NEURAL MECHANISMS OF SELECTIVE AUDITORY ATTENTION IN LOWER SOCIOECONOMIC STATUS PRESCHOOLERS: INDIVIDUAL DIFFERENCES, GENETIC INFLUENCES, AND GENE × INTERVENTION INTERACTIONS

by

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Selective attention refers to the ability to enhance the processing of relevant stimuli, while suppressing the processing of irrelevant distractors. The neural mechanisms of selective attention are vulnerable in children from lower socioeconomic status families, yet these neural mechanisms can also be enhanced with evidence-based, targeted training.

The series of studies presented in this dissertation investigated the individual differences in development and neuroplasticity of selective auditory attention in association with nonverbal cognitive abilities, in relation to genetic influences, and in the context of gene × intervention interactions. To this end, a multi-method approach was adopted, combining several methodologies such as event-related potentials (ERPs), behavioral measures, molecular genetics, and a randomized, controlled intervention design.

In the first study, individual differences in neural mechanisms of selective auditory attention were studied, in association with nonverbal cognitive abilities. More robust ERP selective attention effects were associated with superior nonverbal IQ performance. These results indicated a noteworthy relationship between neural mechanisms of selective attention and nonverbal IQ performance in lower socioeconomic status (SES) preschoolers. In the second study, the relationship between 5-HTTLPR polymorphism and neural mechanisms of selective auditory attention was assessed. ERPs of selective
attention effect were larger in children who carried at least one short allele of 5-HTTLPR, in comparison to long-homozygotes. These results associated being homozygous for the long allele with weaker neural mechanisms of selective attention in lower SES children. In the third study, these genetic influences were investigated in the context of an effective family-based training program previously shown to improve neural mechanisms of selective attention in lower SES preschoolers. The long-homozygote children, who initially displayed more attenuated ERPs of selective auditory attention than their short-carrier peers, showed robust ERPs of selective attention at posttest, but only if they were randomly assigned to the training program. These findings demonstrated that an effective family-based training could moderate the genetic influences of 5-HTTLPR on the neural mechanisms of selective attention. Taken together, the studies presented in this dissertation contribute to elucidating individual differences in development and neuroplasticity of selective auditory attention in lower SES preschoolers.

This dissertation includes unpublished co-authored material.
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TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. GENERAL INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>II. INDIVIDUAL DIFFERENCES IN NEURAL MECHANISMS OF SELECTIVE AUDITORY ATTENTION IN LOWER SOCIOECONOMIC STATUS</td>
<td>7</td>
</tr>
<tr>
<td>PRESCHOOLERS</td>
<td></td>
</tr>
<tr>
<td>Introduction</td>
<td>7</td>
</tr>
<tr>
<td>Attention as a Critical Element of Nonverbal Cognitive Abilities</td>
<td>8</td>
</tr>
<tr>
<td>Neural Indices of Auditory Selective Attention in Lower SES Children</td>
<td>10</td>
</tr>
<tr>
<td>Present Study</td>
<td>11</td>
</tr>
<tr>
<td>Method</td>
<td>12</td>
</tr>
<tr>
<td>Participants</td>
<td>12</td>
</tr>
<tr>
<td>Socioeconomic Status (SES)</td>
<td>13</td>
</tr>
<tr>
<td>Nonverbal Intelligence</td>
<td>14</td>
</tr>
<tr>
<td>Electrophysiological Assessment of Selective Auditory Attention</td>
<td>14</td>
</tr>
<tr>
<td>Stimuli</td>
<td>14</td>
</tr>
<tr>
<td>Procedure</td>
<td>16</td>
</tr>
<tr>
<td>EEG Recording and Analysis</td>
<td>17</td>
</tr>
<tr>
<td>Results</td>
<td>21</td>
</tr>
<tr>
<td>Discussion</td>
<td>35</td>
</tr>
<tr>
<td>Selective Auditory Attention and Nonverbal Cognitive Performance</td>
<td>36</td>
</tr>
<tr>
<td>Individual Differences in Selective Attention in Lower SES Children</td>
<td>39</td>
</tr>
<tr>
<td>Conclusions</td>
<td>41</td>
</tr>
</tbody>
</table>
### Chapter III. 5-HTTLPR POLYMORPHISM IS LINKED TO NEURAL MECHANISMS OF SELECTIVE AUDITORY ATTENTION IN LOWER SOCIOECONOMIC STATUS PRESCHOOLERS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>43</td>
</tr>
<tr>
<td>Method</td>
<td>47</td>
</tr>
<tr>
<td>Participants</td>
<td>47</td>
</tr>
<tr>
<td>Socioeconomic Status (SES)</td>
<td>48</td>
</tr>
<tr>
<td>Electrophysiological Assessment of Selective Auditory Attention</td>
<td>48</td>
</tr>
<tr>
<td>Procedure</td>
<td>49</td>
</tr>
<tr>
<td>EEG Recording and Analysis</td>
<td>50</td>
</tr>
<tr>
<td>Genotyping</td>
<td>52</td>
</tr>
<tr>
<td>Results</td>
<td>53</td>
</tr>
<tr>
<td>Discussion</td>
<td>60</td>
</tr>
<tr>
<td>Conclusions</td>
<td>66</td>
</tr>
</tbody>
</table>

### Chapter IV. FAMILY-BASED TRAINING MODERATES GENETIC INFLUENCES ON NEURAL MECHANISMS OF SELECTIVE AUDITORY ATTENTION IN LOWER SES PRESCHOOLERS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>68</td>
</tr>
<tr>
<td>Method</td>
<td>73</td>
</tr>
<tr>
<td>Participants</td>
<td>73</td>
</tr>
<tr>
<td>Creating Connections</td>
<td>74</td>
</tr>
<tr>
<td>Comparison Group (HS-alone)</td>
<td>75</td>
</tr>
<tr>
<td>Chapter</td>
<td>Page</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Genotyping</td>
<td>76</td>
</tr>
<tr>
<td>Electrophysiological Assessment of Selective Auditory Attention</td>
<td>76</td>
</tr>
<tr>
<td>Procedure</td>
<td>77</td>
</tr>
<tr>
<td>EEG Recording and Analysis</td>
<td>78</td>
</tr>
<tr>
<td>Results</td>
<td>79</td>
</tr>
<tr>
<td>Discussion</td>
<td>89</td>
</tr>
<tr>
<td>Conclusions</td>
<td>94</td>
</tr>
<tr>
<td>V. GENERAL DISCUSSION</td>
<td>96</td>
</tr>
<tr>
<td>Summary of Findings</td>
<td>96</td>
</tr>
<tr>
<td>Implications and Future Directions</td>
<td>98</td>
</tr>
<tr>
<td>APPENDICES</td>
<td>103</td>
</tr>
<tr>
<td>A. SUPPLEMENTARY INFORMATION FOR CHAPTER III</td>
<td>103</td>
</tr>
<tr>
<td>B. SUPPLEMENTARY INFORMATION FOR CHAPTER IV</td>
<td>107</td>
</tr>
<tr>
<td>REFERENCES CITED</td>
<td>116</td>
</tr>
</tbody>
</table>
LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapter II</td>
<td></td>
</tr>
<tr>
<td>1. Electrode configuration for event-related brain potential recordings</td>
<td>18</td>
</tr>
<tr>
<td>2. Relationship between standardized nonverbal IQ residuals and ERP mean amplitude difference over the anterior electrodes</td>
<td>23</td>
</tr>
<tr>
<td>3. Relationship between standardized nonverbal IQ residuals and ERP mean amplitude difference over the central electrodes</td>
<td>23</td>
</tr>
<tr>
<td>4. Relationship between standardized nonverbal IQ residuals and ERP mean amplitude difference over the posterior electrodes</td>
<td>24</td>
</tr>
<tr>
<td>5. Grand average ERPs elicited by the attended and unattended conditions for the bottom third nonverbal IQ group</td>
<td>31</td>
</tr>
<tr>
<td>6. Grand average ERPs elicited by the attended and unattended conditions for the middle third nonverbal IQ group</td>
<td>32</td>
</tr>
<tr>
<td>7. Grand average ERPs elicited by the attended and unattended conditions for the top third nonverbal IQ group</td>
<td>33</td>
</tr>
<tr>
<td>8. Difference waves (attended – unattended) are plotted for the three IQ groups at frontocentral and central electrode sites</td>
<td>35</td>
</tr>
<tr>
<td>Chapter III</td>
<td></td>
</tr>
<tr>
<td>1. Grand-average ERP waveforms showing ERPs elicited by the attended and unattended conditions</td>
<td>56</td>
</tr>
<tr>
<td>2. Mean amplitudes (µV) of ERP difference waves</td>
<td>60</td>
</tr>
<tr>
<td>Chapter IV</td>
<td></td>
</tr>
<tr>
<td>1. ERP mean amplitudes selective attention effect (µV)</td>
<td>84</td>
</tr>
<tr>
<td>2. Pre-test grand-average ERP waveforms</td>
<td>87</td>
</tr>
<tr>
<td>3. Post-test grand-average ERP waveforms</td>
<td>88</td>
</tr>
</tbody>
</table>
## LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chapter II</strong></td>
<td></td>
</tr>
<tr>
<td>1. Correlation values ( (r) ) between mean amplitudes for the selective attention effect and composite nonverbal IQ scores</td>
<td>22</td>
</tr>
<tr>
<td>2. Summary of regression analysis for variables predicting raw nonverbal IQ scores</td>
<td>26</td>
</tr>
<tr>
<td>3. Descriptives for the nonverbal IQ terciles</td>
<td>27</td>
</tr>
<tr>
<td>4. ANOVA results by nonverbal IQ group</td>
<td>28</td>
</tr>
<tr>
<td>5. Mean amplitudes differences</td>
<td>30</td>
</tr>
<tr>
<td><strong>Chapter III</strong></td>
<td></td>
</tr>
<tr>
<td>1. Age, SES, and story comprehension question accuracy for the 5-HTTLPR genotypes</td>
<td>54</td>
</tr>
<tr>
<td>2. Analyses of variance for age, SES, comprehension accuracy, and ERP mean amplitudes</td>
<td>57</td>
</tr>
<tr>
<td>3. Mean differences (( \mu V )), confidence intervals (95% CI), and effect sizes for the selective attention effect as measured by ERPs</td>
<td>58</td>
</tr>
<tr>
<td><strong>Chapter IV</strong></td>
<td></td>
</tr>
<tr>
<td>1. Descriptives for age, pre-test comprehension accuracy, post-test comprehension accuracy, and SES</td>
<td>81</td>
</tr>
<tr>
<td>2. ERP mean amplitude and standard deviations of the selective attention effect (( \mu V ))</td>
<td>83</td>
</tr>
<tr>
<td>3. Paired-samples t-test statistics comparing ERP mean amplitudes</td>
<td>86</td>
</tr>
</tbody>
</table>
CHAPTER I
GENERAL INTRODUCTION

The SES achievement gap has widened at an alarming rate over the last three decades in the United States (Reardon, 2011, 2013). The achievement gap between individuals raised in high versus low income families has become roughly 30 to 40 percent larger, in comparison to what was observed among those born twenty-five years earlier (Reardon, 2011). The precursors of this gap are already evident at the beginning of kindergarten, as children from lower SES families perform worse on measures of school readiness than their peers (Duncan & Magnuson, 2011; Larson, Russ, Nelson, Olson, & Halfon, 2015). SES disparities in academic skills do not diminish over the elementary and secondary school years (Farkas, 2011). As follows, in comparison to their peers raised in the top SES quintile, young adults raised in the bottom SES quintile are much less likely to complete high school, attend college, and earn a postsecondary degree (Bailey & Dynarski, 2011; Duncan & Magnuson, 2011; Farkas, 2011).

The critical SES disparities observed in academic achievement and adult attainments prompted the investigation into possible links between childhood SES and cognitive skills that are foundational for academic and professional achievements (Bradley & Corwyn, 2002; Brooks-Gunn & Duncan, 1997; Demir & Kuntay, 2014; McLoyd, Mistry, & Hardaway, 2014). Accordingly, a substantial body of research reported associations between childhood SES and various cognitive abilities, such as attention (Boelema et al., 2014; Mezzacappa, 2004), executive function (Hackman, Gallop, Evans, & Farah, 2015; Lawson et al., 2014; Noble, McCandliss, & Farah, 2007), language (Farah et al., 2006; Fernald, Marchman, & Weisleder, 2013; Noble, Norman, &
Farah, 2005; Pakulak & Neville, 2010; Pungello, Iruka, Dotterer, Mills-Koonce, & Reznick, 2009), and working memory (Evans & Schamberg, 2009; Hackman et al., 2014). These studies demonstrated that childhood SES accounts for disparities across a wide range of cognitive abilities, observed from early years of life through adulthood.

Consequently, over the last decade, several studies focused on the alterations in brain development that account for SES related differences in cognitive abilities (Brito & Noble, 2014; Hackman & Farah, 2009; Raizada & Kishiyama, 2010). These studies documented marked differences in neural mechanisms of various cognitive faculties, such as attention, language, reward processing and impulse control (D'Angiulli, Herdman, Stapells, & Hertzman, 2008; Gianaros et al., 2011; Kishiyama, Boyce, Jimenez, Perry, & Knight, 2009; Pakulak & Neville, 2010; Stevens, Lauinger, & Neville, 2009). In addition, childhood SES was associated with structural differences in several brain regions, especially in areas important for attention, executive function, and memory, such as hippocampus and prefrontal cortex (Hanson, Chandra, Wolfe, & Pollak, 2011; Noble et al., 2015; Noble, Houston, Kan, & Sowell, 2012; Staff et al., 2012). Such differences were observed for numerous structural aspects of the brain, including gray matter volume (Hanson et al., 2011; Noble et al., 2012), cortical thickness (Lawson et al., 2014), cortical gyrification patterns (Jednoróg et al., 2012), and cortical surface area (Noble et al., 2015).

Together these functional and structural neuroimaging studies lay bare striking alterations in brain development in lower SES children compared to their higher SES peers. However, very little attention has been paid to individual differences in brain development among lower SES children. In addition to its considerable contributions to
the construction of cognitive theories (Underwood, 1975; Vogel & Awh, 2008), an individual differences approach is applicable to the investigation of risk and resilience in the context of early adversity. This potent approach can refine our understanding of why certain children show heightened vulnerability to the adverse conditions associated with lower SES, while others continue to flourish. Furthermore, this approach can inform evidence-based prevention and intervention efforts that can, in turn, cater to the specific needs of children who are at heightened risk for vulnerability to adversity. This dissertation aims to apply this powerful, yet underutilized, approach to the investigation of neural mechanisms of selective attention in lower SES preschoolers.

Selective attention refers to the ability of enhancing the processing of relevant stimuli, while suppressing the processing of irrelevant distractors (Desimone & Duncan, 1995; Hillyard, Hink, Schwent, & Picton, 1973; Yantis, 2008). In addition to the modification of sensory representations via signal enhancement and distractor suppression, selective attention also influences the efficiency with which sensory input is used to inform decisions, through a late selection mechanism defined as selective read-out of sensory signals (Serences & Kastner, 2014). Selective attention is an essential component of various cognitive abilities, such as learning (Bhatt & Quinn, 2011; Goldstone, Son, & Byrge, 2011), language (Astheimer & Sanders, 2012; Nicolay & Poncelet, 2013), and working memory (Gazzaley, 2011; Giuliano, Karns, Neville, & Hillyard, 2014), and plays a foundational role in academic abilities (Casco, Tressoldi, & Dellantonio, 1998; Commodari & Di Blasi, 2014; Steele, Karmiloff Smith, Cornish, & Scerif, 2012; Stevens & Bavelier, 2012).

Neural mechanisms of this fundamental ability are highly malleable, modified by
altered sensory experience (Bavelier et al., 2000; Neville & Lawson, 1987; Röder et al., 1999), and enhanced with trainings and interventions (Green & Bavelier, 2003; Neville et al., 2013; Stevens, Fanning, Coch, Sanders, & Neville, 2008; Stevens et al., 2013). It has been demonstrated that these highly plastic neural mechanisms are vulnerable in lower SES children (D'Angiulli et al., 2008; Stevens et al., 2009; Stevens, Paulsen, Yasen, & Neville, 2014), yet can also be enhanced with evidence-based, targeted training (Neville et al., 2013). This dissertation focused on individual differences in neural mechanisms of selective auditory attention lower SES preschoolers.

In the studies presented here, neural mechanisms of selective auditory attention were measured with event-related potentials (ERPs). In a seminal study, Hillyard and colleagues (1973) demonstrated that the effects of selective attention on neural processing can be determined by comparing ERPs to the same physical stimuli when attended versus ignored, while keeping the physical stimuli, arousal levels, and task demands constant. This principle has been applied to an extensive body of ERP studies on the neural mechanisms of selective attention in typical adults (Hillyard, 1985; Luck & Kappenman, 2012; Luck, Woodman, & Vogel, 2000; Mangun & Hillyard, 1990). Built on this widely accepted principle, a child-friendly, ecologically valid dichotic listening paradigm was developed and employed to investigate the development and neuroplasticity of selective auditory attention in typically and atypically developing children from various SES backgrounds (Coch, Sanders, & Neville, 2005; Karns, Isbell, Giuliano, & Neville, In press; Sanders, Stevens, Coch, & Neville, 2006; Stevens et al., 2009). In this paradigm, children are instructed to attend selectively to one of two stories presented concurrently. ERPs are recorded to identical probe stimuli superimposed on
both the attended and ignored stories. Neural indices of selective attention are measured by comparing the mean amplitudes of ERPs elicited by these identical probes in the attended versus unattended stories.

Along with this well-established ERP paradigm, this dissertation employed behavioral measures, molecular genetics, and a randomized, controlled trial design. These methods were combined to investigate individual differences in neural mechanisms of selective attention in association with nonverbal cognitive abilities (Chapter II), genetic influences on these individual differences (Chapter III), and how these individual differences occur in the context of gene × intervention interactions (Chapter IV).

