The University Of Sheffield.

Sensory Processing and Cortical Plasticity in Typical and Atypical Development

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A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy

The University of Sheffield

Faculty of Science

Department of Psychology

June, 2019

Acknowledgements

It’s only when you write something like this, that you realise how truly lucky you are to be surrounded by such an amazing group of people, and how your life is better for having them in it.

Many thanks firstly go to my supervisors, Dr Liat Levita and Prof. Elizabeth Milne, whose knowledge, support, and encouragement have been invaluable throughout these past few years, and I aspire to become the role model that they both were for me.

I’d like to thank my fellow colleagues from the Developmental Affective Neuroscience Lab, with a particular special mention for Dr Samantha Linton and Dr Isobel Williams who have given me the greatest advice and been so uplifting. There are many people from the Department of Psychology who have helped me in so many ways, and I’d like to thank all of the following people for giving me their friendship, support and humour: Meghann Matthews, Dr Jodie Stevenson, Stephanie Powell, Stanislava Naneva, Dr Ali Aytemur, Jose Sepulveda, Ligia Orellana, Ana-Maria Coneo, Dr Lars Hunger, Alejandro Jimenez, Dr Timothy Riley, Dr Caroline Treweek, Eema Al-Jawahiri, Emma Morgan, Rachel Evans, Dr Kate Adkins, and Dr Kirsten Bartlett.

I would also like to thank my friends, Nicola Robertson, Ruby Oates, Dr Eleanor Little, and Rachael Burgoyne, as well as those who sparked my interest in studying psychology with their fantastic teaching - Phil Badger and Kylie McAteer. I am also very grateful to all the participants and schools who took part in my research studies. Without them, this thesis would not exist.

Above all else, I would like to thank my family. To my brother, Callum, for the little things like always supplying me with cups of tea, picking me up after evening testing sessions, and distracting Stanley long enough for me to finish a paragraph! But mostly to my mum, the best friend I’ll ever have or could wish for, who has given everything to me so that I can achieve my goals and live a happy and fulfilled life. I only hope to be able to give you all you deserve (starting with that holiday!).

Thesis abstract

Impairments in sensory modulation can lead to under- or over-responsiveness and are often associated with mental health conditions. Whilst there is a wealth of research documenting sensory processing difficulties (SPDs) in clinical populations, less is known about the role of sensory responsivity in the psychological and behavioural outcomes of neurotypical (NT) populations, with no research available on sensory responsivity in NT adolescents. Consequently, this doctoral thesis focused on examining the neural mechanisms and functional significance of sensory responsivity in typical and atypical development.

Study 1 found that extreme sensory processing styles were significantly associated with increased negative affect and risk-taking in typically developing adolescents and adults. Studies 2 and 3 investigated the relationship between sensory responsivity and visual cortical plasticity, in typically and atypically developing groups. In typically developing populations, plasticity is thought to be governed by developmental stage. Study 2 showed that exposure to repetitive visual HFS resulted in long-term changes to visually-evoked potentials (VEPs), and that the latency of these changes along the VEP waveform, and how persistent they are across time, are developmentally regulated. In individuals with ASCs, plasticity is thought to be reduced due to altered functioning of NMDA receptors. However, the results of Study 3 failed to show long-term potentiation of VEPs in neurotypical participants or participants with ASCs, although short-term changes to VEPs were observed for both groups. No relationship between sensory responsivity and cortical plasticity was observed in either EEG study. Collectively, this doctoral work provides a basis for which sensory responsivity and cortical plasticity in typically and atypically developing populations can be further investigated.

Contents

Acknowledgements **3**
Thesis abstract **5**
List of Figures **14**
List of Tables **16**
Glossary of Abbreviations **18**
Chapter 1: General Introduction **21**
1.1. Introduction 22
1.2. Theories of sensory processing 22
1.2.1. Sensory Integration Theory 23
1.2.2. Dunn's Model of Sensory Processing 25
1.3. Sensory responsivity and emotion 27
1.4. Sensory processing across development 28
1.4.1. Sensory processing in adolescence 29
1.4.2. Gaps in the sensory responsivity literature 30
1.5. Sensory processing and mental health 31
1.5.1. Autism spectrum conditions 32
1.5.1.1. Sensory processing in Autism Spectrum Conditions 33
1.6. Electroencephalography 34
1.6.1. The Visual P1 35
1.6.2. The Visual N1 36
1.6.3. The Visual P2 36
1.6.4. Age-dependent changes in VEPs 37
1.6.5. Visual evoked potentials in Autism Spectrum Conditions 38
1.6.6. Summary of electroencephalography methodology 39
1.7. Neuroplasticity 39
1.7.1. NMDA receptor dependent LTP 39
1.7.2. Non-human animal studies of long-term potentiation 42
1.7.3. Sensory-induced potentiation in humans 43
1.7.4. Factors affecting neuroplasticity 45
1.7.4.1. Developmental stage 45
1.7.4.2. NMDA receptor abnormalities and neuroplasticity 46
1.8. Research questions 47
Chapter 2: General Methodology **52**
2.1. Introduction 53
2.2. Participants 53
2.3. Materials & Apparatus 53

