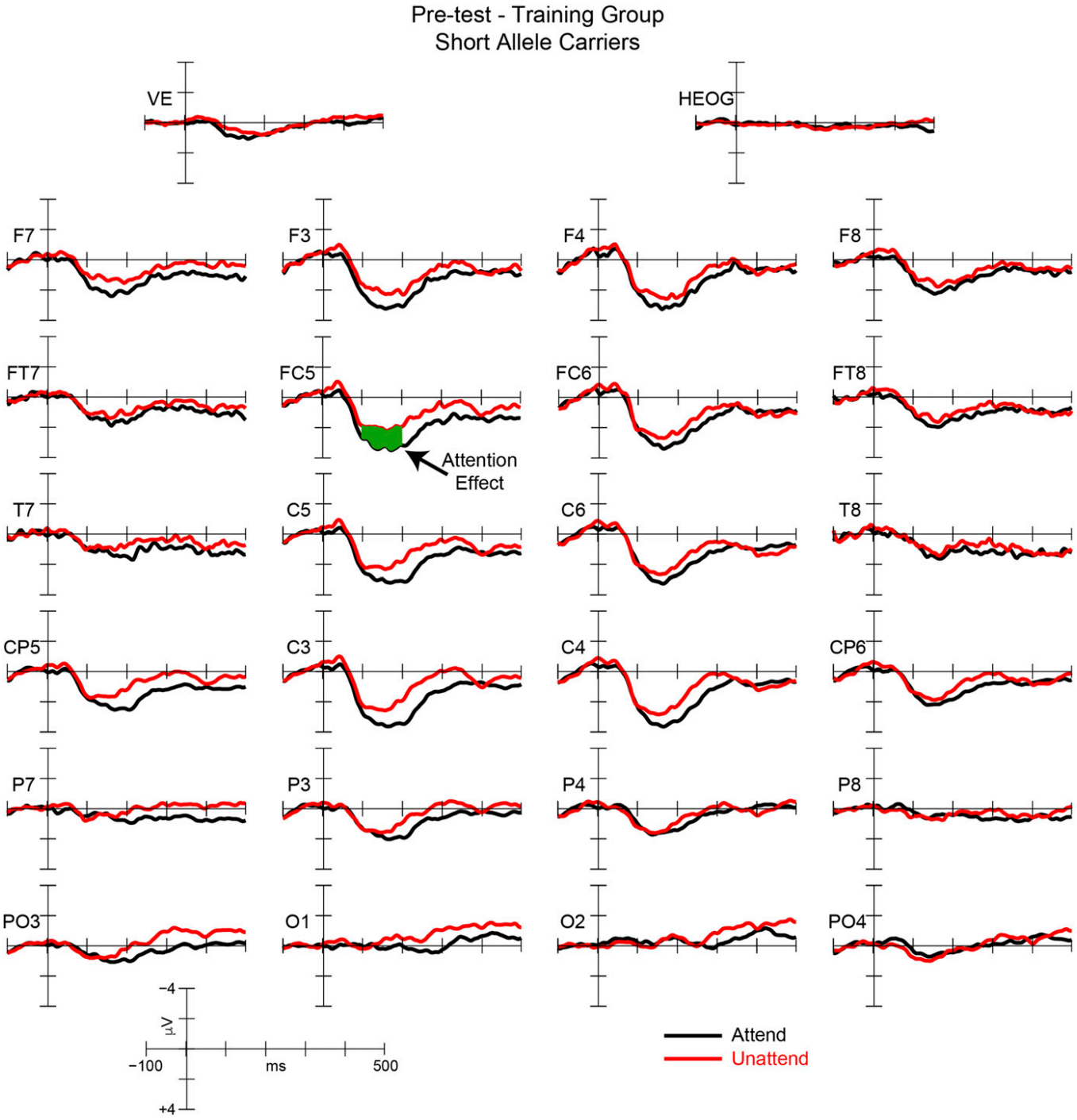

Fig. S3. Pretest grand-average ERP waveforms for short-allele carriers in the training group.