In the study presented in Chapter II, an individual differences approach was adopted to investigate the association between neural mechanisms of selective auditory attention and nonverbal cognitive abilities in lower SES preschoolers. Event-related potentials (ERPs) were recorded during the dichotic listening task described above and nonverbal IQ tasks were administered to lower SES preschoolers. Based on previous research documenting associations between various aspects of attention and nonverbal cognitive abilities with adults and children from predominantly higher SES backgrounds (Astle, Nobre, & Scerif, 2010; Fukuda & Vogel, 2009; Giuliano et al., 2014; Unsworth, Fukuda, Awh, & Vogel, 2014), we examined to what extent neural indices of selective attention account for variability in nonverbal cognitive abilities in lower SES children.

In the study presented in Chapter III, genetic influences on neural mechanisms of selective auditory attention were investigated. In particular, the associations between ERP indices of selective attention and the allelic variations of the serotonin transporter linked polymorphic region (5-HTTLPR) were assessed. Drawing on the literature that
linked the short allele of the 5-HTTLPR polymorphism to superior cognitive performance and enhanced neural processing (Anderson, Bell, & Awh, 2012; Borg et al., 2009; Enge, Fleischhauer, Lesch, Reif, & Strobel, 2011), it was determined to what degree 5-HTTLPR polymorphism predicted individual differences in neural mechanisms of selective attention in lower SES children.

Chapter IV focused on the interactive effects of 5-HTTLPR and a family-based training program shown to improve brain systems for selective attention in lower SES preschoolers. Specifically, it was investigated to what extent an effective family-based program would moderate the influences of 5-HTTLPR on neural mechanisms of selective attention. In the concluding chapter (Chapter V), the implications of the findings and directions for future research were discussed.

This dissertation contains co-authored material. The study described in Chapter II is submitted for publication and co-authored with A. Hampton Wray, and H. J. Neville. The study described in Chapter III is in preparation and co-authored with T. Bell, A. Hampton Wray, and H. J. Neville. The study described in Chapters IV is in preparation to be co-authored with T. Bell and H. J. Neville.
CHAPTER II

INDIVIDUAL DIFFERENCES IN NEURAL MECHANISMS OF SELECTIVE AUDITORY ATTENTION IN LOWER SOCIOECONOMIC STATUS PRESCHOOLERS

This work is in press in Developmental Science. I wrote this manuscript, with my co-authors A. Hampton Wray and H. J. Neville providing feedback and editorial assistance.

Introduction

There is overwhelming evidence for an educational achievement gap between children from lower and higher socioeconomic status (SES) families (Hout & Janus, 2011; Reardon, 2011). Regrettably, the SES achievement gap has widened markedly over the last three decades (Reardon, 2013). Precursors of this gap can be detected as early as kindergarten, with children from lower SES families performing worse on standardized tests of school readiness (Duncan & Magnuson, 2011). The existence of SES disparities at such an early stage in education underscores the importance of characterizing brain functions that are associated with fundamental cognitive abilities during preschool years.

SES disparities have been documented for several aspects of brain development (Hackman & Farah, 2009; Noble, Houston, Kan, & Sowell, 2012; Raizada & Kishiyama, 2010). In this study, we focused on neural mechanisms of one specific cognitive function, selective attention. This fundamental ability is posited as a critical component of foundations for education (Stevens & Bavelier, 2012). Neural mechanisms of
selective attention are particularly vulnerable in children from lower SES families (Stevens, Lauinger, & Neville, 2009; Stevens, Paulsen, Yasen, & Neville, 2014). However, despite such heightened vulnerability, these neural mechanisms can also be enhanced via targeted interventions (Neville et al., 2013). Here we assessed individual differences in this malleable brain function in children from lower SES families. Specifically, we investigated the extent to which such individual differences in neural mechanisms of selective attention would account for nonverbal cognitive abilities in lower SES preschoolers, drawing parallels from previous research that linked various aspects of attention to fundamental nonverbal cognitive skills, as discussed below.

**Attention as a critical element of nonverbal cognitive abilities**

Engle and Kane (2004) argue that the domain-general ability to control attention, especially in the presence of internal and external distractors, is a critical element of higher-order cognitive abilities, such as language comprehension and fluid reasoning. In accordance with this proposition, studies of adults have provided ample evidence linking various aspects of attention to nonverbal cognitive abilities. For instance, behavioral and event-related brain potential (ERP) measures of attentional capture were linked to visual working memory performance, as high capacity individuals showed stronger resistance to and faster recovery from capture of attention (Fukuda & Vogel, 2009, 2011). Furthermore, in a study that used steady-state visual evoked potentials (SSVEPs), superior attentional control, specifically early suppression of irrelevant information, was associated with higher visual working memory capacity (Gulbinaite, Johnson, de Jong, Morey, & van Rijn, 2014). Similarly, in a recent ERP study, neural indices of auditory selective attention were linked to individual differences in visual working memory.
capacity in adults (Giuliano, Karns, Neville, & Hillyard, 2014). In line with these findings, adults who performed better on attentional control tasks were found to have higher fluid intelligence scores (Unsworth, Fukuda, Awh, & Vogel, 2014; Unsworth & Spillers, 2010). Moreover, individual differences in self-reports of pre-trial attentional state were linked to individual differences in general fluid intelligence (Unsworth & McMillan, 2014). Participants who reported higher focus before trials, and fewer fluctuations in attentional state during the tasks, demonstrated better fluid intelligence performance. These studies provide converging evidence for links between various aspects of attention and cognitive abilities in adults.

Similar relations between attention skills and nonverbal cognitive abilities have also been reported in studies of children. For example, the ability to sustain attention for targets in the presence of distractor items was linked to both parent ratings and laboratory measures of inhibitory control in 3- to 6-year-old children (Reck & Hund, 2011). Moreover, individual differences in the ability to orient attention were linked to variability in visual short-term memory and visuospatial working memory in children (Astle, Nobre, & Scerif, 2010; Shimi, Nobre, Astle, & Scerif, 2014). Children who were better at using spatial attention cues presented during maintenance of items in visual short term memory had higher visual short-term memory scores and larger visuospatial working memory spans. Furthermore, in a recent ERP study, individual differences in the neural markers of attentional orienting were linked to visual short term memory capacity in 10-year-old children (Shimi, Kuo, Astle, Nobre, & Scerif, 2014). Children who were more similar to adults in their neural responses elicited by spatial cues, which were presented prior to arrays of items to be remembered, had higher visual short-term
memory capacity. Together these findings provide evidence for the pivotal role of attentional skills in nonverbal cognitive abilities in children.

In accordance with the considerable evidence linking various aspects of attention to numerous nonverbal cognitive abilities in adults and children, we posited that selective attention would account for variability in nonverbal cognitive performance in preschoolers from lower SES families. To test this hypothesis, we assessed neural markers of selective attention, a brain function that is both vulnerable and enhanceable in lower SES children (Neville et al., 2013; Stevens et al., 2009; Stevens et al., 2014).

**Neural indices of auditory selective attention in lower SES children**

Selective attention refers to the ability to enhance the processing of particular input while suppressing the information from other concurrent sources (Desimone & Duncan, 1995; Hillyard, Hink, Schwent, & Picton, 1973; Serences & Kastner, 2014; Yantis, 2008). Via an ecologically valid and child-friendly dichotic listening paradigm, the typical neural indices of selective auditory attention have been characterized in children from various SES backgrounds (Coch, Sanders, & Neville, 2005; Sanders, Stevens, Coch, & Neville, 2006; Stevens et al., 2009). In this paradigm, children are instructed to attend selectively to one of two simultaneously presented stories. Event-related potentials (ERPs) are recorded to the same probe stimuli superimposed on both the attended and unattended, or ignored, stories. Neural indices of selective attention are measured by comparing the mean amplitudes of ERPs elicited by the identical probes in the attended and unattended stories. Earlier studies that used this paradigm reported a significant effect of selective attention on ERPs as early as 100 to 200 ms in typically developing children from higher SES families (Coch et al., 2005; Sanders et al., 2006;
Stevens et al., 2009). This attention effect was characterized as larger, more positive ERP mean amplitudes for probes embedded in the attended stories versus probes in the unattended stories.

Using this paradigm, Stevens and colleagues (2009) investigated SES-related disparities in neural indices of auditory selective attention in children. In line with previous studies that used this paradigm (Coch et al., 2005; Sanders et al., 2006), a significant effect of attention on ERPs was documented in both higher and lower SES children. However, when the groups were compared, the magnitude of the attention effect was significantly reduced in the lower SES group compared to the higher SES group. These results suggested that neural mechanisms of selective attention were vulnerable in lower SES children.

**Present study**

In the current study, we proposed that, despite its aggravated vulnerability in children from lower SES families, neural mechanisms of selective attention would still account for variability in nonverbal cognitive abilities among this at-risk population. To test this proposal, we employed an individual differences approach to evaluate neural indices of selective auditory attention. To measure selective attention, we recorded ERPs in the child-friendly dichotic listening task described above. This task allowed us to focus on neural mechanisms of selective attention without overt response demands.

The associations between neural mechanisms of attention and nonverbal cognitive abilities have been mainly reported in studies of visual attention (Fukuda & Vogel, 2011; Gulbinaite et al., 2014; Shimi, Kuo, et al., 2014). However, we employed an auditory selective attention paradigm because the ERP indices of this paradigm have been well
characterized in young children (Coch et al., 2005; Sanders et al., 2006; Stevens, Sanders, & Neville, 2006). Furthermore, in a recent study that used this ERP paradigm with university students, the magnitude of the early auditory selective attention effect (the P1 component) was associated with individual differences in visual working memory; adults who had a larger, more positive P1 also had higher visual working memory capacity (Giuliano et al., 2014).

Using this well-established paradigm, we assessed individual differences in selective attention in young children from lower SES families. Based on the previous research that documented links between various measures of attention and tests of nonverbal cognition, we expected a notable association between neural markers of selective attention and performance on nonverbal tests of cognition in lower SES children. Specifically, we anticipated that a larger (i.e. more positive in mean amplitude) ERP attention effect would predict better nonverbal cognitive abilities, as measured by tasks of nonverbal intelligence.

**Method**

**Participants**

Participants were 124 children (77 females) between the ages of 40 and 67 months ($Mean = 54$ months, $SD = 6.5$ months). They were recruited from 12 Head Start (HS) preschool sites in Oregon, a program for families living at or below the poverty line. Based on parent report, children with diagnosed behavioral or neurological problems (e.g. 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 who passed a hearing
screening at 20 dB HL at 500, 1000, 2000 and 4000 Hz in both the right and left ears. From a total of 158 children who met these criteria, 23 were excluded due to low ERP data quality (excessive EEG artifacts and/or less than 75 trials per condition), and 11 were excluded for having less than 50% accuracy on the comprehension questions presented during the ERP task. In the final sample, 58% of the children were White/Caucasian, 1% Black/African American, 4% American Indian, 16% more than one ethnicity, and 21% unreported.

Informed consent was obtained from parents or other caregivers. In addition, verbal assent was obtained from child participants. Behavioral measures and ERPs were collected in two different sessions, separated by no more than 30 days. All families were paid for participation. Study procedures were approved by the University of Oregon Institutional Review Board.

**Socioeconomic status (SES)**

Parents/caregivers filled out a questionnaire which gathered information on the education level and profession of the primary caregivers. Socioeconomic status (SES) of the child was coded by trained research assistants according to the Hollingshead Four Factor Index of Social Status (Hollingshead, 1975). SES questionnaire information was incomplete or missing for 13 children. However, since all participants were recruited from a Head Start program, which requires at least 90 percent of the enrolled children to be from low-income families, and we used HS enrollment as a proxy for lower SES, we did not exclude these children from our final sample. For the children for whom we had complete SES questionnaire information (n = 111), the mean SES was 29.80 (SD = 11.43) according to the Hollingshead index (range = 8-66). There was one SES outlier (3
SD above the mean), therefore all the analysis that included the SES variable were conducted with and without this child. Exclusion of this child did not change the direction or strength of the results. Since this child was originally selected for our study based on HS enrollment, which we used as the proxy for lower SES, we included this child in all analyses.

**Nonverbal intelligence**

As a part of a battery of behavioral measures, children completed three subtests of the Stanford-Binet 5th Edition (SB-5) nonverbal IQ scale. The subtests included were Fluid Reasoning, Quantitative Reasoning, and Working Memory. The nonverbal Fluid Reasoning subtest measured the child’s ability to identify sequences of pictured objects and complete matrices of figures and geometric patterns. The nonverbal Quantitative Reasoning subtest focused on mathematical reasoning. The lower levels of this subtest, which were designed for younger children, measured basic concepts (e.g. bigger/smaller), counting, addition using objects and pictures, and recognition of numbers. The nonverbal Working Memory subtest consisted of a Delay Response activity, which used a memory paradigm of hiding objects under cups, and the Block Span activity, which required children to recall a sequence of block taps. The range of possible raw scores on each subtest was between 0 and 19. A composite nonverbal IQ score was obtained by averaging the raw scores from the three subtests.

**Electrophysiological assessment of selective auditory attention**

from the *Classic Munch* series (Munsch & Martchenko, 1988; Munsch & Martchenko, 1989; Munsch & Martchenko, 1992; Munsch & Petricic, 2004) were digitally recorded (16 bit, 22 kHz) using an Electro Voice 1750 microphone connected to a Macintosh computer running a sound-editing program (SOUNDEDIT 16, Version2). Either a male or a female narrator read the stories at a normal speaking rate in a child-directed manner. Pauses were edited such that they did not exceed 1 s in order to lessen the opportunity to switch attention to the other channel and to equate the length of pairs of stories. The average amplitude of each story was equated and high amplitude noises created by bursts of airflow were deleted. Following editing, 16 stereo files (four stories x four series) were created. The stereo files differed in location (left/right speaker) and narration voice (male/female). Each file was 2.5-3.5 min in length. The stories were presented at an average of 60 dB SPL (A-weighted).

Two probe stimuli were created by digitizing a token of the syllable *ba* spoken by a female voice (different from the female narrators) and scrambling the order of 4-6 ms segments of that token to create a nonlinguistic sound with similar acoustic characteristics. The two probes were 100 ms in length and were presented at 70 dB SPL. Across the stories, an equal number (N~180-206) of linguistic and non-linguistic probes were presented in each channel. The probes were presented in a pseudo-random order at an interstimulus interval (ISI) of either 200, 500, or 1000 ms in one of the two channels. Probes were never presented simultaneously in the attended and ignored channels.

Color pictures from the sixteen stories were scanned and edited such that the image presented on the computer monitor directly in front of the participant subtended a visual angle of no more than 5° in the vertical or horizontal directions. 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. A small green arrow pointing to the left or right was superimposed at the bottom of each image to indicate the attended side.

**Procedure.** Children arrived at the laboratory with their parents and were provided time to acclimate to their environment before placement of the electrode cap began. Once the EEG cap was in place, children were seated in a comfortable chair in an electrically shielded, sound-attenuating booth. They were instructed not to move or lean from side to side. Two speakers were placed on either side of the participant (90° to the left and right of the chair). A computer monitor was positioned approximately 145 cm in front of the participant. Before the data were recorded, participants received instructions to attend to the story played from one speaker while ignoring the story presented on the other speaker. They were told either a male or a female speaker would narrate the story. An arrow at the bottom of the screen would point to the speaker they should attend to and the attended story would correspond to the pictures on the screen. They were also instructed that unrelated sounds (‘bas’ and ‘buzzes’) would be presented but should be ignored.

At the beginning of each story, participants were presented with a sound sample of the narrator to which they should attend. They were instructed to listen carefully to the story from this narrator and ignore the other voice. Participants attended to a total of four narratives selected from the four story sets, attending twice to the right side and twice to the left side (order either RLLR or LRRL). All participants were presented with two stories narrated by a female and two stories narrated by a male. For the duration of the experiment, participants were monitored by an intercom system and a video camera.
Throughout the experiment, an adult trained for behavioral management accompanied the child in the booth. The stories were paused briefly if excessive EEG artifacts were present, such as too many saccades or drifts, or if an electrode needed readjustment. After each story, the experimenter asked the participants three basic comprehension questions about the attended story. These questions were designed to reinforce to the child to attend to a single story at a time, and also to assess whether the child’s comprehension of the stories were above chance (6 or more correct answers out of 12). The comprehension questions were always about the attended story and had two alternatives. A response of “I don’t know” was considered an incorrect response. Only children who performed with at least 50% accuracy on the comprehension questions were included in the EEG analyses.

**EEG recording and analysis.** EEG was recorded at a sampling rate of 1024 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, Amsterdam, Netherlands), which does not require impedance measurements, an online reference, or gain adjustments. The electrode configuration for event-related brain potential recordings is illustrated in Figure 1.
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 re-referenced off-line to the algebraic average of the left and right mastoid. Left and right horizontal eye channels were re-referenced to one another.

ERP analyses were carried out using EEGLAB (Delorme & Makeig, 2004) and ERPLAB (Lopez-Calderon & Luck, 2014). Data were down-sampled to 256 Hz to speed computation and band-pass filtered from 0.1 to 40 Hz. The EEG data was epoched offline between 100 ms prior to and 500 ms after stimulus onset, using the 100 ms pre-stimulus-onset for baseline correction. Artifact rejection was initially executed using 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 for almost all included participants. However, on the basis of the visual inspection of the epoched EEG data, individual artifact rejection parameters were selected if the automatic rejection protocol
was not sufficient. Moreover, trained research assistants performed a subsequent artifact rejection step to exclude additional epochs containing eye movements and muscle artifacts from further analysis. Out of ~400 trials per condition, an average of 253 trials ($SD = 58$) per participant were accepted for the attended condition, and 253 trials ($SD = 55$) were accepted for the unattended condition.

For a total of 4 participants with otherwise clean EEG data, faulty electrodes were replaced with the average mean amplitude of the 3 neighboring electrodes. The neighboring electrodes were determined based on the rows described below, within the hemisphere of interest.

The mean amplitudes of ERPs were measured between 100 to 200 ms post-stimulus onset, collapsed across the linguistic and nonlinguistic conditions, consistent with previous studies using this paradigm with young children from lower SES families (Neville et al., 2013; Stevens et al., 2009; Stevens et al., 2014). In line with a recent study that measured ERPs in lower SES preschoolers with the same paradigm (Neville et al., 2013), three electrode aggregates were created 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.