2.3.1. Electroencephalography (EEG) 53
2.3.1.1. EEG Recording 53
2.3.1.2. EEG Processing 53
2.3.1.3. Visual Steady State Response 59
2.3.1.4. Stimuli 60
2.3.2. Questionnaires 61
2.3.2.1. The Life Span Risk-Taking Inventory 61
2.3.2.2. The RT-18 72
2.3.2.3. The Adolescent/Adult Sensory Profile (AASP) 73
2.3.2.4 Glasgow Sensory Questionnaire (GSQ) 75
2.3.2.5. Depression Anxiety and Stress Scale (short-form version; DASS-21) 75
2.4. Procedure 77
2.4.1. Tasks 77
2.4.1.1. Visual Cortical Plasticity Paradigm 77
2.4.1.2. Resting State EEG 78
2.4.2. Statistical analyses 78
2.4.2.1. Behavioural analyses 79
2.4.2.2. EEG analyses 79
2.4.2.3 Questionnaire analyses 81
2.4.2.4. Multiple comparison corrections 81
2.4.2.5. Assumptions of Statistical Analyses 82
Chapter 3: Investigating the relationships between sensory processing, risk-taking, and negative affect in the transition from adolescence to adulthood 85
Abstract 86
3.1. Introduction 87
3.1.1. Developmental changes in sensory responsivity 87
3.1.2. Mental health issues in adolescence 88
3.1.3. Risk-taking behaviour in adolescence 90
3.1.4. Aims of the present study 91
3.2. Method 92
3.2.1. Participants 92
3.2.2. Questionnaires 92
3.2.2.1. Adolescent Adult Sensory Profile (AASP) 92
3.2.2.2. Depression Anxiety and Stress Scale (short form version; DASS-21) 92
3.2.2.3. RT-18 92
3.2.3. Procedure 92
3.2.3.1. Statistical Analysis 93
3.3. Results 94

3.3.1. Age-related differences in sensory processing scores 95
3.3.2. Age-related differences in DASS-21 scores 96
3.3.3. Age-related differences in RT-18 scores 97
3.3.4. The relationship between age and sensory processing on negative affect 98
3.3.4.1. The relationship between Sensory Sensitivity and negative affect 99
3.3.4.2. The relationship between Sensory Avoiding and negative affect 100
3.3.4.3. Low Registration as a moderator between age and negative affect 101
3.3.5. The relationship between age and sensory processing on risk-taking 104
3.3.5.1. The relationship between Low Registration and risk taking 104
3.3.5.2. The relationship between Sensation Seeking and risk-taking 105
3.3.5.3. The relationship between Sensory Sensitivity and risk-taking 105
3.3.6. Assessing Internal Reliability of Questionnaires 105
3.4. Discussion 106
3.4.1. Sensory processing style during the transition from early adolescence to adulthood 106
3.4.2. Sensory processing and mental wellbeing 107
3.4.3. Sensory processing and risk-taking 109
3.4.4. Study Limitations and Future Directions 110
3.4.5. Conclusion 111
Chapter 4: Investigating cortical plasticity in the visual cortex of typically developing adolescents and adults 114
Abstract 115
4.1. Introduction 116
4.1.1. Aims of the present study 118
4.2. Method 119
4.2.1. Participants 119
4.2.2. Experimental paradigm 119
4.2.3. EEG Processing and Analysis 120
4.2.3.1. EEG Processing 120
4.2.3.2. Selecting Time Windows for Analysis 120
4.2.3.3. Selecting Electrodes for Analysis 121
4.2.4. Questionnaires 123
4.2.4.1 Adolescent Adult Sensory Profile (AASP) 123
4.2.4.2 Glasgow Sensory Questionnaire (GSQ) 123
4.2.4.3 Depression Anxiety and Stress Scale (short-form version; DASS-21) 123
4.2.5. Statistical Analyses 123
4.3. Results 123
4.3.1. Visual Evoked Potential Analyses 123
4.3.1.1. Assessing differences between baseline VEP assessments 123