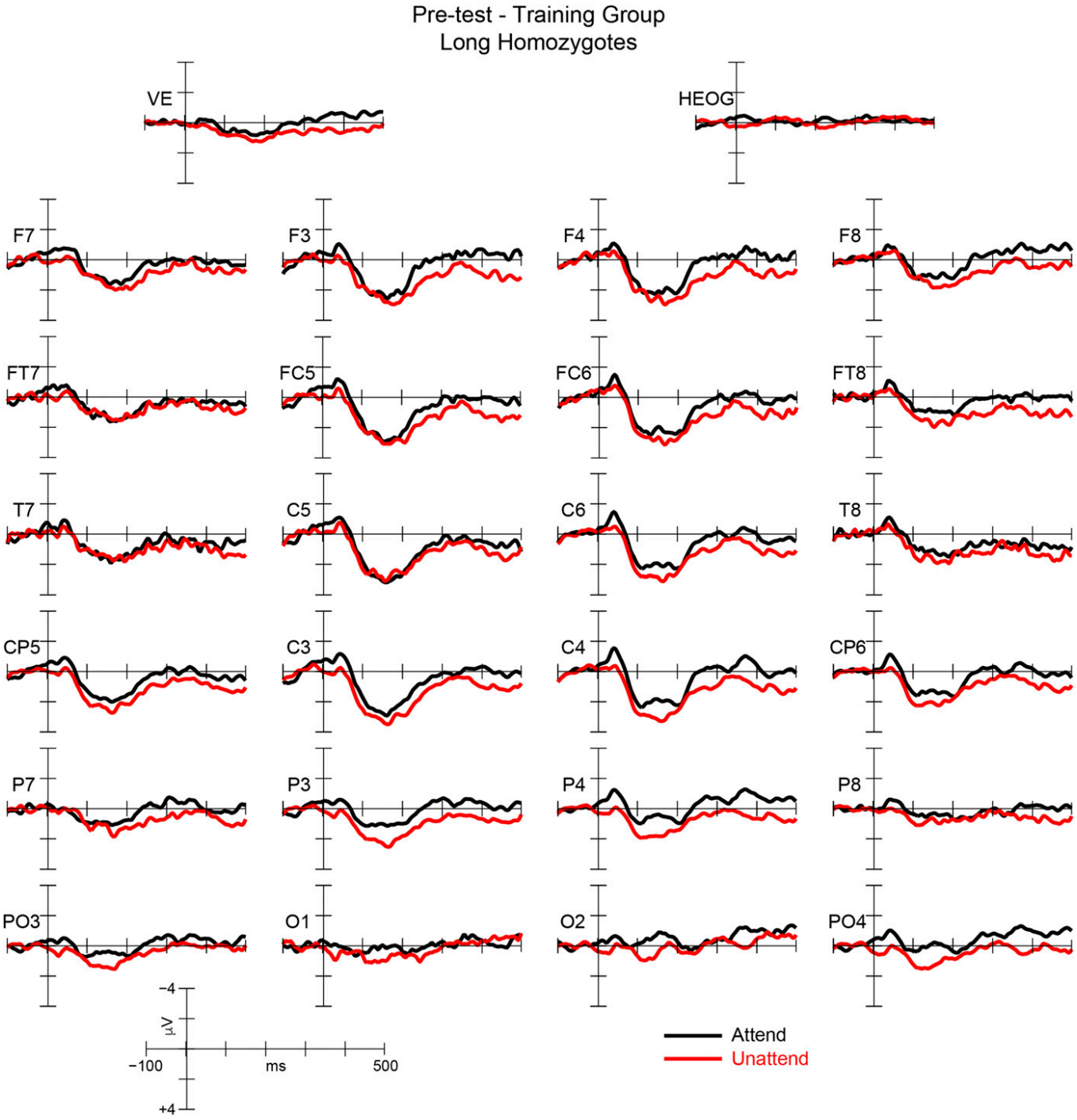

Fig. S4. Pretest grand-average ERP waveforms for long homozygotes in the training group.