The ERP effect of selective attention was operationalized as the mean amplitude difference between ERPs to probes embedded in attended versus unattended stories. Difference waves are a strong method for isolating an individual component of interest (Luck, 2014), in this study, the attention effect. Furthermore, the difference wave approach was consistent with a recent study that measured ERPs with the same dichotic listening paradigm in adults and used difference waves to assess correlations between ERPs of selective auditory attention and visual working memory (Giuliano et al., 2014).
To assess the link between neural indices of selective attention and nonverbal IQ, first, separate correlational analyses were conducted for each electrode aggregate. These correlation analyses avoid a multicollinearity problem that would occur in the presence of highly correlated predictors (electrode aggregates). Such high correlations between predictors would increase the instability of the regression model, inflate the standard errors, and create erroneous beta values for the predictors. Therefore, to avoid the multicollinearity problem, we reported the correlation coefficients between the electrode aggregates and nonverbal IQ. These initial analyses allowed us to demonstrate the contributions of frontal, central, and posterior rows of electrodes in a straightforward fashion. Additionally, to control for multiple comparisons resulting from 3 levels of scalp distribution, the significance level was set at $\alpha = .017$.

However, in a supplementary analysis that utilized a multiple regression approach, to avoid the collinearity problem due to the high correlation between ERP mean amplitudes of anterior and central electrode locations ($r = .80$), these electrode aggregates were averaged together to form a single fronto/central predictor.

To further illustrate the association between neural mechanisms of selective attention and nonverbal IQ, an omnibus ANOVA was also included with the between-subject factor of IQ group (described below; top, middle, bottom) and within-subject factors of attention (attended, unattended) and electrode location (anterior, central, posterior). Greenhouse-Geisser corrections were applied when the degrees of freedom was greater than one. Uncorrected degrees of freedom but corrected $p$ values are reported.
Results

There was a significant zero-order correlation between the raw nonverbal IQ composite scores and age, $r (124) = .40, p < .001$. Therefore, we regressed nonverbal IQ on age and used the residuals for further analyses of the relationship between neural mechanisms of selective attention and nonverbal IQ. Then, we created three aggregate measures of ERPs by averaging across 8 electrodes within the anterior, central, and posterior rows (electrodes included in each row are detailed in the Method section). The zero-order correlations between age and these aggregates were not significant, all $ps > .10$. There were no outliers +/- 3 SD for the nonverbal IQ measure. There were also no outliers +/- 3 SD for the anterior electrode aggregate of the ERPs. However, there was one outlier for the central electrode aggregate (< -3 SD) and one outlier for the posterior electrode aggregate (< -3 SD). Initially, all analyses were conducted with and without these outliers. The direction and strength of the results were consistent with and without these outliers. To be inclusive and reflect the whole spectrum of results, we reported the results from the complete data set.

The associations between neural mechanisms of selective attention and nonverbal IQ were first assessed with correlation analyses. For these correlation analyses, to control for multiple comparisons resulting from 3 levels of scalp distribution, the significance level was set at $\alpha = .017$. The mean amplitude difference between ERPs to probes embedded in attended versus unattended stories was significantly correlated with nonverbal IQ scores (see Table 1 for the correlation statistics).
Table 1. Correlation values (r) between mean amplitudes for the selective attention effect and composite nonverbal IQ scores

<table>
<thead>
<tr>
<th>Measure</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Nonverbal IQ</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. ERPs over anterior electrodes</td>
<td>.24**</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. ERPs over central electrodes</td>
<td>.24**</td>
<td>-</td>
<td>.80***</td>
<td></td>
</tr>
<tr>
<td>4. ERPs over posterior electrodes</td>
<td>-.02</td>
<td>.14</td>
<td>.49***</td>
<td>-</td>
</tr>
</tbody>
</table>

**p < .01, ***p < .001

Note. For the nonverbal IQ measure, higher scores are indicative of better performance. For the ERP measures, which reflect the mean amplitude difference between attended and unattended conditions, higher values are indicative of larger selective attention effects.

These significant links were observed only for the ERPs measured over the anterior and central rows of electrodes (as illustrated in Figures 2 and 3), but not the posterior rows of electrodes (Figure 4). Overall, the more positive in amplitude was the difference between the attended and unattended conditions, the higher the nonverbal IQ scores were.
Figure 2. Relationship between standardized nonverbal IQ residuals and ERP mean amplitude difference (attended - unattended conditions) in µV over (a) anterior electrodes.

Figure 3. Relationship between standardized nonverbal IQ residuals and ERP mean amplitude difference (attended - unattended conditions) in µV over central electrodes.
Figure 4. Relationship between standardized nonverbal IQ residuals and ERP mean amplitude difference (attended - unattended conditions) in µV over posterior electrodes.

In addition, a multiple regression analysis was conducted to assess the extent to which the neural mechanisms of selective attention accounted for individual differences in nonverbal IQ, above and beyond the effects of age, gender, and SES. In this analysis, only children for whom we had complete SES questionnaire information were included (n = 111). Age, gender, and SES were entered as covariates, and neural mechanisms of selective attention were entered as the predictors. As described in the Method section, to avoid the collinearity problem due to the high correlation between ERP mean amplitudes of anterior and central electrode locations (r = .80), the frontal and central electrode aggregates were averaged together to form a single fronto/central predictor. Along with this fronto/central electrode aggregate, the posterior electrode aggregate was also entered as a predictor in this analysis. Since age was included as a covariate, the dependent
variable was raw nonverbal IQ scores.

The results of this regression analysis are summarized in Table 2. This analysis indicated that age, gender, and SES together explained a significant portion of variance in nonverbal IQ scores, $R^2 = .14, F(3, 107) = 5.87, p = .001$. Among the covariates, while age was a significant predictor of nonverbal IQ scores ($p < .01$), gender and SES were not significant predictors ($p = .91$ and $p = .16$, respectively). The addition of fronto-central and posterior ERP variables significantly contributed to the model, $\Delta R^2 = .07, F(2, 105) = 4.87, p = .01$. In this model, only the fronto-central ERP index of selective attention was a significant predictor of nonverbal IQ, $p < .01$. Larger, more positive ERP mean amplitudes for the selective attention effect were associated with higher nonverbal IQ scores. The posterior ERP index of selective attention was not a significant predictor of nonverbal IQ, $p = .12$. 
Table 2. Summary of regression analysis for variables predicting raw nonverbal IQ scores (n = 111)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1</th>
<th></th>
<th></th>
<th></th>
<th>Model 2</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>SE B</td>
<td>β</td>
<td>p</td>
<td>B</td>
<td>SE B</td>
<td>β</td>
<td>p</td>
</tr>
<tr>
<td>Age</td>
<td>1.22</td>
<td>.32</td>
<td>.34</td>
<td>&lt; .001</td>
<td>1.15</td>
<td>.31</td>
<td>.32</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Gender</td>
<td>-.04</td>
<td>.36</td>
<td>-.01</td>
<td>.91</td>
<td>-.13</td>
<td>.35</td>
<td>-.03</td>
<td>.72</td>
</tr>
<tr>
<td>SES</td>
<td>.02</td>
<td>.02</td>
<td>.13</td>
<td>.16</td>
<td>.02</td>
<td>.02</td>
<td>.10</td>
<td>.29</td>
</tr>
<tr>
<td>Fronto-central ERPs</td>
<td>.42</td>
<td>.14</td>
<td>.29</td>
<td>&lt; .01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posterior ERPs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-.17</td>
<td>.11</td>
<td>-.15</td>
<td>.12</td>
</tr>
</tbody>
</table>

To further illustrate the relationship between neural indices of selective attention and nonverbal IQ, participants were ranked from high to low performance based on the nonverbal IQ residuals, then divided into three groups based on their ranking as follows: higher (top third), middle, and lower (bottom third) IQ performance. Univariate ANOVAs revealed that there were no significant between-group differences in age, accuracy on the comprehension questions asked during the selective attention task, or the average number of ERP trials included in the analyses. For the subset of children for whom we had complete SES questionnaire information (n = 111), SES also did not differ between nonverbal IQ groups. Descriptive information on age, SES, comprehension question accuracy, nonverbal IQ scores, and average number of accepted ERP trials are presented in Table 3 and the ANOVA statistics are presented in Table 4.
Table 3

Descriptive statistics for age, SES, accuracy for comprehension questions answered during the ERP task, nonverbal IQ performance, and the number of ERP trials included in the analyses for each nonverbal IQ tercile

<table>
<thead>
<tr>
<th>Variable</th>
<th>Bottom IQ group</th>
<th>Middle IQ group</th>
<th>Top IQ group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Age</td>
<td>41</td>
<td>4.60</td>
<td>.58</td>
</tr>
<tr>
<td>SES</td>
<td>37</td>
<td>27.93</td>
<td>10.43</td>
</tr>
<tr>
<td>Comprehension</td>
<td>41</td>
<td>8.27</td>
<td>1.47</td>
</tr>
<tr>
<td>accuracy</td>
<td></td>
<td>1.36</td>
<td>1.20</td>
</tr>
<tr>
<td>Nonverbal IQ</td>
<td>41</td>
<td>14.19</td>
<td>1.20</td>
</tr>
<tr>
<td>ERP trials</td>
<td>41</td>
<td>481.22</td>
<td>118.66</td>
</tr>
</tbody>
</table>
Table 4

ANOVA results by nonverbal IQ group (bottom, middle, top) for age, comprehension accuracy, SES, number of accepted ERP trials, attention (attended vs. unattended), and electrode location (anterior, central, posterior)

<table>
<thead>
<tr>
<th></th>
<th>$F$</th>
<th>$df$</th>
<th>$p$</th>
<th>partial $\eta^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>.49</td>
<td>2, 121</td>
<td>.61</td>
<td>.01</td>
</tr>
<tr>
<td>SES</td>
<td>.74</td>
<td>2, 108</td>
<td>.48</td>
<td>.04</td>
</tr>
<tr>
<td>Comprehension accuracy</td>
<td>.52</td>
<td>2, 121</td>
<td>.60</td>
<td>.01</td>
</tr>
<tr>
<td>ERP trials accepted</td>
<td>2.19</td>
<td>2, 121</td>
<td>.12</td>
<td>.04</td>
</tr>
</tbody>
</table>

ERP indices of attention

<table>
<thead>
<tr>
<th></th>
<th>$F$</th>
<th>$df$</th>
<th>$p$</th>
<th>partial $\eta^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
<td>3.29</td>
<td>1, 121</td>
<td>.07</td>
<td>.03</td>
</tr>
<tr>
<td>Electrode</td>
<td>199.69</td>
<td>2, 242</td>
<td>&lt; .001***</td>
<td>.62</td>
</tr>
<tr>
<td>IQ group</td>
<td>.51</td>
<td>2, 121</td>
<td>.60</td>
<td>.01</td>
</tr>
<tr>
<td>Attention x electrode</td>
<td>5.32</td>
<td>2, 242</td>
<td>.02*</td>
<td>.04</td>
</tr>
<tr>
<td>Attention x IQ group</td>
<td>3.44</td>
<td>2, 121</td>
<td>.04*</td>
<td>.05</td>
</tr>
<tr>
<td>IQ group x electrode</td>
<td>1.89</td>
<td>4, 242</td>
<td>.14</td>
<td>.03</td>
</tr>
<tr>
<td>IQ group x attention x electrode</td>
<td>2.64</td>
<td>4, 242</td>
<td>.06</td>
<td>.04</td>
</tr>
</tbody>
</table>

* $p < .05$, *** $p < .001$

Using these groups as a between-subjects factor in a mixed model ANOVA, we evaluated the effect of selective auditory attention on ERPs as a function of IQ performance group. This ANOVA included the between-group factor of IQ performance
group (top, middle, bottom), and 2 within-group factors: attention (attended, unattended) and electrode location (anterior, central, and posterior). The ANOVA statistics are reported in Table 4. There was a significant main effect of electrode location and a significant interaction between attention and electrode location. There was also a significant interaction between attention and IQ group. There were no other significant main effects or interaction effects.

Subsequent step-down analyses were conducted to unpack the interaction between attention and electrode location. Paired samples t-tests revealed that the mean amplitude of ERPs were significantly larger, more positive, for the probes in the attended versus unattended stories over the anterior and central electrodes ($t (123) = 2.40, p = .02; t (123) = 2.57, p = .01$, respectively). The ERPs for the attended versus unattended stories did not differ over the posterior electrodes ($t (123) = -.05, p = .63$).

In addition, subsequent step-down analyses were conducted to unpack the interaction between attention and IQ group. Since there was not a significant three-way interaction between Attention x Electrode x IQ Group, these step-down analyses were conducted with an aggregate measure of all channels included in the analyses. In addition, to provide a more detailed account of what we observed in the grand average plots, mean amplitude differences and 95% confidence intervals are reported for the three rows of electrodes (anterior, central, and posterior) in Table 5.
Table 5

Mean amplitude differences (µV), standard deviations (SD), and 95% confidence intervals (Lower Lever, LL, and Upper Level, UL) for the ERPs elicited by probes in the attended versus unattended stories for the bottom, middle, and top tercile nonverbal IQ groups.

<table>
<thead>
<tr>
<th>95% CI</th>
<th>Mean (µV)</th>
<th>SD</th>
<th>LL</th>
<th>UL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bottom IQ group (n = 41)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior electrodes</td>
<td>-.24</td>
<td>1.23</td>
<td>-.62</td>
<td>.15</td>
</tr>
<tr>
<td>Central electrodes</td>
<td>-.16</td>
<td>1.21</td>
<td>-.54</td>
<td>.23</td>
</tr>
<tr>
<td>Posterior electrodes</td>
<td>-.09</td>
<td>1.68</td>
<td>-.62</td>
<td>.44</td>
</tr>
<tr>
<td>All electrodes</td>
<td>-.16</td>
<td>1.10</td>
<td>-.51</td>
<td>.18</td>
</tr>
<tr>
<td>Middle IQ group (n = 42)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior electrodes</td>
<td>.42</td>
<td>1.60</td>
<td>-.08</td>
<td>.92</td>
</tr>
<tr>
<td>Central electrodes</td>
<td>.32</td>
<td>1.60</td>
<td>-.18</td>
<td>.85</td>
</tr>
<tr>
<td>Posterior electrodes</td>
<td>-.08</td>
<td>1.72</td>
<td>-.61</td>
<td>.46</td>
</tr>
<tr>
<td>All electrodes</td>
<td>.22</td>
<td>1.35</td>
<td>-.20</td>
<td>.64</td>
</tr>
<tr>
<td>Top IQ group (n = 41)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior electrodes</td>
<td>.78</td>
<td>1.42</td>
<td>.33</td>
<td>1.22</td>
</tr>
<tr>
<td>Central electrodes</td>
<td>.80</td>
<td>1.17</td>
<td>.43</td>
<td>1.17</td>
</tr>
<tr>
<td>Posterior electrodes</td>
<td>-.04</td>
<td>1.40</td>
<td>-.48</td>
<td>.41</td>
</tr>
<tr>
<td>All electrodes</td>
<td>.51</td>
<td>1.03</td>
<td>.19</td>
<td>.84</td>
</tr>
</tbody>
</table>
The ERP grand average plots are shown in Figure 5 for the bottom IQ group, Figure 6 for the middle IQ group, and Figure 7 for the top IQ group.

Figure 5. Grand average ERPs elicited by the attended and unattended conditions for the bottom third nonverbal IQ group. For this, and all subsequent ERP figures, negative is plotted upward. There was no significant attention effect for the bottom third nonverbal IQ group, i.e. no significant differences between the ERP mean amplitudes elicited by identical probes embedded in stories when attended versus unattended.
Figure 6. Grand average ERPs elicited by the attended and unattended conditions for the middle third nonverbal IQ group. There was no significant attention effect for the middle third nonverbal IQ group.
Figure 7. Grand average ERPs elicited by the attended and unattended conditions for the top third nonverbal IQ group. The top third group revealed a significant attention effect. ERPs elicited by the probes in the attended stories were significantly larger (more positive) than ERPs elicited by the probes in the unattended stories.

The paired samples t-tests revealed that there was no significant effect of attention on ERPs (i.e. no significant differences between the ERPs to probes in the attended versus unattended stories) in the bottom IQ group (Figure 3), $t(40) = -0.95, p = .35$. 
Although the grand average plot hinted at an emerging attention effect for the middle third IQ group (Figure 4), there was no significant effect of selective attention on ERPs in this group either, $t(41) = 1.06, p = .29$. In contrast, there was a significant selective attention effect on ERPs in the top IQ group, $t(40) = 3.19, p < .01$. The mean amplitudes of the ERPs were more positive for the attended condition versus the unattended condition. As illustrated in Figure 7, this attention effect was most evident over the anterior and central rows of electrodes.

To complement these analyses and directly compare the nonverbal IQ groups, Helmert contrasts were conducted with the ERP difference waves. Helmert contrasts revealed that the top third IQ group exhibited a larger attention effect than the middle and bottom third IQ groups, $t(121) = 2.16, p = .03$. The attention effect did not significantly differ between the middle and bottom third IQ groups, $t(121) = 1.50, p = .14$. Figure 8 illustrates the difference waves (attended – unattended) for the three IQ groups overlaid at representative frontocentral and central electrode sites.

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1 We also conducted post-hoc analyses separately for the attended and unattended conditions. The results of these analyses were inconclusive. Since we did not have any a priori predictions about why one mechanism would have more predictive power than the other, and our post-hoc analyses did not allow us to draw firm conclusions, we did not include the speculative reporting of these inconclusive results.
Figure 8. Difference waves (attended – unattended) are plotted for the three IQ groups at frontocentral and central electrode sites. The top third IQ group exhibited a larger attention effect than the middle or bottom third IQ groups. There were no significant differences between the middle and the bottom third IQ groups.