4.3.1.2. Grand-averaged ERPs and scalp topographies 124
4.3.1.3. Assessing the effect of visual-HFS on VEP components in adolescents and adults 130
4.3.2. Hypothesis: Adolescents will display greater change in VEP amplitude following HFS compared to adults 135
4.3.2.1. N1 analyses 135
4.3.2.2. P2 analyses 136
4.3.3. Hypothesis: There will be no group differences in HFS-driven VSSR power. 138
4.3.4. Hypothesis: HFS-driven VSSR power predicts degree of VEP change 139
4.3.5. Assessing group differences in number of trials and EEG channels removed during processing of EEG data. 140
4.3.5.1. Number of trials removed during EEG processing. 140
4.3.5.2. Number of channels removed during EEG processing. 141
4.3.6. Analysis of Parieto-Occipital Clusters 141
4.3.7. Task performance 141
4.3.7.1. Reaction times to oddball targets. 141
4.3.7.2. Response Accuracy to Oddball Targets 142
4.3.7.3. Changes in Target Reaction Time and Absolute VEP Change 143
4.3.8. Questionnaire analyses 144
4.3.8.1. Assessing Internal Reliability of Questionnaires 144
4.3.8.2. Age-related differences in questionnaire measures 146
4.3.8.3. Assessing the Relationship between Sensory Responsivity and VEP Amplitude 146
4.3.9. Summary of results 149
4.4. Discussion 151
4.4.1. Age-dependent differences in changes to the N1 and P2 visual components 151
4.4.2. Degree of VEP change following visual-HFS 153
4.4.3. HFS-Driven Visual Steady State Response 154
4.4.4. Sensory Responsivity and Visual Cortical Plasticity 154
4.4.5. Study Limitations and Future Directions 155
4.4.6. Conclusion 156
Chapter 5: Investigating cortical plasticity in the visual cortex of adults with Autism Spectrum Conditions 157
Abstract 158
5.1. Introduction 159
5.1.1. Aims of the present study 161
5.2. Method 162
5.2.1. Participants 162
5.2.2. Experimental paradigm 162
5.2.3. EEG Processing and Analysis 163

5.2.3.1. EEG Processing 163
5.2.3.2. Selecting Time Windows for EEG analysis 163
5.2.3.3. Selecting Electrodes for EEG Analysis 165
5.2.4. Questionnaire Measures 165
5.2.4.1. Adolescent Adult Sensory Profile (AASP) 165
5.2.4.2. Glasgow Sensory Questionnaire (GSQ) 165
5.2.4.3. Depression Anxiety and Stress Scale (short-form version; DASS-21) 165
5.2.4.4. Social Responsiveness Scale (SRS-2) 166
5.2.4.5. Wechsler Abbreviated Scale of Intelligence (2-Subtest Version) 167
5.2.5. Statistical Analyses 167
5.3. Results 168
5.3.1. Visual Evoked Potential Analyses 168
5.3.1.1. Assessing differences between baseline VEP assessments 168
5.3.1.2. Grand-averaged ERPs and scalp topographies 169
5.3.1.3. Assessing the effect of visual-HFS on VEP components in ASCs 173
5.3.2. Hypothesis: There will be no group differences in HFS-driven VSSR power. 175
5.3.2.1. Hypothesis: HFS-driven VSSR power predicts degree of VEP change 175
5.3.3. Assessing group differences in number of trials and EEG channels removed during processing of EEG data 176
5.3.3.1. Number of trials removed during EEG processing 176
5.3.3.2. No significant differences in number of channels removed between groups . 176
5.3.4. Task performance 177
5.3.4.1. Response Accuracy to Oddball Targets 177
5.3.4.2. Reaction Times to Oddball Targets 177
5.3.5. Questionnaire analyses 178
5.3.5.1. Internal Reliability of Questionnaires 179
5.3.5.2. Group differences in questionnaire measures 179
5.3.6. The Relationship between Sensory Sensitivity and Visual Evoked Potentials 183
5.3.6.1. Hypothesis: Participants with higher sensory responsivity scores will show larger visual evoked potentials at baseline. 183
5.3.6.2. Hypothesis: Participants with higher sensory responsivity scores will show a smaller degree of change in VEP amplitude following high-frequency stimulation ... 184
5.3.7. Summary of Results 184
5.4. Discussion 186
5.4.1. No long-term effect of visual HFS on VEPs 186
5.4.2. Sensory Responsivity and Visual Plasticity 188
5.4.5. Conclusion 188
Chapter 6: General Discussion 191
6.1. Key findings and general discussion 192

6.1.1. Sensory processing is significantly related to psychological and behavioural outcomes in the transition from adolescence to adulthood in typically developing individuals 192