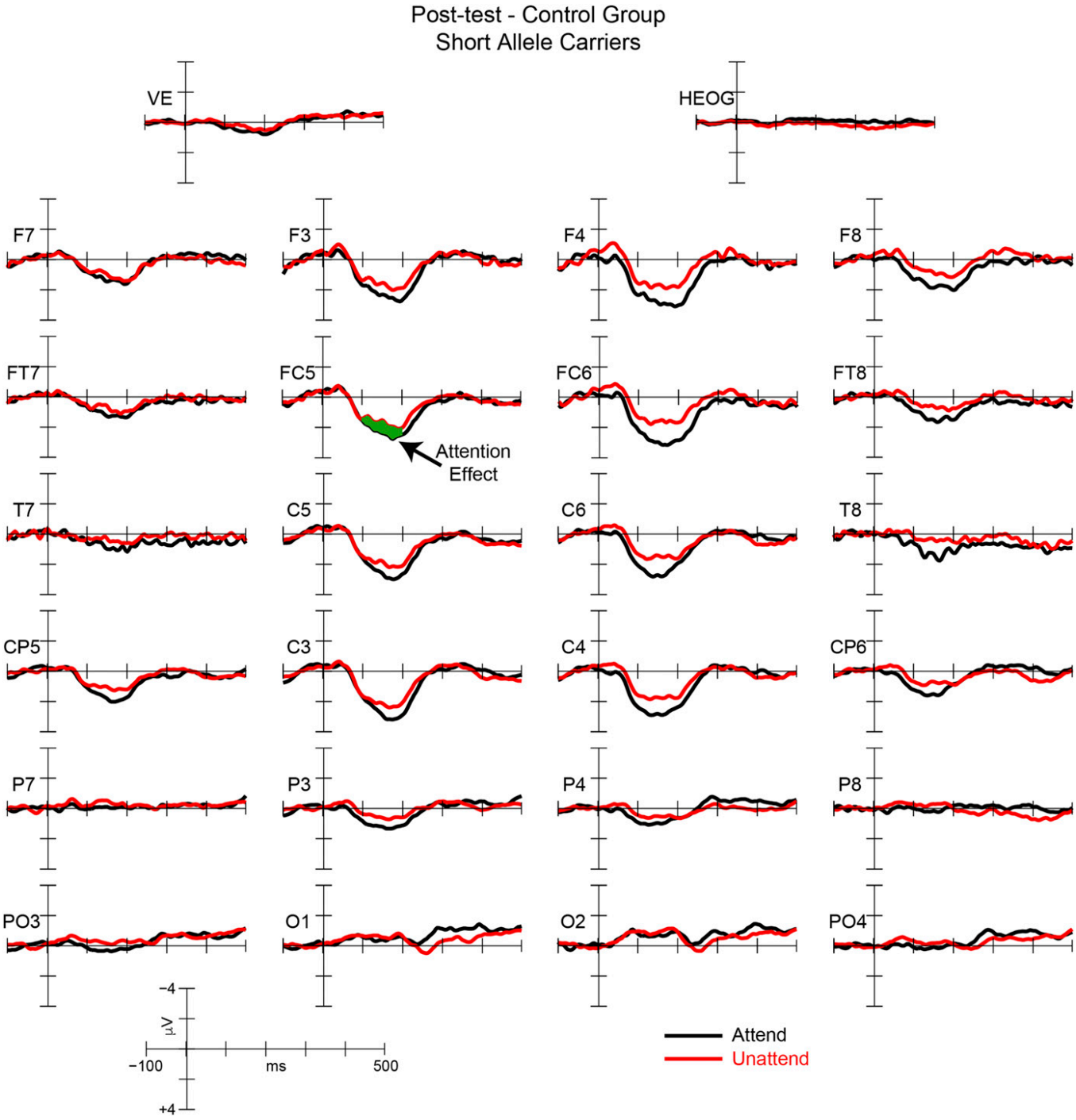

Fig. S5. Posttest grand-average ERP waveforms for short-allele carriers in the control group.