Discussion

The present study provided evidence for a noteworthy relationship between neural mechanisms of selective attention and nonverbal IQ performance in young children from lower SES families. We documented prominent individual differences in neural indices of sustained selective auditory attention in lower SES children. These individual differences, as measured by ERPs in a dichotic listening paradigm, were associated with
nonverbal IQ scores. In particular, higher nonverbal IQ scores were observed in children who displayed larger mean amplitude differences between ERPs elicited by identical probes embedded in attended versus unattended stories.

Previous studies with higher SES children documented the effects of selective auditory attention largest over the anterior and central electrode locations in the 100-200 ms time window (Coch et al., 2005; Sanders et al., 2006). Consistent with these findings, we also documented the effects of selective auditory attention over the anterior and central electrodes in this sample of preschoolers from lower SES households. Furthermore, the associations between neural indices of selective auditory attention and nonverbal IQ performance were also observed over these anterior and central electrode locations, where the effects of selective auditory attention were evident.

**Selective auditory attention and nonverbal cognitive performance**

Our results align with the argument that attentional abilities are critical for performance in various aspects of nonverbal cognition (Engle & Kane, 2004). Previously, studies of adults and children linked various aspects of attention to nonverbal cognitive abilities using behavioral measures (Astle et al., 2010; Shimi, Nobre, et al., 2014; Unsworth et al., 2014; Unsworth & Spillers, 2010). Additionally, several studies associated neural mechanisms of attention with performance on tasks of nonverbal cognition in adults (Fukuda & Vogel, 2011; Giuliano et al., 2014; Gulbinaite et al., 2014; Kuo, Stokes, & Nobre, 2012), and a recent developmental cognitive neuroscience study demonstrated a similar link in children (Shimi, Kuo, et al., 2014). Here we extend these findings to young children from lower SES families, a population at elevated risk for
poorer attentional skills than their higher SES peers (Mezzacappa, 2004; Stevens et al., 2009).

Due to the high temporal resolution of ERPs, we were able to pinpoint relatively early mechanisms of selective attention (100-200 ms) in lower SES preschoolers and demonstrate a relationship between this early selective attention effect and nonverbal cognitive performance. The associations between neural mechanisms of attention and nonverbal cognitive abilities have been mainly reported in studies of visual attention (Fukuda & Vogel, 2011; Gulbinaite et al., 2014; Shimi, Kuo, et al., 2014). Our results extend these findings to the auditory modality in young children, in line with a recent study that linked a relatively early index of auditory selective attention to visual working memory capacity in adults (Giuliano et al., 2014).

The current study is the examination of ERPs from a large group of young children from lower income families. Our sample size was relatively large compared to many developmental neuroscience studies conducted with similar age groups. This large sample provided a representative portrayal of variability in neural mechanisms of selective attention in lower SES children. Yet, it is important to note that the effect sizes (as indicated by the correlation coefficients) we report here are in general smaller than what have been reported in previous studies that linked neural mechanisms of attention to nonverbal cognitive abilities (Giuliano et al., 2014; Shimi, Kuo, et al., 2014). One speculation is that the young children in our study might have provided noisier ERP data in general. Noisier ERP data, which would lead to lower signal-to-noise ratio, might have reduced our statistical power to detect stronger associations between selective attention and nonverbal IQ. Another possibility is that the association between neural
mechanisms of selective attention and nonverbal cognitive abilities may be weaker in lower SES children compared to higher SES populations. Nevertheless, our results provide an important, initial line of evidence associating individual differences in neural mechanisms of selective attention to nonverbal IQ performance in children from disadvantaged backgrounds.

Interestingly, among this sample of children, SES was not a significant predictor of nonverbal IQ. There may be at least two explanations for this finding. First, our study included only lower SES children and consequently, a restricted range of SES. Within this restricted range, SES may not be a significant predictor of nonverbal IQ. Second, the questionnaire we used for the assessment of SES may not be sensitive enough to distinguish SES disparities in neural mechanisms of selective attention or nonverbal cognition within such a restricted range of SES.

It should also be noted that the sample of children we tested had similar developmental and sociodemographic characteristics (typically developing, right-handed monolingual native speakers of English, from primarily Caucasian households). Although this stringent selection allowed us to elude numerous potential confounds of ERP studies, we acknowledge that we cannot be certain the degree to which these results would generalize to other groups of lower SES children. However, given that our findings linked attention to nonverbal cognition, in coherence with previous research conducted with adults and children on this topic, we would expect our results to extend at least to other populations of typically developing children from lower SES households, despite their differing sociodemographic characteristics.
The current results may imply that neural mechanisms of selective attention support nonverbal cognitive development in lower SES children. However, due to the design of our study, we cannot establish the direction of causality between selective attention and nonverbal IQ. It is possible that there are more basic underlying mechanisms responsible for the subpar performance in both domains of cognition. For instance, in a recent study with adolescents, lower maternal education levels were linked to less efficient auditory processing, as indexed by weaker, more variable, and noisier neural responses to auditory stimuli (Skoe et al., 2013). SES disparities in perceptual mechanisms may drive differences in performance on laboratory measures of higher cognitive abilities, such as attention and nonverbal IQ. Future research would benefit from the inclusion of more specific and diverse cognitive tasks to determine which other cognitive factors may mediate or account for the association between neural mechanisms of selective attention and nonverbal intelligence. Furthermore, an intervention design would be necessary to establish a causal relationship between selective attention and nonverbal IQ.

**Individual differences in selective attention in lower SES children**

Recently, many studies reported SES disparities in the neural indices of various cognitive functions (Gianaros et al., 2011; Kishiyama, Boyce, Jimenez, Perry, & Knight, 2009; Sheridan, Sarsour, Jutte, D'Esposito, & Boyce, 2012; Stevens et al., 2009). However, there has been a paucity of research addressing individual differences in brain functioning among children growing up in lower SES families. Our findings contribute to and extend this understudied area of research. Here we document a considerable amount of variability among lower SES children for neural indices of selective attention.
When children were divided into 3 groups based on their nonverbal IQ scores, only children in the top third group showed a significant effect of attention on ERPs. In contrast, we did not find a significant modulation of ERPs by selective attention in children whose nonverbal IQ scores fell into the middle or bottom thirds. Likewise, when we directly compared the ERP attention effects between these IQ groups, children in the top IQ group displayed more enhanced neural indices of selective attention compared to the children in the middle and bottom IQ groups.

It is important to note that we created these categorical groups to better illustrate our ERP results. Due to testing time constraints, we were able to administer only a subset of tasks from the full battery of the nonverbal IQ assessment. While keeping the testing session relatively short with such young children to reduce fatigue and improve performance, the lack of a full IQ battery precludes us from considering clinical classifications or cut-off points. The terciles in our study are based on the scores of the sample rather than previously established norms or standards; therefore, the exact categorization criteria of the groups should be interpreted with caution. Nevertheless, our results emphasize that lower SES children do not constitute a homogenous group of at-risk children who show similar levels of alterations in neural mechanisms of selective attention.

The underlying mechanisms of these individual differences in selective attention remain to be investigated in order to understand the interactions between genetic and familial factors. Polymorphisms of several candidate genes have been linked to individual differences in attention abilities in typically developing individuals (Blasi et al., 2005; Fan, Fossella, Sommer, Wu, & Posner, 2003; Green et al., 2008; Parasuraman,
Greenwood, Kumar, & Fossella, 2005; Rueda, Rothbart, McCandliss, Saccomanno, & Posner, 2005). However, it is unclear how genetic effects might manifest in lower SES children. While some studies found stronger genetic influences in lower SES populations (Nobile et al., 2007; Nobile et al., 2010; Sadeh et al., 2010; Williams et al., 2008), others reported suppressed genetic influences in lower SES households (Rhemtulla & Tucker-Drob, 2012; Tucker-Drob, Rhemtulla, Harden, Turkheimer, & Fask, 2011; Turkheimer, Haley, Waldron, D'Onofrio, & Gottesman, 2003). Further research is warranted to understand the potential genetic underpinnings of individual differences in selective attention in lower SES children.

Furthermore, the role of familial factors in the emergence of individual differences in selective attention has yet to be explored. Previous research has demonstrated that lower SES children are at greater risk for unfavorable household characteristics, such as low cognitive stimulation, high stress, and poor parenting skills (Bradley & Corwyn, 2002; Brooks-Gunn & Duncan, 1997; Evans, 2004) and a few training and intervention studies have demonstrated that some of the negative outcomes associated with such adversity could be ameliorated (Bierman, Nix, Greenberg, Blair, & Domitrovich, 2008; Campbell, Pungello, Miller-Johnson, Burchinal, & Ramey, 2001; Mackey, Hill, Stone, & Bunge, 2011; Neville et al., 2013). It remains crucial to delineate which familial characteristics compromise versus promote the neural mechanisms of selective attention in lower SES children.

**Conclusions**

The present study provides initial evidence for noteworthy individual differences in neural indices of selective attention in young children from lower SES families. These
individual differences in neural indices of selective attention were associated with nonverbal IQ performance. Children who revealed more pronounced attention effects, as measured by ERPs, also demonstrated superior nonverbal cognitive abilities. Further research is warranted to pinpoint the factors that account for the variability observed in neural mechanisms of selective attention in children from disadvantaged backgrounds.
CHAPTER III

5-HTTLPR POLYMORPHISM IS LINKED TO NEURAL MECHANISMS OF SELECTIVE AUDITORY ATTENTION IN LOWER SOCIOECONOMIC STATUS PRESCHOOLERS

This work is in preparation for submission. I wrote this manuscript, with my co-authors T. A. Bell, A. Hampton Wray and H. J. Neville providing feedback and editorial assistance.

Introduction

Attentional control, the ability to sustain attention on a task in the presence of internal and external distractors, is one of the strongest predictors of school readiness and academic success (Duncan et al., 2007; Stevens & Bavelier, 2012). At the beginning of kindergarten, and during early school years, lower SES children already show poorer attentional skills than their higher SES counterparts (Duncan & Magnuson, 2011; Mezzacappa, 2004; Noble, McCandliss, & Farah, 2007). Therefore, it remains crucial to elucidate the underlying mechanisms of poorer attentional control skills in lower SES children, especially before they start school.

Here we focused particularly on selective attention as a critical component of attentional control. Selective attention refers to the ability to prioritize relevant stimuli in the presence of irrelevant, competing distractors (Desimone & Duncan, 1995; Hillyard, Hink, Schwent, & Picton, 1973; Serences & Kastner, 2014). This ability is proposed to be fundamental for the foundations of language, literacy, and mathematics (Astheimer & Sanders, 2012; Casco, Tressoldi, & Dellantonio, 1998; Commodari & Di Blasi, 2014;
Stevens & Bavelier, 2012). In addition, neural indices of this ability have been associated with crucial nonverbal cognitive skills in adults and children (Gazzaley, 2011; Giuliano, Karns, Neville, & Hillyard, 2014; Isbell, Hampton Wray, & Neville, 2015). Neural mechanisms of selective attention are at greater risk for deficits in children from lower socioeconomic status (SES) families in comparison to higher SES children (Stevens, Lauinger, & Neville, 2009; Stevens, Paulsen, Yasen, & Neville, 2014). Yet, there is also remarkable variability in neural indices of selective attention among this at risk population (Isbell et al., 2015). Genetic influences on such variability remain to be investigated. The present study addresses this gap by focusing on the link between the allelic variations of the serotonin transporter linked polymorphic region (5-HTTLPR) and neural mechanisms of selective attention.

5-HTTLPR has been the most investigated genetic polymorphism in psychology (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010). There are two predominant allelic variants of the serotonin transporter linked polymorphic region (5-HTTLPR) of the serotonin transporter gene, SLC6A4: short allele and long allele (Heils et al., 1996). Compared to the long 5-HTTLPR allele, the short allele produces less serotonin transporter mRNA and protein (Canli & Lesch, 2007). The functional and structural neural outcomes of this polymorphism are still under investigation. While some studies did not find a significant role of 5-HTTLPR in binding at serotonin transporter sites (Jedema et al., 2010; Parsey et al., 2006), others reported lower binding values in short allele carrier humans and rhesus macaques (Christian et al., 2013; David et al., 2005; Fisher et al., 2015). The short allele was also associated with lower gray matter density in limbic, cerebellar, and frontal regions (Canli et al., 2005; Jedema et al., 2010; Pezawas
While a substantial body of research focused on the short allele of 5-HTTLPR in the context of vulnerability or resilience to psychopathology (Caspi et al., 2010; Karg, Burmeister, Shedden, & Sen, 2011; van Ijzendoorn, Belsky, & Bakermans-Kranenburg, 2012), several studies also linked the short allele to superior cognitive functions in adults. For instance, the short allele was linked to better performance in a visual working memory task (Anderson, Bell, & Awh, 2012). Comparably, short-carriers were found to perform better than the long homozygotes in Wisconsin Card Sorting Test, which taps into various cognitive skills such as set-shifting, working memory, and attention (Borg et al., 2009). Similar performance advantages were reported for cognitive control, especially for adults homozygous for the short allele (Enge, Fleischhauer, Lesch, Reif, & Strobel, 2011; Strobel et al., 2007).

Differential cognitive performance among 5-HTTLPR genotypes was also assessed with neurophysiological measures in adults. For example, in an event-related potentials (ERP) study with a sequential-letter n-back task, N2 amplitudes were compared between 5-HTTLPR genotypes across different load and target conditions (Enge, Fleischhauer, Lesch, Reif, et al., 2011). The differentiation in N2 amplitude between 0-back and load-conditions was smaller in amplitude in the long-homozygotes than the short-carriers. Furthermore, long-homozygotes displayed smaller N2 amplitudes than short-carriers in the 0-back condition, and also for non-targets across conditions. These results were interpreted as less efficient executive functioning in long-homozygotes compared to the short-genotypes. More pronounced neural responses in short allele carriers compared to their long homozygotes were also observed for N1 in an
auditory oddball paradigm, in interaction with personality traits (Enge, Fleischhauer, Lesch, & Strobel, 2011), and for gamma band activity in the Attention Network Test, in interaction with other genes (Enge, Fleischhauer, Lesch, Reif, & Strobel, 2014).

In line with these findings, a rhesus macaque ortholog of the 5-HTTLPR polymorphism (rh5-HTTLPR) was linked to cognitive outcomes similar to those observed in humans (Jedema et al., 2010). Across various cognitive tasks, short allele carrier rhesus macaques were found to integrate feedback better for subsequent choices compared to the long allele carriers. These results concurred with the human adult findings in that the individuals who carry one or two copies of the short allele of 5-HTTLPR performed better on a variety of cognitive tasks.

Drawing on the literature that linked the 5-HTTLPR polymorphism to cognitive performance, here we investigated whether the 5-HTTLPR polymorphism would account for individual differences in neural mechanisms of selective attention in lower SES children. Based on the cognitive advantage observed for the short allele carriers, we hypothesized that the short carrier lower SES children would show superior neural mechanisms of selective attention. To measure neural indices of selective attention, we recorded ERPs in lower SES preschoolers using a child-friendly dichotic listening task. This task has been used with young children from diverse SES backgrounds (Coch, Sanders, & Neville, 2005; Neville et al., 2013; Sanders, Stevens, Coch, & Neville, 2006; Stevens et al., 2009). In this task, children are instructed to attend to one of the two stories that are presented simultaneously, while ignoring the other one. ERPs are recorded to the identical probe stimuli superimposed on both the attended and unattended stories. Neural indices of selective attention are measured by comparing the mean
amplitudes of ERPs evoked by the identical probes embedded in the attended versus unattended stories.

In typically developing children from higher SES families, a significant effect of selective attention on ERPs has been observed as early as 100 to 200 ms, in the form of a larger, more positive mean amplitude for the ERPs to probes in the attended stories compared to ERPs to probes in the unattended stories (Coch et al., 2005; Sanders et al., 2006; Stevens et al., 2009). In typically developing lower SES children, the magnitude of this selective attention effect was linked to nonverbal cognitive abilities (Isbell, Hampton Wray, & Neville, 2015). Children who had larger, more positive mean amplitudes for the ERP selective attention effect also performed better on a nonverbal intelligence test.

Using this well-established ERP paradigm, we tested the hypothesis that the short carrier lower SES children would show a more enhanced ERP selective attention effect than long homozygotes. Specifically, we predicted a larger, more positive ERP selective attention effect in children who carry at least one short allele of 5-HTTLPR compared to long homozygote children.

**Method**

**Participants**

Participants were 121 children (76 females) between the ages of 40 and 67 months (Mean = 55 months, SD = 6.5 months). They were recruited in Oregon, from 12 preschool sites of Head Start (HS), a program for families living at or below the poverty line. Based on parent reports, children with diagnosed behavioral or neurological problems (e.g. 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 from whom DNA was collected. All children passed a hearing screening at 20 dB HL at 500, 1000, 2000 and 4000 Hz in both the right and left ears. From a total of 157 children who met these criteria, 23 were excluded due to low ERP data quality (excessive EEG artifacts and/or less than 75 trials per condition). In addition, 11 children were excluded for having less than 50% accuracy on the comprehension questions presented during the ERP task. In the final sample, 59% of the children were White/Caucasian, 1% Black/African American, 4% American Indian or Alaskan, 15% more than one ethnicity, 1% unknown, and 20% unreported. Excluding the unknown/unreported children, our sample was predominantly (74%) White/Caucasian.

Informed consent was obtained from parents or other caregivers. In addition, verbal assent was obtained from child participants. Behavioral measures and ERPs were collected in two different sessions, separated by no more than 30 days. DNA was collected either at the behavioral or ERP sessions. All families were paid for participation. Study procedures were approved by the University of Oregon Institutional Review Board.

**Socioeconomic status (SES)**

Parents/caregivers filled out a short questionnaire about the education level and profession of the primary caregivers. Socioeconomic status (SES) of the child was coded by trained research assistants according to the Hollingshead Four Factor Index of Social Status (Hollingshead, 1975).