6.1.2. Visual tetanic stimulation is a safe and non-invasive method of examining LTP-like changes in the visual cortex, but more research is needed to establish the influence of low-frequency stimulus presentation in VEP assessments on VEP changes 195

6.1.2.1. Visual tetanic stimulation produces developmentally regulated changes to VEPs in typically developing adolescents and adults 196

6.1.2.2. More research is needed to establish whether visual tetanic stimulation produces altered LTP-like changes in individuals with ASCs, compared to neurotypical individuals 198

6.1.3. No relationships were observed between sensory responsivity measures and visual cortical plasticity 199

6.1.4. Using a variety of methodological techniques is the best approach for examining sensory processing and cortical plasticity in typical and atypical development 201

6.2. Recommendations for future research 201

6.2.1. Replication and extension 201

6.2.1.1. Sensory Responsivity in Typically Developing Adolescents 202

6.2.1.2. The Visual Cortical Plasticity Paradigm 202

6.2.2. Longitudinal studies 206

6.2.3. Interventions 206

6.6.4. Alternative self-report measures of sensory responsivity 207

6.7. Final conclusions 207

References 210

Appendix 246

Appendix 1 – The Life Span Risk-Taking Inventory 247

Appendix 2 – Supplementary analyses for Chapter 4 250

Appendix 3 – Supplementary analyses for Chapter 4 251

List of Figures

Figure 1.1: Dunn's model of sensory processing……26

Figure 1.2: An example of a typical ERP waveform in response to a visual cue……...35

Figure 1.3: Schematic for the structure of the NMDA receptor complex……40

Figure 1.4: Schematic for NMDA receptor long-term potentiation……41

Figure 2.1: Processing stream for EEG data……54

Figure 2.2: ICA component plots for the same participants after applying different high-pass filters……..……56

Figure 2.3: Component topographies for ocular artefacts…..……58

Figure 2.4: Visual Cortical Plasticity Paradigm: timeline and stimuli……77

Figure 3.1: Mean AASP scale scores for each age group…….....95

Figure 3.2: Mean DASS-21 scale scores for each age group……...96

Figure 3.3: Mean RT-18 scale scores for each age group……97

Figure 3.4: Scatter graphs depicting the relationships between Low Registration scores and measures of negative affect……..103

Figure 4.1: Visual Cortical Plasticity Paradigm: timeline and stimuli……...……120

Figure 4.2: Scalp topographies depicting mean amplitudes for P1, N1, and P2 time windows……...121

Figure 4.3: Grand-grand-averaged VEPs for each age group at posterior electrode sites…....122

Figure 4.4: Scalp topographies depicting mean amplitude for P1, N1, and P2 time windows for data averaged across all participants and all VEP assessment blocks…...……..…126

Figure 4.5: Grand average visual evoked potentials (VEPs) elicited by the standard circle for early-adolescents (n = 18) across posterior electrode sites and VEP assessment blocks……..127

Figure 4.6: Grand average visual evoked potentials (VEPs) elicited by the standard circle for late-adolescents (n = 19) across posterior electrode sites and VEP assessment blocks…….……..128

Figure 4.7: Grand average visual evoked potentials (VEPs) elicited by the standard circle for adults (n = 20) across posterior electrode sites and VEP assessment blocks…….....129

Figure 4.8: A: Mean N1 amplitude for each VEP assessment and age group. B: Mean P2 amplitude for each VEP assessment and age group……133

Figure 4.9: Grand-averaged visual evoked potentials elicited by the standard circle for early-adolescents, late-adolescents and adults for the averaged occipital cluster for each VEP assessment……...134

Figure 4.10: Mean VEP change in each VEP assessment for each age group……...137

Figure 4.11: Power spectra of EEG recorded during HFS……138

Figure 5.1: Visual Cortical Plasticity Paradigm: timeline and stimuli…….……..163

Figure 5.2: Grand-grand-averaged VEPs from posterior electrode sites……...164

Figure 5.3: Scalp topographies depicting mean amplitude across N1 and P2 time windows for data averaged across all participants and VEP assessments……165

Figure 5.4: Grand-averaged VEPs elicited by the standard circle for ASC participants across posterior electrode sites and VEP assessments……170

Figure 5.5: Grand-averaged VEPs elicited by the standard circle for NT participants across posterior electrode sites and VEP assessments……171

Figure 5.6: Scalp topographies depicting mean N1 and P2 amplitude grand-averaged data in VEP assessments……..172

Figure 5.7: Grand-averaged VEPs elicited by the standard circle for ASC and NT participants over the occipital electrode cluster for all VEP assessments...……174