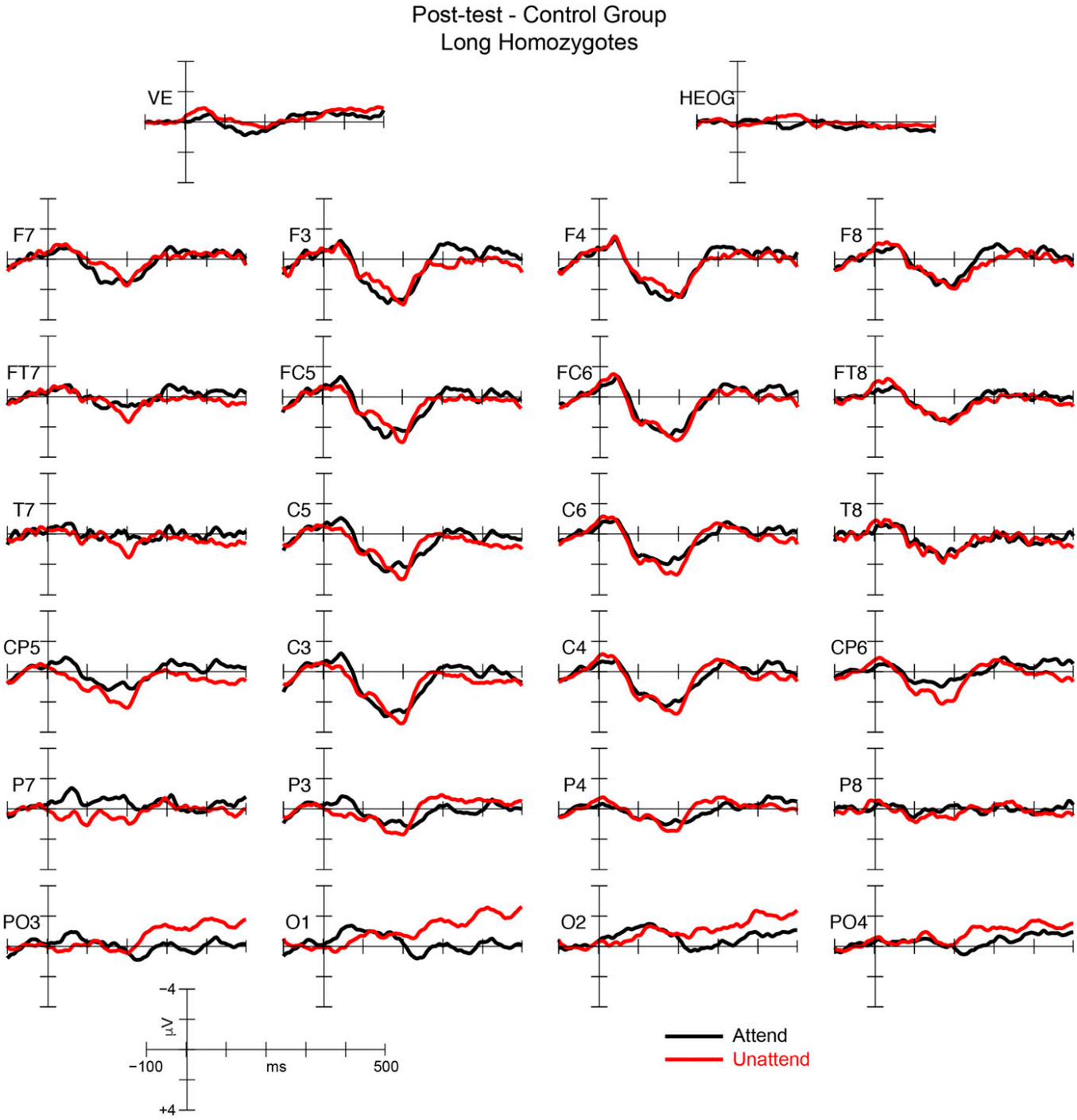

Fig. S6. Posttest grand-average ERP waveforms for long homozygotes in the control group.