**Electrophysiological assessment of selective auditory attention**

We recorded ERPs in a spatial selective auditory attention ERP paradigm,
described in detail in previous studies with lower SES preschoolers (Neville et al., 2013). Briefly, sixteen narrative stories were digitally recorded (16 bit, 22 kHz). Half of the stories were read by a female narrator, and half were read by a male narrator at a normal speaking rate in a child-directed manner. The 16 stereo files differed in location (left/right audio speaker) and narration voice (male/female). Each file was 2.5-3.5 min in length. The stories were presented at an average of 60 dB 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. A small green arrow pointing to the left or right was superimposed at the bottom of each image to indicate the attended side.

Two probe stimuli were created by digitizing a token of the syllable \( ba \) spoken by a female voice (different from the female narrators) and scrambling the order of 4-6 ms segments of that token to create a nonlinguistic sound with similar acoustic characteristics. Both probes were 100 ms in length and were presented at 70 dB SPL. An equal number of linguistic and non-linguistic probes were presented across the stories. Approximately 200 linguistic and 200 nonlinguistic probes (N~180-206) were presented to each child. The probes were presented in a pseudo-random order at an interstimulus interval (ISI) of either 200, 500, or 1000 ms in one of the two channels. Probes were never presented simultaneously in the attended and unattended channels.

**Procedure.** Children arrived at the laboratory with their parents and were provided time to acclimate to their environment before placement of the electrode cap began. Once the EEG cap was in place, children were seated in a comfortable chair in an electrically shielded, sound-attenuating booth. They were instructed not to move or lean from side to side. 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 approximately 57 inches in front of the child. Before the data were recorded, children received instructions to attend to the story played from one speaker while ignoring the story presented on the other speaker. They were told either a male or a female speaker would narrate the story. An arrow at the bottom of the screen would point to the speaker they should attend to and the attended story would correspond to the pictures on the screen. They were also instructed that unrelated sounds (‘bas’ and ‘buzzes’) would be presented but should be ignored.

At the beginning of each story, participants were presented with a sound sample of the narrator to which they should attend. They were instructed to listen carefully to the story from this narrator and ignore the other voice. Participants attended to a total of four narratives selected from the four story sets, attending twice to the right side and twice to the left side (order either RLLR or LRRL). All participants were presented with two stories narrated by a female and two stories narrated by a male. For the duration of the experiment, participants 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 participants 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 an incorrect response. Only children who performed with at least 50% accuracy on the comprehension questions were included in the EEG analyses.

**EEG recording and analysis.** EEG was recorded at a sampling rate of 1024 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, Amsterdam, Netherlands), which does not require impedance measurements, an online reference, or gain adjustments. 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 re-referenced off-line to the algebraic average of the left and right mastoid. Left and right horizontal eye channels were re-referenced to one another.

ERP analyses were carried out using EEGLAB (Delorme & Makeig, 2004) and ERPLAB (Lopez-Calderon & Luck, 2014). Data were down-sampled to 256 Hz to speed computation and band-pass filtered from 0.1 to 40 Hz. The EEG data was epoched offline between 100 ms prior to and 500 ms after stimulus onset, using the first 100 ms as the pre-stimulus-onset baseline. On the basis of the visual inspection of the epoched EEG data, individual artifact rejection parameters were selected for each subject. Artifact rejection was executed using 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 for almost all included participants. Trained research assistants performed a subsequent artifact rejection step to exclude additional epochs containing eye movements and muscle artifacts from further analysis. Out of ~ 400 trials per condition, an average of 250 trials ($SD = 63$) per participant were accepted for the attend condition, and 250 trials ($SD = 61$) were accepted for the unattend condition.

For a total of 3 participants with otherwise clean EEG data, faulty electrodes were replaced with the average mean amplitude of the 3 neighboring electrodes. The neighboring electrodes were determined based on the rows described below, within the
hemisphere of interest.

The mean amplitudes of ERPs were measured between 100 to 200 ms post-stimulus onset, collapsed across the linguistic and nonlinguistic conditions, consistent with previous studies using this paradigm with young children from low income families (Neville et al., 2013; Stevens et al., 2009; Stevens et al., 2014). ERP attention effect was operationalized as the mean amplitude difference between the ERPs to the probes in the attended versus unattended stories (attend - unattend). ERP data were analyzed using mixed-model ANOVAs. The within-group factor included three levels of anterior/posterior electrode location (anterior, central, posterior). The three rows of 8 electrodes were created 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. The electrode configuration for event-related brain potential recordings is illustrated in Chapter II, Figure 1. Greenhouse-Geisser corrections were applied for all ANOVAs with greater than one degree of freedom. Uncorrected degrees of freedom but corrected p values are reported. The between-group factor was 5-HTTLPR genotype with 3 levels: long/long (l/l), short/long (s/l), and short/short (s/s).

**Genotyping.** Buccal epithelial cells were collected with cotton swabs. For each child, 2 swabs were collected. Genotyping was conducted at the University of Oregon. Genomic DNA was isolated from the swabs using QuickExtract V1.0 (Epicentre Biotechnologies, Madison, WI) according to their protocol. Approximately 1% of this preparation was used for each amplification. The promoter region of *SLC6A4* was amplified using the primers reported in Deckert et al. (Deckert et al.). The polymerase chain reaction was modified to include 0.2 µM of each primer, 1.75 mM MgCl₂, 0.2 mM
dNTPs, 0.64 M betaine, 0.05 U/µl Taq polymerase with its 1× reaction buffer (NH₄)SO₄ (Fermentas, Glen Burnie, MD). The amplification was performed in a PTC-200 or 225 thermocycler (MJ Research/Bio-Rad, Hercules, CA) as follows: 94°C 3 min, followed by 35 cycles of 94°C 30 sec, 65°C 1 min, and 72°C 30 sec, finishing with 72°C for 3 min. The amplified fragments were separated on a 2% agarose gel (Sigma-Aldrich, St. Louis, MO) and visualized with ethidium bromide staining.

Allele frequencies of 5-HTTLPR were 57% for the l allele and 43% for the s allele. According to the Hardy-Weinberg equilibrium, the expected distribution of 5-HTTLPR genotypes would be 33% for l/l, 49% for s/l, and 18% for s/s. In our sample, genotype frequencies were 29% for l/l (n = 35), 56% for s/l (n = 68), and 15% for s/s (n = 18). Chi-square tests revealed no significant differences between the observed frequencies and the expected frequencies according to the Hardy-Weinberg equilibrium ($\chi^2(2) = 2.54, p = .28$).

Results

Exploratory data analyses were conducted for both behavioral performance and ERP data, for all children as a group, as well as independently for each 5-HTTLPR genotype group [long/long, short/long, and short/short]. No outliers (+/- 3 SD) were detected, and therefore all children with acceptable ERP data, based on the criteria explained above, were included in the analyses.

Table 1 displays the descriptive statistics by the 5-HTTLPR genotype groups. The descriptive statistics are reported for age, SES, number of correct answers children gave for the comprehension questions asked during the ERP task, and number of clean ERP trials that were used in the analyses. SES information was missing for 11 children (3
long-long, 8 short-long children).

Table 1

<table>
<thead>
<tr>
<th>5-HTTLPR Genotypes</th>
<th>Age</th>
<th>SES</th>
<th>Comprehension Accuracy</th>
<th>Number of ERP trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-long (n = 35)</td>
<td>4.48 (0.51)</td>
<td>30.79 (10.74)</td>
<td>8.00 (1.41)</td>
<td>504 (123)</td>
</tr>
<tr>
<td>Short-long (n = 68)</td>
<td>4.51 (0.56)</td>
<td>28.98 (11.90)</td>
<td>8.62 (1.54)</td>
<td>507 (121)</td>
</tr>
<tr>
<td>Short-short (n = 18)</td>
<td>4.81 (0.52)</td>
<td>31.11 (11.96)</td>
<td>8.83 (1.38)</td>
<td>468 (130)</td>
</tr>
</tbody>
</table>

Note. SES information was missing for 3 long-long, and 8 short-long children (n=11).

Using univariate ANOVAs, we tested whether age, SES, comprehension accuracy, or number of ERP trials varied as a function of 5-HTTLPR genotype. There were no main effects of 5-HTTLPR genotype on age, SES, comprehension accuracy, and number of ERP trials. The ANOVA statistics are reported in Table 2.

Chi-Square tests revealed no significant differences in gender distribution between the 5-HTTLPR genotype groups, $\chi^2(2) = .03, p = .98$. Ethnicity variable was recoded as follows: white, not white, unknown/unreported. Chi-Square tests revealed no significant
differences in ethnicity distribution between the 5-HTTLPR genotype groups, \(\chi^2(4) = .78, p = .94\). Similarly, when the children with unknown/unreported ethnicity information were excluded \((n = 26)\), there were no significant differences in the ethnicity distribution between the genotype groups, \(\chi^2(2) = .12, p = .94\).

The effect of selective auditory attention was measured as the difference in mean amplitude between ERPs to probes embedded in attended versus unattended stories. Three aggregate measures of ERPs were created by averaging across 8 electrodes within the anterior, central, and posterior rows (electrodes included in each row are detailed in the Method section). The grand average ERP waveforms at two representative central electrodes are illustrated in Figure 1, separately for each genotype group. The grand average ERP waveforms including all electrodes included in the analyses are illustrated in Supplementary Figures.
Figure 1. Grand-average ERP waveforms showing ERPs elicited by the attended and unattended conditions at representative central electrodes C5 (left hemisphere) and C6 (right hemisphere), for 5-HTTLPR genotype groups (long-long, short-long, and short-short). Negative is plotted upward.

We used a mixed-model ANOVA to evaluate whether the ERPs of attention effect varied as a function of 5-HTTLPR genotype. The ANOVA included the between-group factor of three 5-HTTLPR genotypes (long/long, short/long, and short/short), and the within-group factor of three levels of electrode locations (anterior, central, posterior).

For the effect sizes in ANOVAs, $\eta^2$ was reported.

Initially, the ANOVA test included age and gender as covariates. The effects of these covariates did not reach statistical significance in the ERP analyses. Consequently,
to have a parsimonious model, these covariates were dropped from the final model. The results of the initial analysis that included these covariates are reported in the Supplementary Materials (Supplementary Table 1).

The statistics of the final model are shown in Table 2. There was no significant main effect of electrode locations on neural indices of selective attention, as measured by the ERP mean amplitudes. The interaction between electrode location and 5-HTTLPR genotype also was not significant. There was a significant main effect of 5-HTTLPR genotype on the ERPs of the selective attention effect.

Table 2
Analyses of variance for age, SES, comprehension accuracy, and ERP mean amplitudes of the attention effect by 5-HTTLPR genotype (long-long, short-long, short-short)

<table>
<thead>
<tr>
<th></th>
<th>F</th>
<th>df</th>
<th>p</th>
<th>partial η²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>2.60</td>
<td>2, 118</td>
<td>.08</td>
<td>.04</td>
</tr>
<tr>
<td>SES</td>
<td>.38</td>
<td>2, 106</td>
<td>.69</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>Comprehension accuracy</td>
<td>2.65</td>
<td>2, 118</td>
<td>.08</td>
<td>.04</td>
</tr>
<tr>
<td>Number of ERP trials</td>
<td>.76</td>
<td>2,118</td>
<td>.47</td>
<td>.01</td>
</tr>
<tr>
<td>ERP mean amplitudes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-HTTLPR</td>
<td>3.05</td>
<td>2, 118</td>
<td>.01*</td>
<td>.07</td>
</tr>
<tr>
<td>Electrode location</td>
<td>2.44</td>
<td>2, 236</td>
<td>.09</td>
<td>.02</td>
</tr>
<tr>
<td>5-HTTLPR x electrode location</td>
<td>.31</td>
<td>4, 236</td>
<td>.78</td>
<td>&lt; .01</td>
</tr>
</tbody>
</table>

*p < .05
For effect sizes, Cohen’s $d$ values were computed. Given the unequal sample sizes of the genotype groups, pooled standard deviation was used in Cohen’s $d$ calculations. Mean differences with 95% confidence intervals and Cohen’s $d$ values are displayed in Table 3, for 3 levels of electrode locations, as well as across all electrode sites.

Table 3
Mean differences (µV), confidence intervals (95% CI), and effect sizes for the selective attention effect as measured by ERPs

<table>
<thead>
<tr>
<th></th>
<th>Mean difference (µV)</th>
<th>95% CI</th>
<th>Effect size (Cohen’s $d$)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-carriers vs. long-long</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior electrodes</td>
<td>0.67</td>
<td>[0.09, 1.23]</td>
<td>0.46</td>
</tr>
<tr>
<td>Central electrodes</td>
<td>0.68</td>
<td>[0.14, 1.23]</td>
<td>0.50</td>
</tr>
<tr>
<td>Posterior electrodes</td>
<td>0.68</td>
<td>[0.05, 1.31]</td>
<td>0.43</td>
</tr>
<tr>
<td>All electrodes</td>
<td>0.68</td>
<td>[0.21, 1.14]</td>
<td>0.58</td>
</tr>
<tr>
<td><strong>Short-short vs. short-long</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior electrodes</td>
<td>0.08</td>
<td>[-0.70, 0.86]</td>
<td>0.01</td>
</tr>
<tr>
<td>Central electrodes</td>
<td>0.31</td>
<td>[-0.40, 1.03]</td>
<td>0.15</td>
</tr>
<tr>
<td>Posterior electrodes</td>
<td>0.54</td>
<td>[-0.27, 1.34]</td>
<td>0.31</td>
</tr>
<tr>
<td>All electrodes</td>
<td>0.31</td>
<td>[-0.29, 0.91]</td>
<td>0.27</td>
</tr>
</tbody>
</table>
Helmert contrasts were used to compare the ERPs of the selective attention effect a) between the children who are homozygous for the long allele versus children who carry at least one short allele, and b) between the children who carry one versus two copies of the short allele. These contrasts revealed a significant difference in the mean amplitudes of the selective attention effect between the children homozygous for the long-allele (long-long) and the children who carry at least one copy of the short allele (short-long and short-short), $t(118) = -3.05, p = .003, d = -.58$. The selective attention effect was more attenuated (smaller, less positive in amplitude) in the long-homozygotes than the short-carriers. The mean amplitudes of the selective attention effect did not significantly differ between the children who carry one versus two copies of the short allele (s/l vs. s/s), $t (118) = -1.00, p = .32, d = -.27$. Figure 2 shows the ERP mean amplitudes of the selective attention effect for the 5-HTTLPR genotype groups, averaged across all electrode locations.
Figure 2. Mean amplitudes (µV) of ERP difference waves (attended-unattended), averaged across all channels included in the analyses. Long-long children had smaller ERP mean amplitudes than children who carried at least one short allele. Error bars represent +/- 1 SE. * p < .05

Discussion

In the present study, we investigated the relationship between 5-HTTLPR polymorphism and neural mechanisms of selective auditory attention in lower SES preschoolers. Our results indicated a noteworthy association between 5-HTTLPR and neural indices of selective attention, as measured by ERPs. Specifically, the ERPs for the selective attention effect was larger, more positive in mean amplitude in the short
carriers than the long homozygotes. Such larger, more positive mean amplitudes for the early ERP selective attention were previously linked to better performance in nonverbal tasks of cognition in adults and children (Giuliano et al., 2014, Isbell, Hampton Wray, & Neville, 2015). While the short-carrier children showed a more pronounced ERP selective attention effect compared to the long-homozygotes, there were no notable differences between the children who carried one versus two copies of the short allele.

Our results support the hypothesis that the short allele of 5-HTTLPR would relate to more favorable outcomes for neural mechanisms of selective attention. These findings are in line with the studies that linked the short allele to superior performance across cognitive abilities such as working memory, cognitive control, and decision making (Anderson et al., 2012; Borg et al., 2009; Enge, Fleischhauer, Lesch, Reif, et al., 2011; Jedema et al., 2010). Our study extends the findings of cognitive advantage for the 5-HTTLPR short allele to young children from lower SES families.

A substantial body of research linked the short allele of 5-HTTLPR to various unfavorable outcomes in the face of adverse environmental conditions (Caspi et al., 2010; Karg et al., 2011). While the reliability of this link was contested by some (Blakely & Veenstra-VanderWeele, 2011; Munafo, Durrant, Lewis, & Flint, 2009; Risch et al., 2009), others concurred in findings of heightened stress vulnerability for short allele carriers under adverse conditions (Conway et al., 2012; Jenness, Hankin, Abela, Young, & Smolen, 2011; Starr, Hammen, Conway, Raposa, & Brennan, 2014). Furthermore, several studies displayed that the short allele carriers were more sensitive not only to adversity, but also to supportive and enriching environments, compared to their long homozygote counterparts (Belsky et al., 2009; Belsky & Pluess, 2009; Bogdan, Agrawal, 2009; Belsky & Pluess, 2009; Bogdan, Agrawal, 2009).
Along with the studies that showed a cognitive advantage for the short allele in adults (Anderson et al., 2012; Borg et al., 2009; Enge, Fleischhauer, Lesch, Reif, et al., 2011), our results imply that the short allele of 5-HTTLPR may not only signify sensitivity to adverse or beneficial environmental factors, but also index favorable cognitive outcomes.

It is important to mention that several studies reported greater bias to attend to emotionally salient or threatening stimuli in short allele carriers compared to the long homozygotes (Beevers, Wells, Ellis, & McGeeary, 2009; Canli et al., 2005; Osinsky et al., 2008; Thomason et al., 2010). Integrating such reports with findings of cognitive advantage in short-carriers, it was argued that the short allele is rather a marker of hypervigilance, displayed as elevated sensitivity to relevant environmental stimuli (Dobson & Brent, 2013; Homberg & Lesch, 2011). Accordingly, such hypervigilance can predict psychopathology or cognitive advantage depending on the environmental conditions. To speculate, this hypervigilance framework may account for our findings of superior neural mechanisms of selective attention in short allele carriers, measured in a dichotic listening paradigm with no apparent emotional salience. The proposed hypervigilance of short allele carriers may be manifest as pronounced attentional abilities in the absence of emotionally salient or threatening stimuli.

Our findings link the short allele of 5-HTTLPR to more pronounced neural indices of selective attention in lower SES children. Based on these findings, we also infer that being homozygous for the long allele may be a risk factor for the development of selective attention in lower SES preschoolers. While our results provide initial evidence for the association between 5-HTTLPR genotypes and individual differences in
selective attention in typically developing lower SES children, certain limitations of our study require consideration. One limitation of our study was that our participants were predominantly Caucasian. This raises the question as to whether our findings would generalize beyond a predominantly Caucasian sample. It has been demonstrated that the frequency and functional characteristics of 5-HTTLPR may differ across racial and ethnic groups (Chiao & Blizinsky, 2010; Odgerel, Talati, Hamilton, Levinson, & Weissman, 2013; van Ijzendoorn et al., 2012). For instance, being homozygous for the short allele was associated with lower serotonin function in the central nervous system in European-Americans, and higher serotonin function in African-Americans (Williams et al., 2003). As another example, differential susceptibility of the short allele to environmental factors was observed mainly in samples composed of primarily White children (van Ijzendoorn et al., 2012), while in a sample of predominantly Black children, homozygous long allele carriers were found to show greater susceptibility to environmental effects (Davies & Cicchetti, 2014). On the other hand, studies that showed a cognitive advantage for the short allele carriers were either conducted with participants of European descent or their ethnicity was not reported (Anderson et al., 2012; Borg et al., 2009; Enge, Fleischhauer, Lesch, Reif, et al., 2011). Therefore, it remains a question at large to what extent any findings related to 5-HTTLPR polymorphism attained from a predominantly Caucasian sample like ours would generalize to more diverse populations of lower SES children.

Another limitation was the biallelic categorization of the 5-HTTLPR allelic variations. In our study, we focused on the two common allelic variants that occur either as a shorter sequence of 14 repeats (short allele) or a longer sequence of 16 repeats (long allele). However, other lengths have also been reported (Kraft, Slager, McGrath,
Furthermore, instead of a biallelic categorization, a triallelic classification was proposed based on the single nucleotide variant (A to G) detected on the long allele (Hu et al., 2006; Kraft et al., 2005). The variant designated L_A was associated with higher serotonin transporter binding, whereas the variant designated L_G was associated with lower serotonin binding (Hu et al., 2006; Praschak-Rieder et al., 2007). Several psychopathology studies used this categorization to group the L_G variant together with the short allele, in comparison to the L_A/L_A genotype assigned to long homozygosity (Davies & Cicchetti, 2014; Mileva-Seitz et al., 2011). If we had used this triallelic categorization, some children would have been included in the heterozygous group instead of the long homozygote group. It will be important to test this triallelic variation approach in future studies of 5-HTTLPR genotype and brain functioning.

In addition to these methodological considerations, the present study brings out several directions for future investigation. First and foremost, it remains crucial to understand how 5-HTTLPR polymorphism interacts with environmental factors in lower SES children, who are at greater risk for chronic stress exposure. In comparison with their higher SES counterparts, lower SES children experience more adverse familial and environmental conditions concurrently (Baum, Garofalo, & Yali, 1999; Evans, 2004). These stressors include stressful familial experiences such as persistent economic hardship, crowding, family dissolution, and moves, and neighborhood characteristics such as violence, crime, environmental hazards, and noise pollution (Bradley & Corwyn, 2002; Evans, 2004; Evans & Kim, 2010). Such chronic stress in childhood has been identified as a potential mechanism by which SES alters the development of the brain and
consequently, cognitive functioning (Blair, 2010; Blair et al., 2011). Our findings put forward for consideration that the cognitive advantages associated with the short allele may be evident even in children who are at greater risk for stress exposure and alterations in brain functioning.

However, without an objective and validated measure of stress in young children, we cannot assess how 5-HTTLPR genotypes act under stress in predicting neural mechanisms of selective attention. Karg and colleagues (2011) reported that the genetic moderation by 5-HTTLPR in studies of depression was weaker if they included self-report questionnaires and stronger if an objective measure of stress or in-person interviews were included. Therefore, inclusion of a validated chronic stress measure for young children could uncover a genetic moderation we did not find in this study. Furthermore, lower SES families largely differ in various protective factors that are predictive of cognitive outcomes, such as parental responsiveness and stimulating home environments (Bradley & Corwyn, 2002; Lengua, Honorado, & Bush, 2007; Tong, Baghurst, Vimpani, & McMichael, 2007). Again, inclusion of validated measures of supportive environments for young children could reveal genetic moderations we could not assess in our study. Incorporating indicators of protective factors, along with indices of risk, is an important future direction to assess the role of 5-HTTLPR polymorphism in the development of neural mechanisms of selective attention. Such assessments would also appraise whether the stress reactivity or differential susceptibility frameworks applied to neural mechanisms of selective attention.

In addition, as no single candidate gene can solely account for variability in any cognitive ability, it remains crucial to investigate how 5-HTTLPR interacts with other
polymorphisms linked to attentional abilities in children. In adults, single nucleotide polymorphisms (SNPs) of various genes have been linked to cognitive abilities (Green et al., 2008; Savitz, Solms, & Ramesar, 2006). Among these, polymorphisms of several genes have been associated with attentional abilities (Stormer, Passow, Biesenack, & Li, 2012). These genes include, but are not limited to, catecholamine-O-methyltransferase (COMT) gene, cholinergic receptor, nicotinic, alpha 4 (CHRNA4) gene, dopamine receptor D4 (DRD4) gene, and dopamine active transporter 1 gene (DAT1). In typically developing infants and children, variability in attentional abilities have also been linked to COMT and DAT1 polymorphisms (Holmboe et al., 2010; Markant, Cicchetti, Hetzel, & Thomas, 2014; Rueda, Rothbart, McCandliss, Saccomanno, & Posner, 2005). A more comprehensive array of candidate genes, and assessment of their interactions with each other, would greatly advance our understanding of biological foundations of individual differences in neural mechanisms of selective attention.

**Conclusions**

The present study demonstrated a link between 5-HTTLPR polymorphism and neural indices of selective attention in lower SES preschoolers. Compared to their long homozygote peers, children who carried at least one copy of the short allele displayed more pronounced attention effects, as measured by ERPs. These findings suggest that being homozygous for the long allele may confer weaker neural mechanisms of selective attention in lower SES children. Further research is requisite to understand the elaborate interactions between 5-HTTLPR and other candidate genes in the context of diverse environmental conditions. Future studies that address these issues can advance our understanding of the biological bases for neural mechanisms of selective attention, which
are at risk in lower SES children (Stevens et al., 2009; Stevens et al., 2014). By and large, combining neuroimaging with the study of specific genes carries the potential to greatly improve our understanding of how individual differences in cognitive abilities emerge and develop (Posner, Rothbart, & Sheese, 2007).

The study presented in Chapter III linked being homozygous for the long allele of 5-HTTLPR polymorphism to greater vulnerability in neural mechanisms of selective auditory attention in lower SES preschoolers. The study presented in Chapter IV evaluated the interactive effects of this polymorphism and a family-based training program shown to improve neural mechanisms of selective attention in lower SES preschoolers. Specifically, this study compared the ERP indices of selective attention in long-homozygote and short-carrier children, before and after 8 weeks of being assigned to either the family-based training program or a comparison group.
CHAPTER IV
FAMILY-BASED TRAINING MODERATES GENETIC INFLUENCES ON NEURAL MECHANISMS OF SELECTIVE AUDITORY ATTENTION IN LOWER SES PRESCHOOLERS

This work is in preparation to be submitted for publication. I wrote this manuscript, with my co-authors T. A. Bell, A. Hampton Wray and H. J. Neville providing feedback and editorial assistance.

Introduction

Selective attention refers to the ability to enhance the processing of relevant stimuli while suppressing the processing of irrelevant, competing distractors (Desimone & Duncan, 1995; Hillyard, Hink, Schwent, & Picton, 1973; Yantis, 2008). Selective attention is critical for various cognitive abilities, such as language and working memory (Astheimer & Sanders, 2012; Gazzaley, 2011; Giuliano, Karns, Neville, & Hillyard, 2014; Nicolay & Poncelet, 2013), and is crucial for academic skills (Casco, Tressoldi, & Dellantonio, 1998; Commodari & Di Blasi, 2014; Steele, Karmiloff Smith, Cornish, & Scerif, 2012; Stevens & Bavelier, 2012).

Neural mechanisms of this fundamental ability are highly malleable, displaying enhancements after altered sensory experience (Bavelier et al., 2000; Neville & Lawson, 1987; Röder et al., 1999), and upon participation in trainings and interventions (Green & Bavelier, 2003; Neville et al., 2013; Stevens, Fanning, Coch, Sanders, & Neville, 2008; Stevens et al., 2013). It has been demonstrated that these highly plastic neural
mechanisms are vulnerable in lower SES children (D’Angiulli, Herdman, Stapells, & Hertzman, 2008; Stevens, Lauinger, & Neville, 2009; Stevens, Paulsen, Yasen, & Neville, 2014). Yet, in a previous randomized control trial study, we documented that neural mechanisms of selective attention in lower SES preschoolers can be enhanced with a family-based training program (Neville et al., 2013). Briefly, this family-based training program, Creating Connections (previously known as Parents and Children Making Connections - Highlighting Attention), was designed to improve brain systems that support selective attention in preschool children. A unique characteristic of this program was the combination of attention training exercises for children with parenting training for their parents/caregivers. The child component of the training program was designed to increase self-regulation of attention and emotional states. 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. In this randomized controlled trial study, the control groups were a training comparison program that primarily focused on child classroom training, with greatly reduced parent involvement, and a comparison group who only received Head Start services as usual.

In a relatively short time frame of 8 weeks, children assigned to the family-based training program showed enhancements in neural mechanisms of selective attention, along with improvements in nonverbal intelligence and language. Importantly, these enhancements were observed relative to both the contrasting child-focused training program and the services as usual group. In the present study, we investigated how this effective training program contributes to the neuroplasticity of selective attention in
interaction with genetic influences.

Advances in molecular genetics permit the investigation of interactions between gene polymorphisms and particular environmental factors in relation to behavioral outcomes and brain functions (Caspi & Moffitt, 2006; Cicchetti, 2007; Moffitt, Caspi, & Rutter, 2006; Rutter, 2012; Thapar, Harold, Rice, Langley, & O'Donovan, 2007). Although the majority of the studies that assessed gene × environment interactions were correlational in design, a growing body of work utilized randomized control trials (Bakermans-Kranenburg & van IJzendoorn, 2015; Belsky & van IJzendoorn, 2015; van Ijzendoorn & Bakermans-Kranenburg, 2015; van IJzendoorn et al., 2011).

Such experimental gene × environment studies provide distinct advantages over correlational studies by manipulating the environment and randomly assigning this environment to the intervention group versus control groups. This randomized control design reduces the risk that the results will be contaminated by gene-environment correlations (rGE), and also by inadequate assessment and characterization of the environment (van IJzendoorn & Bakermans-Kranenburg, 2015; van IJzendoorn et al., 2011). Most importantly, a gene × intervention design provides causal evidence that genotype effects can be moderated by changes in the environment.

Previous studies that focused on the interactive effects of family-based interventions and candidate genes mainly focused on various markers of developmental psychopathology (Albert et al., 2015; Bakermans-Kranenburg, Van IJzendoorn, Pijlman, Mesman, & Juffer, 2008; Beach, Brody, Lei, & Philibert, 2010; Brett et al., 2015; Cleveland et al., 2015; van den Hoofdakker et al., 2012). In this context, particular attention was paid to the interactive effects of genes and interventions on problem behavior.
behaviors, especially on externalizing behavior problems from toddlerhood through adolescence (Albert et al., 2015; Bakermans-Kranenburg et al., 2008; Brett et al., 2015; Musci et al., 2014) and the use of substances such as tobacco and alcohol in adolescence (Beach et al., 2010; Brody et al., 2014; Brody, Yu, & Beach, 2015; Cleveland et al., 2015; Musci et al., 2015). Here, we extended the application of this powerful approach to the investigation of gene × intervention interactions with regard to neural mechanisms of selective attention in lower SES preschoolers.

In particular, we focused on the interactive effects of our family-based training program and serotonin transporter linked polymorphic region (5-HTTLPR) genotypes. Although other variants and classifications have been reported (Hu et al., 2006; Kraft, Slager, McGrath, & Hamilton, 2005; Nakamura, Ueno, Sano, & Tanabe, 2000), there are two predominant allelic variants of 5-HTTLPR: short allele and long allele (Heils et al., 1996). Studies that examined the link between 5-HTTLPR and various aspects of cognition suggested that the short-allele confers superior performance in various cognitive abilities, such as attention, working memory, cognitive control, and executive functioning, (Anderson, Bell, & Awh, 2012; Borg et al., 2009; Enge, Fleischhauer, Lesch, Reif, & Strobel, 2011, 2014; Strobel et al., 2007).

In general, superior behavioral performance was reported either for individuals who carried at least one copy of the short allele, or especially for individuals who were homozygous for the short allele (Anderson et al., 2012; Borg et al., 2009; Strobel et al., 2007). Similarly, the short-allele was linked to more enhanced neural mechanisms of attention and working memory, either directly (Enge, Fleischhauer, Lesch, Reif, et al., 2011), or in interaction with personality traits (Enge, Fleischhauer, Lesch, & Strobel,
In line with these findings, previously we reported that the short-allele of the 5-HTTLPR was linked to more enhanced neural mechanisms of selective auditory attention in lower SES preschoolers (Isbell, Bell, Hampton Wray, & Neville, 2015). Specifically, we found that children who carried at least one copy of the short allele showed larger ERP mean amplitudes for the selective attention effect, compared to their long-homozygote counterparts. However, there were no differences between children who carried either one or two copies of the short allele. These results implied that being homozygous for the long allele conferred risk for attenuated neural mechanisms of selective attention in preschoolers from lower SES families.

In the present study, we examined the interactive effects of 5-HTTLPR polymorphism and our family-based training program shown to improve neural mechanisms of selective attention in lower SES preschoolers (Neville et al., 2013). Participants were 71 lower SES preschoolers who attended Head Start. Children were randomly assigned to either the family-based training (Creating Connections) or the control group who received only Head Start services as usual (HS-alone).

Neural indices of selective auditory attention were measured with a well-established, child-friendly dichotic listening paradigm previously used with lower SES preschoolers (Neville et al., 2013; Stevens et al., 2009). In this task, children were presented with two stories concurrently and instructed to listen to only one of them. Identical probe stimuli were superimposed on both the attended and unattended stories. 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 collected before and after the 8-week intervention period.

Here, we categorized children either as short-carriers (children who carry at least one copy of the short-allele) or long-homozygotes (children who carry two long alleles). We compared the ERPs of selective attention between short-carriers versus long-homozygotes, randomly assigned to either the training or the control groups. We investigated the extent to which our effective family-based training program moderated the association between 5-HTTLPR and neural mechanisms of selective auditory attention.

Method

Participants

All children were recruited in Oregon, from 12 preschool sites of Head Start (HS), 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 was available for both pre-test and post-test sessions. Based on parent reports, children with diagnosed behavioral or neurological problems (e.g. 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, 1000, 2000 and 4000 Hz in both the right and left ears.

From a total of 97 children who were randomly assigned to either the family-based training program or the control group and from whom ERPs were collected, DNA data was available for 95 children. From this sample, we excluded children who had low ERP quality due to excessive EEG artifacts, less than 75 trials per condition, and/or less than
50% accuracy on the comprehension questions presented during the ERP tasks.

Accordingly, 15 children were excluded due to low ERP quality at pre-test and 9 children were excluded due to low ERP quality at post-test.

The final sample included 71 children (46 females) between the ages of 41 and 66 months (Mean = 55 months, SD = 6.1 months). 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. Children were randomly assigned to the training group or the control group. There were 36 children in the family-based training group (25 females) and 35 children (21 females) in 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 pre-test or post-test sessions. All families were paid for participation. Study procedures were approved by the University of Oregon Institutional Review Board.

**Creating Connections**

The family-based training program, previously known as Parents and Children Making Connections – Highlighting Attention, included both a child-directed component, and a parent directed component, described in detail in Neville et al. (2013). 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 (4-6 children, 2 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 Creating Connections included eight, 50-minute child sessions held concurrently with the parenting sessions in a separate room.

The parent component of Creating Connections was adapted from the Linking the Interests of Families and Teachers (LIFT) curriculum developed at the Oregon Social Learning Center (Reid, Eddy, Fetrow, & Stoolmiller, 1999). In each session, an interventionist delivered parenting strategies in small group format (the parents of 4-6 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, two-hour 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 HS classes over the eight-week evaluation period. Within the HS curriculum, there are no specific attention training components. Furthermore, although HS has a parent education component, there is no required parent-guidance curriculum and parents are contacted primarily to share information regarding HS policies and services available for families.
Genotyping

Buccal epithelial cells were collected with cotton swabs. For each child, 2 swabs were collected. Genotyping was conducted at the University of Oregon. Genomic DNA was isolated from the swabs, as described in Anderson et al. (2009). In the present study, allele frequencies of 5-HTTLPR were 62% for the l allele and 38% for the s allele. According to the Hardy-Weinberg equilibrium, the expected distribution of 5-HTTLPR genotypes would be 38% for l/l (n = 27), 47% for s/l (n = 33), and 15% for s/s (n = 10). In our sample, genotype frequencies were 30% for l/l (n = 21), 59% for s/l (n = 41), and 12% for s/s (n = 9). Chi-square tests revealed no significant differences between the observed frequencies and the expected frequencies according to the Hardy-Weinberg equilibrium (X2 (2) = 3.33, p = .19).

Electrophysiological assessment of selective auditory attention

We recorded ERPs in a spatial selective auditory attention ERP paradigm, described in detail in previous studies with lower SES preschoolers (Neville et al., 2013; Isbell, Hampton Wray, Neville, 2015). Briefly, sixteen narrative stories were digitally recorded (16 bit, 22 kHz). Half of the stories was read by a female narrator, and half was read by a male narrator at a normal speaking rate in a child-directed manner. The 16 stereo files differed in location (left/right audio speaker) and narration voice (male/female). Each file was 2.5-3.5 min in length. The stories were presented at an average of 60 dB 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. A small green arrow pointing to the left or right was superimposed at the bottom of each image to indicate the attended side.
Two probe stimuli were created by digitizing a token of the syllable ba spoken by a female voice (different from the female narrators) and scrambling the order of 4-6 ms segments of that token to create a nonlinguistic sound with similar acoustic characteristics. Both probes were 100 ms in length and were presented at 70 dB SPL. An equal number of linguistic and non-linguistic probes were presented across the stories. Approximately 200 linguistic and 200 nonlinguistic probes (N~180-206) were presented to each child. The probes were presented in a pseudo-random order at an interstimulus interval (ISI) of either 200, 500, or 1000 ms in one of the two channels. Probes were never presented simultaneously in the attended and unattended channels.