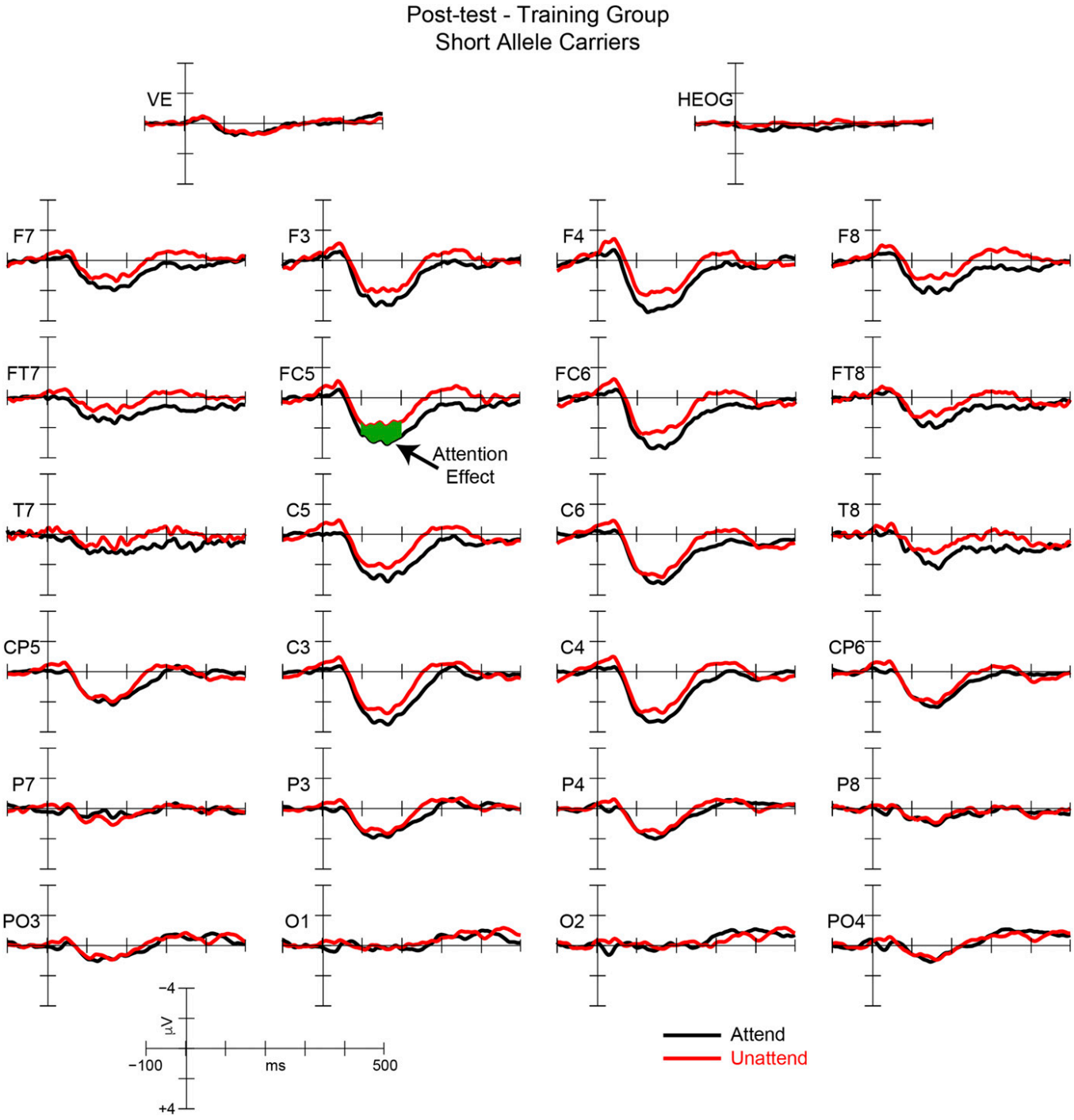

Fig. S7. Posttest grand-average ERP waveforms for short-allele carriers in the training group.