**Procedure.** Children arrived at the laboratory with their parents and were provided time to acclimate to their environment before placement of the electrode cap began. Once the EEG cap was in place, children were seated in a comfortable chair in an electrically shielded, sound-attenuating booth. They were instructed not to move or lean from side to side. 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 approximately 57 inches in front of the child. Before the data were recorded, children received instructions to attend to the story played from one speaker while ignoring the story presented on the other speaker. They were told either a male or a female speaker would narrate the story. An arrow at the bottom of the screen would point to the speaker they should attend to and the attended story would correspond to the pictures on the screen. They were also instructed that unrelated sounds (‘bas’ and ‘buzzes’) would be presented but should be ignored.

At the beginning of each story, participants were presented with a sound sample of
the narrator to which they should attend. They were instructed to listen carefully to the story from this narrator and ignore the other voice. Participants attended to a total of four narratives selected from the four story sets, attending twice to the right side and twice to the left side (order either RLLR or LRRL). All participants were presented with two stories narrated by a female and two stories narrated by a male. For the duration of the experiment, participants 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 participants 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 an incorrect response. Only children who performed with at least 50% accuracy on the comprehension questions were included in the EEG analyses.

**EEG recording and analysis.** EEG was recorded at a sampling rate of 1024 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, Amsterdam, Netherlands). 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 re-referenced off-line to the algebraic average of the left and right mastoid. Left and right horizontal eye channels were re-referenced to one another.

ERP analyses were carried out using EEGLAB (Delorme & Makeig, 2004) and ERPLAB (Lopez-Calderon & Luck, 2014). Data were down-sampled to 256 Hz to speed computation and band-pass filtered from 0.1 to 40 Hz. The EEG data was epoched
offline between 100 ms prior to and 500 ms after stimulus onset, using the first 100 ms as the pre-stimulus-onset baseline. On the basis of the visual inspection of the epoched EEG data, individual artifact rejection parameters were selected for each child. Artifact rejection was executed using 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 for almost all participants. Trained research assistants performed a subsequent artifact rejection step to reject additional epochs containing eye movements and muscle artifacts.

The mean amplitudes of ERPs were measured between 100 to 200 ms post-stimulus onset, collapsed across the linguistic and nonlinguistic conditions, consistent with previous studies using this paradigm with young children from low income families (Neville et al., 2013; Stevens et al., 2009; Stevens et al., 2014). ERP attention effect was operationalized as the mean amplitude difference between the ERPs to the probes in the attended versus unattended stories (attended - unattended). 24 electrodes were included in the analyses, initially grouped into three rows of 8 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.

Results

At pre-test, children were randomly assigned to the Creating Connections program or the HS-alone comparison group. We further categorized children based on 5-HTTLPR genotypes. When the genotype groups were divided into the training and comparison groups, there were only a few short-homozygous children in each group (Creating Connections n = 5, HS-alone n = 4). Since we previously did not find any differences in ERPs of selective attention between children who carried one or two copies of the short
allele, in all analyses, short-homozygous children were included within the short-carrier group, along with the children who carried only one short allele. This categorization resulted in the following four groups: long homozygotes in the training group (n = 11), long homozygotes in the control group (n = 10), short-carriers in the training group (n = 25), and short-carriers in the control group (n = 25). Exploratory data analyses were conducted to ensure there were no outliers for ERPs (3 SD +/-). No outliers were detected either at pre-test or post-test, across all children or within the 5-HTTLPR x training groups. Therefore, all children with quality ERP data were included in the subsequent analyses.

To test for differences between these four groups in age, number of comprehension questions answered correctly at pre-test and post-test, and SES, we conducted univariate ANOVAs with two between group factors: training group (Creating Connections vs. HS-alone) and 5-HTTLPR genotype (long-long vs. short-carriers). The descriptives (means and standard deviations) are reported in Table 1.
Table 1. Descriptives for age, pre-test comprehension accuracy, post-test comprehension accuracy, and SES.

<table>
<thead>
<tr>
<th></th>
<th>HS-Alone</th>
<th>Creating Connections</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>L-homozygote</td>
<td>S-carrier</td>
</tr>
<tr>
<td>n</td>
<td>mean</td>
<td>n</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>10</td>
<td>4.50</td>
</tr>
<tr>
<td></td>
<td>.43</td>
<td>.56</td>
</tr>
<tr>
<td>Pre-test</td>
<td>8.20</td>
<td>9.00</td>
</tr>
<tr>
<td>comprehension</td>
<td>1.32</td>
<td>1.53</td>
</tr>
<tr>
<td>Post-test</td>
<td>9.10</td>
<td>9.24</td>
</tr>
<tr>
<td>comprehension</td>
<td>1.66</td>
<td>1.67</td>
</tr>
<tr>
<td>SES</td>
<td>10</td>
<td>30.95</td>
</tr>
<tr>
<td></td>
<td>10.34</td>
<td>11.97</td>
</tr>
</tbody>
</table>

There were no significant differences between the four groups in age or number of comprehension questions answered correctly at pre-test and post-test, $ps > .45$. SES information was incomplete for 6 children. For children whom complete SES information was available, there were no significant differences between the four groups in SES, $p = .99$. The summary statistics for these ANOVAs are provided in Supplementary Table 1. There were no gender differences between the training x genotype groups, $\chi^2(3) = 5.30, p = .15$. 

81
For the ERPs of selective attention effect, we first conducted mixed model ANOVAs. Initially, all analyses were conducted with electrode location included as a within-group factor. Across all analyses, there was a main effect of electrode location, such that the ERPs were more positive in amplitude over the anterior and central electrodes. However, since there were no interactions between electrode locations and the other factors (attention, 5-HTTLPR, training), this factor was dropped from the analyses, and all subsequent analyses were conducted with an aggregate ERP measure derived from the average of the 24 electrodes. For ANOVAs, partial $\eta^2$ was used to measure effect sizes. For pairwise comparisons, effect sizes were computed with Cohen’s $d$.

The analyses of pre-test and post-test ERPs were conducted with between-group ANOVAs, including the between-group factors of training group (Creating Connections vs. HS-alone) and 5-HTTLPR genotype (short-carriers vs. long-homozygotes). The descriptives for the pre-test and post-test ERPs are reported in Table 2.
Table 2. ERP mean amplitude and standard deviations (SD) of the selective attention effect (µV) at pre-test, post-test, and gain from pre-test to post-test, for the training x 5-HTTLPR groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Pre-test</th>
<th>Post-test</th>
<th>Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>HS-alone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-carriers</td>
<td>.51</td>
<td>1.29</td>
<td>.52</td>
</tr>
<tr>
<td>Long-homozygotes</td>
<td>-.39</td>
<td>1.07</td>
<td>-.14</td>
</tr>
<tr>
<td>Creating Connections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-carriers</td>
<td>.41</td>
<td>.96</td>
<td>.47</td>
</tr>
<tr>
<td>Long-homozygotes</td>
<td>-.54</td>
<td>1.37</td>
<td>1.05</td>
</tr>
</tbody>
</table>

Figure 1 shows the bar graphs for the ERP mean amplitudes of selective auditory attention effect for pre-test and post-test for training x 5-HTTLPR groups. At pre-test, there was a significant effect of genotype on ERPs of selective attention, $F(1, 67) = 9.38$, $p < .01$, partial $\eta^2 = .12$. Children who were homozygous for the long allele had more attenuated ERPs for the selective attention effect than short-allele carriers, $d = -.81$. As expected in a random assignment design, there was no main effect of training group at pre-test, $F(1, 67) = .16$, $p = .69$, partial $\eta^2 = < .01$. There was also no significant interaction between genotype and training, $F(1, 67) = .01$, $p = .92$, partial $\eta^2 < .01$. 
Figure 1. ERP mean amplitudes of selective attention effect (µV) at pre-test and post-test, for the 5-HTTLPR groups, assigned to either HS-alone or Creating Connections groups. Error bars represent +/- 1 SE. Positive ERP mean amplitudes denote more pronounced neural indices of selective attention.

Initially, in the ANOVA analysis for post-test ERPs, pre-test ERPs were entered as a covariate. However, pre-test ERP was not a significant covariate $F(1, 66) < .01, p = .93, partial \eta^2 = < .01$. For parsimony and easier interpretation of ERP grand averages, this covariate was dropped from further analyses. At post-test, there was no significant main effect of genotype on ERPs, $F(1, 67) = .03, p = .87, partial \eta^2 < .01$. However,
there was a significant main effect of training on ERPs, $F(1, 67) = 5.22, p = .03$, partial $\eta^2 = .07$. Children in the Creating Connections group had larger post-test ERP mean amplitudes than children in the HS-alone group, $d = .32$. There was also a significant interaction between genotype and training, $F(1, 67) = 6.04, p = .02$, partial $\eta^2 = .08$.

To unpack the interaction between training and genotype, we conducted simple effect tests. To control for multiple comparisons, we set the alpha value at $p = .025$. At post-test, there were no significant differences in ERPs of selective attention between the short-carriers in Creating Connections or HS-alone groups, $F(1,67) = .03, p = .88, d = .05$. In contrast, there was a significant difference between ERPs of selective attention between long-homozygotes assigned to Creating Connections group versus HS-alone group, $F(1, 67) = 7.98, p < .01, d = 1.19$. Long-homozygotes in the Creating Connections training had larger mean amplitudes for ERP indices of selective attention than long-homozygotes in the HS-alone group.

We did not have an a priori prediction about whether the training program would result in larger post-test ERPs in the long-homozygotes or short-carriers. However, to determine whether one genotype group outperformed the other following training, we ran a post-hoc independent samples t-test. This t-test did not reveal any significant differences between the long-homozygotes and short-carriers within the training group ($t(34) = 1.55, p = .13$), but the effect size for this difference was moderate ($d = .56$).

To supplement these pre-test and post-test mixed model ANOVA analyses, we initially conducted a series of within-group ANOVAs to further delineate the effects of selective attention on ERPs at pre-test and post-test, separately for each genotype group by training assignment. These initial analyses were conducted with electrode location
included as a within-group factor. Across all analyses, there was a main effect of electrode location in each group, such that the ERPs were more positive in amplitude over the anterior and central electrodes. However, since there were no interactions between attention and electrode locations, this factor was dropped from the analyses, and all subsequent analyses were conducted with the aggregate of 24 electrodes. Consequently, the within-group group analyses included only one factor: attention (attended vs. unattended). Therefore, paired-samples t-test statistics are reported. The summary statistics for these t-tests are presented in Table 3.

Table 3. Paired-samples t-test statistics comparing ERP mean amplitudes for the attended versus unattended conditions, at pre-test and post-test, by training x 5-HTTLPR groups

<table>
<thead>
<tr>
<th>Group</th>
<th>df</th>
<th>Pre-test</th>
<th></th>
<th></th>
<th></th>
<th>Post-test</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>t</td>
<td>p</td>
<td>d</td>
<td></td>
<td>t</td>
<td>p</td>
</tr>
<tr>
<td>HS-alone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-homozygotes</td>
<td>9</td>
<td>-1.16</td>
<td>.28</td>
<td>-.34</td>
<td></td>
<td>-1.16</td>
<td>.28</td>
<td>-.34</td>
</tr>
<tr>
<td>Short-carriers</td>
<td>25</td>
<td>1.96</td>
<td>.06</td>
<td>.47</td>
<td></td>
<td>1.96</td>
<td>.06</td>
<td>.47</td>
</tr>
<tr>
<td>Creating Connections</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-homozygotes</td>
<td>11</td>
<td>-1.32</td>
<td>.22</td>
<td>-.51</td>
<td></td>
<td>1.32</td>
<td>.22</td>
<td>-.51</td>
</tr>
<tr>
<td>Short-carriers</td>
<td>25</td>
<td>2.16</td>
<td>.04</td>
<td>.42</td>
<td></td>
<td>2.16</td>
<td>.04</td>
<td>.42</td>
</tr>
</tbody>
</table>

Note: A negative t statistic denotes that the mean amplitude of ERPs in the attended condition were smaller (less positive) than the mean amplitude of ERPs in the unattended condition.
Figure 2 shows pre-test ERPs at a representative mediocentral electrode site (C5). At pre-test, there was no significant selective attention effect in the long-homozygotes assigned either to the HS-alone group or the Creating Connections group, $p = .22$ and $p = .28$, respectively. There was a trend toward statistical significance in the short-carriers assigned to the HS-alone group, $p = .06$, and a significant selective attention effect in the short-carriers assigned to the Creating Connections group, $p = .04$.

![Figure 2. Pre-test grand-average ERP waveforms showing ERPs elicited by the attended and unattended conditions at a representative central electrode for 5-HTTLPR genotype groups assigned to the HS-alone and Creating Connections groups. For this, and all subsequent ERP figures, negative is plotted upward.](image_url)
Figure 3 shows ERPs at the same representative electrode site at post-test. At post-test, the effect of selective attention on ERPs was significant in both groups of short-carriers, regardless of whether they were assigned to the Creating Connections or the HS-alone groups, $p = .02$ and $p = .02$, respectively. However, among the long-homozygotes, there was a significant ERP selective attention effect only in children who were assigned to the Creating Connections group, $p = .02$. Selective attention did not significantly modulate auditory ERPs in long-homozygotes who were assigned to the HS-alone group, $p = .47$.

Figure 3. Post-test grand-average ERP waveforms showing ERPs elicited by the attended and unattended conditions at a representative central electrode for 5-HTTLPR genotype groups assigned to the HS-alone and Creating Connections groups.
Discussion

Prior research demonstrated interactive effects of family-based interventions and candidate genes on various markers of developmental psychopathology (Albert et al., 2015; Bakermans-Kranenburg et al., 2008; Beach et al., 2010; Brett et al., 2015; Cleveland et al., 2015; van den Hoofdakker et al., 2012). Here we extended this powerful approach to the investigation of gene × training interactions with regard to the neuroplasticity of a fundamental cognitive ability. Specifically, we examined the interactive effects of 5-HTTLPR and an effective family-based training program, Creating Connections, which was previously shown to enhance neural mechanisms of selective auditory attention in lower SES preschoolers (Neville et al., 2013).

At pre-test, lower SES children homozygous for the long allele showed more attenuated neural indices of selective attention than children with at least one short allele. This result was consistent with the findings of previous studies that reported superior performance for short-allele carriers in several aspects of cognition, such as attention, working memory, and executive functioning (Anderson et al., 2012; Borg et al., 2009; Enge, Fleischhauer, Lesch, Reif, et al., 2011).

There were no differences in ERP indices of selective attention between the Creating Connections and HS-alone groups at pre-test. However, after a relatively short time frame of 8 weeks, differences were observed between these groups. Children who were assigned to the Creating Connections program showed more enhanced neural indices of selective attention than children in the HS-alone group. This effect was qualified by an interaction between 5-HTTLPR and training group. At post-test, ERPs of selective attention did not differ between the short-carriers assigned to the Creating
Connections or the HS-alone group. In contrast, after participating in the Creating Connections program, long-homozygotes had more enhanced neural indices of selective attention at post-test than their long-homozygotes in the HS-alone group. Furthermore, the neural indices of selective attention were no longer more attenuated in the long-homozygotes in comparison to their short-carrier peers in the training group. These results suggest that an effective training program can mitigate the unfavorable outcomes associated with being homozygous for the long allele of 5-HTTLPR, with respect to neural mechanisms of selective attention in lower SES preschoolers.

Our study is among the first to illustrate a causal pathway for how supportive environments can moderate genetic effects on neural mechanisms of cognition in children. It has been argued that one of the advantages of gene × intervention studies is that they do not require as large sample sizes as would be needed in gene × environment studies in which the environment is not controlled (van IJzendoorn et al., 2011). Consistent with this argument, the randomized controlled design of our study and the powerful electrophysiological measures allowed us to document prominent gene × intervention effects in young children even with limited sample sizes.

Previous gene × intervention studies particularly focused on the extent to which certain genotypes confer differential responsiveness to intervention effects (Albert et al., 2015; Bakermans-Kranenburg et al., 2008; Brett et al., 2015; Cleveland et al., 2015). A few studies that tested this differential susceptibility model in the context of parenting interventions reported differential benefits for children and youth who either carried at least one short-allele (Brody, Beach, Philibert, Chen, & Murry, 2009) or were short-homozygous (Brett et al., 2015; Drury et al., 2012). In the present study, we did not find
support for the hypothesis that the carriers of the short-allele are differentially susceptible to the effects of interventions. Training group status did not make a difference for the short-carriers. In fact, the long-homozygotes and not the short-carriers appeared to benefit more from participating in the training program.

One potential explanation for why we did not find differential responsiveness to the training in short-carriers is that our study focused on a cognitive ability, instead of a mental health index. Traditionally, the short-allele of 5-HTTLPR has been linked to unfavorable outcomes in terms of psychopathology, especially in the face of adverse environmental conditions (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010; Karg, Burmeister, Shedden, & Sen, 2011). Not surprisingly, the extent to which short-carriers show differential susceptibility to environmental influences has been tested mainly for socioemotional outcomes and psychopathology in children and adolescents (Cicchetti & Rogosch, 2012; Dalton, Hammern, Najman, & Brennan, 2014; Hankin et al., 2011; van Ijzendoorn, Belsky, & Bakermans-Kranenburg, 2012).