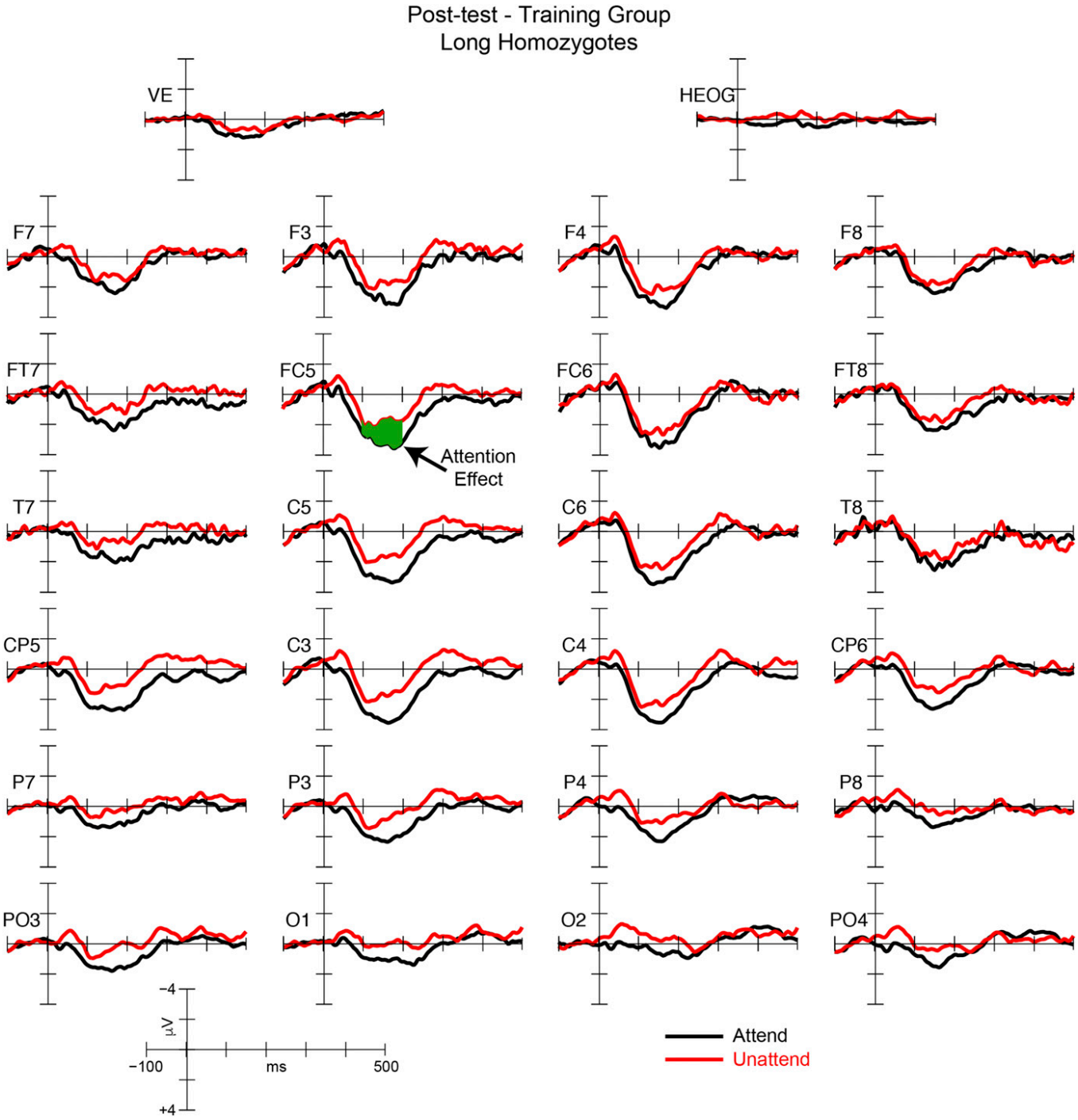

Fig. S8. Posttest grand-average ERP waveforms for long homozygotes in the training group.

Table S1. Descriptive statistics

Variable	Control group, HS-alone		Training group, PCMC-A	
	Short-allele carriers, mean (SD)	Long homozygotes, mean (SD)	Short-allele carriers, mean (SD)	Long homozygotes, mean (SD)
Age, y	4.55 (0.56)	4.50 (0.44)	4.59 (0.49)	4.57 (0.52)
SES	31.62 (12.27)	30.95 (10.36)	30.08 (12.47)	31.33 (10.34)
Pretest				
Comprehension accuracy	9.13 (1.42)	8.20 (1.32)	8.64 (1.44)	8.50 (1.24)
Anterior ERPs, μV	0.86 (1.48)	−0.22 (1.55)	0.69 (1.52)	−0.34 (1.19)
Central ERPs, μV	0.82 (1.50)	−0.08 (1.19)	0.60 (1.15)	−0.47 (1.27)
Posterior ERPs, μV	0.10 (1.76)	−0.88 (1.25)	0.10 (1.21)	−0.83 (2.43)
Posttest				
Comprehension accuracy	9.29 (1.68)	9.10 (1.66)	8.84 (1.38)	9.75 (0.97)
Anterior ERPs, μV	0.72 (1.09)	0.24 (0.58)	0.82 (1.20)	0.83 (1.30)
Central ERPs, μV	0.70 (1.19)	−0.37 (0.90)	0.52 (1.19)	1.11 (1.29)
Posterior ERPs, μV	0.36 (1.19)	−0.30 (1.30)	0.08 (1.25)	0.97 (1.59)

SES is given in units of maternal and paternal education and occupation metrics of the Hollingshead Four Factor Index of Social Status. Comprehension accuracy is measured by the number of correct answers given for the comprehension accuracy questions during the ERP task. Anterior, central, and posterior ERPs measure mean amplitude.