However, with respect to cognitive abilities, the short allele has been linked to superior performance (Anderson et al., 2012; Borg et al., 2009; Enge, Fleischhauer, Lesch, Reif, et al., 2011). Likewise, the short-carrier preschoolers in our study had enhanced neural mechanisms of selective attention at pre-test relative to their long-homozygote peers. Indeed, among the children assigned to the training group, short-carriers already showed a significant modulation of ERPs by selective attention at pre-test, while this significant selective attention effect was absent in the long-homozygotes. Only after participating in the Creating Connections program, the long-homozygotes showed a significant modulation of ERPs by selective attention. Therefore, it is plausible
that the short-carriers might not have needed a boost in selective attention as much as the long-homozygote children. Yet, it is also plausible that being homozygous for the long allele confer differential sensitivity to training effects, at least in the context of cognitive abilities. Although we did not find a significant difference between the long-homozygotes and short-carriers in the training group at post-test, the effect size of this comparison was moderate, favoring the long-homozygotes. Further investigations with independent and larger samples are warranted to determine whether such an effective training program either helps long-homozygous children catch up with short-carriers, or outperform them.

A larger and more diverse sample would also allow us to test for any moderation effects of race and gender on genetic influences. The lower SES children in our sample were predominantly Caucasian. As the frequency and functional characteristics of 5-HTTLPR tend to differ across racial and ethnic groups (Chiao & Blizinsky, 2010; Davies & Cicchetti, 2014; Odgerel, Talati, Hamilton, Levinson, & Weissman, 2013; Williams et al., 2003), it remains to be investigated the extent to which our results would generalize to other populations of lower SES children. In addition, the relatively small sample size prevented us from testing for gender specific effects. It has been shown that gender can moderate the interactive effects of 5-HTTLPR and supportive parenting (Dalton et al., 2014; Li, Berk, & Lee, 2013). Therefore, it also remains to be investigated whether our results would be qualified by gender differences.

Despite these limitations due to our restricted sample sizes, the present study provides initial evidence for how an efficient family-based training program can moderate the influence of 5-HTTLPR on neural mechanisms of selective auditory
attention in lower SES preschoolers. The importance of selective attention for fundamental cognitive abilities and academic outcomes (Commodari & Di Blasi, 2014; Gazzaley, 2011; Giuliano et al., 2014; Steele et al., 2012; Stevens & Bavelier, 2012) warrants further research with regard to the interactive effects of genes and trainings on the development and plasticity of this fundamental brain function in lower SES children, who are at heightened risk for deficits in selective attention (Stevens et al., 2009; Stevens et al., 2014). One crucial future direction is the investigation of how the moderation of genetic influences is mediated by specific training components. It has been shown that 5-HTTLPR polymorphism interacts with supportive family environments in predicting socioemotional development and resilience to psychopathology (Dalton et al., 2014; Hankin et al., 2011; Kochanska, Kim, Barry, & Philibert, 2011; Li et al., 2013). It remains to be assessed which specific parenting practices that are targeted and improved by a family-based training program mediate the interactive effects of 5-HTTLPR and the family-based training.

Another important future direction is the assessment of parental 5-HTTLPR genotypes as parents themselves may differentially benefit from participating in a family-based training program as a result of their genotypic characteristics. Indeed, it has been demonstrated that the 5-HTTLPR genotypes of parents influence their parental behavior, especially in interaction with intermarital conflict and parenting stress (Beaver & Belsky, 2012; Mileva-Seitz et al., 2011; Sturge-Apple, Cicchetti, Davies, & Suor, 2012). Previously, we documented that after participating in the family-based training program, parents showed greater reductions in parenting stress in comparison to control groups (Neville et al., 2013). Therefore, another potential mediator is the interactive effects of
parental 5-HTTLPR genotype and reductions in family stress brought upon by a successful family-based training program.

It also remains crucial to investigate how 5-HTTLPR interacts with other candidate polymorphisms. Previous studies reported gene × intervention effects for polymorphisms of various candidate genes, such as dopamine D4 receptor (DRD4) gene (Bakermans-Kranenburg et al., 2008; Beach et al., 2010; Brody et al., 2014; Kegel, Bus, & van IJzendoorn, 2011; Plak, Kegel, & Bus, 2015), dopamine active transporter (DAT1) gene (van den Hoofdakker et al., 2012), and brain-derived neurotrophic factor (BDNF) gene (Drury et al., 2012; Musci et al., 2014). As no single candidate gene can explain the entirety of any cognitive ability or responsiveness to interventions, investigating the interactions among these polymorphisms carries the potential to provide a more comprehensive account of the genetic underpinnings of individual differences and the neuroplasticity of selective attention in lower SES preschoolers.

Conclusions

The present study applied the powerful gene × intervention approach to investigate the interactive effects of 5-HTTLPR and a family-based training program designed to improve brain systems for selective attention in lower SES preschoolers. We found that the long-homozygote children, who initially displayed more attenuated neural indices of selective auditory attention than their short allele carrier peers, showed prominent gains in a relatively short time frame of 8 weeks, but only if they were randomly assigned to the training program. Following the training, these long-homozygotes were indistinguishable from their short-carrier peers. These findings suggest that an effective family-based training can moderate the genetic influences of 5-HTTLPR on the neural
mechanisms of selective attention. Further research is warranted to elucidate the intricate interactions between genetic and familial influences on neural mechanisms of selective attention in lower SES children.
CHAPTER V

GENERAL DISCUSSION

Summary of Findings

This dissertation research focused on neural mechanisms of selective auditory attention in lower SES preschoolers. The series of studies presented in this dissertation investigated the individual differences, genetic influences, and gene × intervention interactions in the context of development and neuroplasticity of selective auditory attention. To this end, a multi-method approach was adopted, combining ERPs, behavioral measures, molecular genetics, and a randomized, controlled intervention design.

In the first study (Chapter II), individual differences in neural mechanisms of selective auditory attention was studied, in association with nonverbal cognitive abilities. ERPs were recorded from lower SES preschoolers in a dichotic listening paradigm and nonverbal IQ performance was assessed as a measure of nonverbal cognition. The attention effect, i.e. the difference in ERP mean amplitudes elicited by identical probes embedded in stories when attended versus unattended, was significantly correlated with nonverbal IQ scores. Larger, more positive attention effects over the anterior and central electrode locations were associated with superior nonverbal IQ performance. Our findings provide initial evidence for prominent individual differences in neural indices of selective attention in lower SES children. Furthermore, our results indicate a noteworthy relationship between neural mechanisms of selective attention and nonverbal IQ performance in lower SES preschoolers.

In the second study (Chapter III), genetic influences on these prominent individual
differences were examined. Specifically, the relationship between 5-HTTLPR polymorphism and neural mechanisms of selective auditory attention was assessed. It was found that the ERP mean amplitudes for the selective attention effect was larger, more positive in the short-carriers than the long-homozygotes. While the short-carrier children showed a more pronounced ERP selective attention effect compared to the long-homozygotes, there were no notable differences between the children who carried one versus two copies of the short allele. These results suggested that the short-allele of 5-HTTLPR signify more favorable outcomes for neural mechanisms of selective attention in lower SES preschoolers.

In the third study (Chapter IV), these genetic influences were investigated in the context of a family-based training program, previously shown to improve neural mechanisms of selective attention in lower SES preschoolers (Neville et al., 2013). The randomized controlled design of our study and the powerful electrophysiological measures revealed prominent gene × intervention effects in young children, even with the limited sample sizes in this study. At pre-test, influences of 5-HTTLPR were evident, as long-homozygous children showed more attenuated ERPs for the selective attention effect than children who carried at least one short allele. In a relatively short time frame of 8 weeks, the long-homozygote children showed greater enhancements in neural mechanisms of selective attention in comparison to the long-homozygotes assigned to the control group. Furthermore, following the training, these long-homozygotes were indistinguishable from their short-carrier counterparts. These results suggest that an effective training program can mitigate the unfavorable influences of 5-HTTLPR on neural mechanisms of selective attention in lower SES preschoolers. This study is among
the first to illustrate a causal pathway for how supportive environments can moderate genetic effects on neural mechanisms of cognition in children.

**Implications and Future Directions**

As described in the General Introduction, there has been a paucity of research addressing individual differences in brain functioning among lower SES children. Overall, the studies presented in this dissertation contribute to this understudied area of research. Across the studies, we documented considerable amount of variability in neural indices of selective attention among lower SES preschoolers. These findings emphasize that lower SES children do not constitute a homogenous group of at-risk children with similar profiles of vulnerability in neural mechanisms of selective attention. As such, these results underscore that young children from lower SES families begin education and training programs with differing levels of need for improvement of selective attention. It is possible that programs designed to promote selective attention abilities are particularly more beneficial for children who start off with weaker selective attention abilities, indicated by neural markers of this cognitive process. Moreover, it is also possible that additional targeted trainings may be required for children who show deficits in selective attention, to ensure that these children are able to maximally benefit from education and training curriculums. Further research is warranted to determine how individual differences in neural mechanisms come to play in responsiveness to training and education programs.

The ERP methods used in this dissertation provided exquisite temporal resolution for the early neural mechanisms of selective attention in lower SES preschoolers. However, due to sample characteristics required by this powerful method and in
particular by the dichotic listening paradigm used to measure ERPs, only typically developing, right-handed monolingual native speakers of English were included across studies. These restrictions prevented various potential confounds of ERP studies and provided high quality ERP data from such a young population. However, these methodological restrictions also interfered with the inclusion of a more diverse population of lower SES children in this dissertation. Such lack of diversity was especially pertinent to the generalizability of findings on genetic influences and gene × intervention findings. In particular to 5-HTTLPR, it has been demonstrated that the frequency and functional characteristics of this polymorphism may differ across racial and ethnic groups (Chiao & Blizinsky, 2010; Odgerel, Talati, Hamilton, Levinson, & Weissman, 2013; van Ijzendoorn, Belsky, & Bakermans-Kranenburg, 2012). It is crucial to determine to what extent our results across the studies would generalize to more diverse populations of lower SES children.

Another important future direction is the investigation of environmental factors that account for individual differences in neural mechanisms of selective attention. In this regard, one promising line of investigation is the assessment of cumulative risk. In comparison to their higher SES counterparts, lower SES children experience more adverse familial and environmental conditions concurrently (Evans, 2004; Evans, Li, & Whipple, 2013). Greater accumulation of familial and environmental risk factors, as measured by cumulative risk indices, has been linked to poorer outcomes in social and emotional development (Appleyard, Egeland, Dulmen, & Alan Sroufe, 2005; Deater-Deckard, Dodge, Bates, & Pettit, 1998; Ziv & Sorongon, 2011), cognitive development (Burchinal, Roberts, Hooper, & Zeisel, 2000; Mistry, Biesanz, Taylor, Burchinal, & Cox,
Moreover, greater early cumulative risk is linked to poorer academic outcomes from elementary school through high school (Gutman, Sameroff, & Cole, 2003), and more negative outcomes for overall educational attainment and being employed in early years of adulthood (Pungello et al., 2010). Such links between risk accumulation and poorer outcomes across various domains raise the possibility that cumulative risk may account for why some children display greater vulnerability in neural mechanisms of selective attention among lower SES children.

On the other hand, although cumulative risk yields adverse outcomes for children in general, various protective factors play a role in alleviating such adversity. Indeed, it has been demonstrated that factors such as supportive parenting practices (Lengua, Honorado, & Bush, 2007; Mistry, Benner, Biesanz, Clark, & Howes, 2010; Pungello et al., 2010), and Head Start attendance (Hubbs-Tait et al., 2002; Lee, 2011) can buffer the effects of cumulative risk on cognitive development. Therefore, future research on the associations between cumulative risk and selective attention, and how these associations are moderated by protective factors, carry the promise of elucidating pathways through which individual differences in neural mechanisms of selective attention emerge in lower SES children and consequently inform prevention and education programs.

As discussed in Chapters III and IV, this dissertation specifically focused on one polymorphism, 5-HTTLPR. It is crucial to reckon the importance of investigating the contributions of other candidate genes linked to attentional abilities in children, such as COMT, DRD4, and DAT1 (Rueda, Rothbart, McCandliss, Saccomanno, & Posner, 2005;
In addition, it is essential to investigate the contributions of candidate genes that account for individual differences in responsiveness to interventions, once again including genes such as DRD4 and DAT1 (Bakermans-Kranenburg, Van IJzendoorn, Pijlman, Mesman, & Juffer, 2008; Beach, Brody, Lei, & Philibert, 2010; Brody et al., 2014; Kegel, Bus, & van IJzendoorn, 2011; Plak, Kegel, & Bus, 2015; van den Hoofdakker et al., 2012), and BDNF (Drury et al., 2012; Musci et al., 2014). Examining potential gene × gene interactions would provide a more comprehensive account for genetic influences on neural mechanisms of selective attention and the extent to which these influences can be moderated by efficacious trainings and interventions.

Recent advances in research on epigenetics suggest yet another promising line of inquiry. It has been demonstrated that early life experiences can lead to epigenetic changes, mainly through DNA methylation (Lutz & Turecki, 2014; Szyf & Bick, 2013). Especially early and chronic life stress has been linked to differential DNA methylation profiles throughout development (Essex et al., 2013; Naumova et al., 2012; Suderman et al., 2012). In accordance, differential methylation profiles have been observed in individuals raised in lower SES households compared to their higher SES counterparts (Borghol et al., 2012; Tehranifar et al., 2013). These preliminary yet promising results call for further investigation of how risk factors, such as cumulative risk, and protective factors, such as supportive parenting and early childhood programs, moderate genetic influences on neural mechanisms of selective attention in lower SES preschoolers.

The studies presented in this dissertation contribute to elucidating individual differences in development and neuroplasticity of selective auditory attention in lower
SES preschoolers, and provides several new directions for future research. Given that selective attention is a critical component of various other cognitive abilities and academic foundations, it remains crucial to characterize what factors account for individual differences in risk and resilience for this ability in preschoolers from lower SES families. Future research in this area carries the promise of informing preventive and educational programs that target lower SES preschoolers.
APPENDIX A

SUPPLEMENTARY INFORMATION FOR CHAPTER III

Supplementary Table 1

Analyses of variance for the ERP mean amplitudes of the attention effect by 5-HTTLPR genotypes (l/l, s/l, and s/s), with age and gender included as covariates

<table>
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<tr>
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<th>$F$</th>
<th>df</th>
<th>$p$</th>
<th>partial $\eta^2$</th>
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<tr>
<td>Age</td>
<td>1.11</td>
<td>1, 116</td>
<td>.30</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>Gender</td>
<td>1.58</td>
<td>1, 116</td>
<td>.21</td>
<td>.01</td>
</tr>
<tr>
<td>5-HTT</td>
<td>4.18</td>
<td>2, 116</td>
<td>.02*</td>
<td>.07</td>
</tr>
<tr>
<td>Electrode location</td>
<td>.16</td>
<td>2, 232</td>
<td>.74</td>
<td>&lt; .01</td>
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<tr>
<td>Electrode location x age</td>
<td>.30</td>
<td>2, 232</td>
<td>.64</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>Electrode location x gender</td>
<td>.28</td>
<td>2, 232</td>
<td>.65</td>
<td>&lt; .01</td>
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<tr>
<td>Electrode location x 5-HTT</td>
<td>.34</td>
<td>4, 232</td>
<td>.76</td>
<td>&lt; .01</td>
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</table>

* $p < .05$
Supplementary Figure 1. Grand-average ERP waveforms showing ERPs elicited by the attended and unattended conditions for the long-long children. For this, and all subsequent ERP figures, negative is plotted upward.
Supplementary Figure 2. Grand-average ERP waveforms showing ERPs elicited by the attended and unattended conditions for the short-long children.
Supplementary Figure 3. Grand-average ERP waveforms showing ERPs elicited by the attended and unattended conditions for the short-short children.
Supplementary Table 1. Summary of the statistics from the univariate ANOVAs comparing age, pre-test comprehension accuracy, post-test comprehension accuracy, and SES between training groups by genotype.

<table>
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<tr>
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<th>$df$</th>
<th>$p$</th>
<th>partial $\eta^2$</th>
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<tr>
<td><strong>Age</strong></td>
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<td>training</td>
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<td>1, 67</td>
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<td>&lt; .01</td>
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<td>.65</td>
<td>&lt; .01</td>
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<td>training x 5-HTTLPR</td>
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<td>1, 67</td>
<td>.76</td>
<td>.001</td>
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<td><strong>Pre-test comprehension</strong></td>
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<td></td>
<td></td>
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<tr>
<td>training</td>
<td>.02</td>
<td>1, 67</td>
<td>.88</td>
<td>&lt; .001</td>
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<td><strong>Post-test comprehension</strong></td>
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<td></td>
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<td>training</td>
<td>.21</td>
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<td>.65</td>
<td>&lt; .01</td>
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<td>.02</td>
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<tr>
<td>training</td>
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<td>1, 61</td>
<td>.99</td>
<td>&lt; .001</td>
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<tr>
<td>5-HTTLPR</td>
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<td>1, 61</td>
<td>.98</td>
<td>&lt; .001</td>
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<td>training x 5-HTTLPR</td>
<td>.03</td>
<td>1, 61</td>
<td>.85</td>
<td>.001</td>
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</table>
Supplementary Figure 1. Pre-test grand-average ERP waveforms showing ERPs elicited by the attended and unattended conditions for the short-carriers in the HS-alone group. For this, and all subsequent ERP figures, negative is plotted upward.
Supplementary Figure 2. Post-test grand-average ERP waveforms for the short-carriers in the HS-alone group.
Supplementary Figure 3. Pre-test grand-average ERP waveforms for the long-homozygotes in the HS-alone group.
Supplementary Figure 4. Post-test grand-average ERP waveforms for the long-homozygotes in the HS-alone group.
Supplementary Figure 5. Pre-test grand-average ERP waveforms for the short-carriers in the Creating Connections group.
Supplementary Figure 6. Post-test grand-average ERP waveforms for the short-carriers in the Creating Connections group.
Supplementary Figure 7. Pre-test grand-average ERP waveforms for the long-homozygotes in the Creating Connections group.
Supplementary Figure 8. Post-test grand-average ERP waveforms for the long-homozygotes in the Creating Connections group.
REFERENCES CITED

Chapter I


**Chapter II**


123


Chapter III


Chapter IV


138


**Chapter V**