Figure 5.8: A: Mean N1 amplitude for each VEP assessment and group. B: Mean P2 amplitude for each VEP assessment and group……174

Figure 5.9: Power spectra of EEG recorded during HFS……...175

Figure 5.10: Mean Glasgow Sensory Questionnaire scores for ASC and NT groups……...179

Figure 5.11: Mean Adolescent and Adult Sensory Profile scores for ASC and NT groups…..180

Figure 5.12: Mean Social Responsiveness Scale (SRS-2) scores for ASC and NT groups…...181

List of Tables

Table 2.1: Demographic information……...62

Table 2.2: Factor loadings, communalities, M, SD, percentage variance explained, and Cronbach's alpha for the Life Span Risk-Taking Inventory…….64-65

Table 2.3: Cronbach's alpha for and descriptive statistics for Life Span Risk-Taking Inventory subscales…….....66

Table 2.4: Descriptive statistics for Life Span Risk-Taking Inventory subscales……67

Table 2.5: Spearman's rho correlation between Life Span Risk-Taking Inventory's risk-taking subscales and Cognitive Appraisal of Risky Events subscales……...68

Table 2.6: Pearson's correlation between the Life Span Risk-Taking Inventory and State-Trait Personality Inventory……..69

Table 2.7: Spearman's correlation between the Life Span Risk-Taking Inventory subscales…….……71

Table 3.1: Demographic information……...92

Table 3.2: Descriptive statistics and Cronbach's alpha for the AASP, DASS-21, and GSQ questionnaire scales……94

Table 3.3: Summary of the regression coefficients for DASS-21 variables predicted by Sensory Sensitivity score……..99

Table 3.4: Predicted range of mean DASS-21 scores based on Sensory Sensitivity score……100

Table 3.5: Summary of the regression coefficients for DASS-21 variables predicted by Sensation Avoiding score…….100

Table 3.6: Predicted range of mean DASS-21 scores based on Sensation Avoiding score…...101

Table 3.7: Summary of the regression coefficients for RT-18 variables predicted by Low Registration score……..105

Table 4.1: Demographic information…….119

Table 4.2: Marginal means and standard errors for mean ERP amplitudes measured during pre-HFS VEP assessments……..124

Table 4.3: Descriptive statistics for mean amplitude across VEP components measured during baseline and post-HFS assessments for each age group……...131

Table 4.4: Marginal means and standard errors for VEP change scores……136

Table 4.5: Summary of regression analyses predicting change in VEP amplitude from HFS-driven VSSR power……..139

Table 4.6: Mean number of standard circle trials included in each VEP assessment for each age group…….140

Table 4.7: Marginal means for main effects of VEP assessment and age group…….……..142

Table 4.8: Response accuracy to target squares (percentage) for all age groups during VEP assessments……...143

Table 4.9: Descriptive statistics and Cronbach's alpha for AASP, DASS-21, and GSQ questionnaire scales……..145

Table 4.10: Spearman's rho correlation coefficients between sensory questionnaire measures and baseline VEP amplitude…….147

Table 4.11: Spearman's rho correlation coefficients between sensory questionnaire measures and change in VEP amplitude (Post-HFS 3 minus baseline)……148

Table 4.12: Summary of key findings……...…….149

Table 4.13: Summary of all other analyses testing differences between early-adolescents, late-adolescents, and adults……..150

Table 5.1: Demographic information……162

Table 5.2: Mean number of standard circle trials in each block for each group……176

Table 5.3: Descriptive statistics for reaction times (s) and response accuracy to target stimulus……177

Table 5.4: Descriptive statistics and Cronbach's alpha for the AASO, DASS-21, and SRS-2 questionnaire scales……..178

Table 5.5: IQ scores for ASC and NT groups……182

Table 5.6: Bivariate and partial Pearson's correlation coefficients for the relationship between mean VEP amplitude at baseline and sensory responsivity measures……..183

Table 5.7: Summary of key findings……..184

Table 5.8: Summary of all other analyses testing differences between ASC and NT participants……185

Glossary of Abbreviations

AASP	Adolescent and Adult Sensory Profile
ASC	Autism Spectrum Condition
B-H	Benjamini-Hochberg
CARE	Cognitive Appraisal of Risky Events
CNS	Central nervous system
DASS-21	Depression Anxiety and Stress Scale (short-form version)
EC	Eyes closed
EEG	Electroencephalography
EMSM	Ecological Model of Sensory Modulation
EO	Eyes open
ERP	Event related potential
GSQ	Glasgow Sensory Questionnaire
HFS	High frequency stimulation
HNT	High neurological threshold
ICA	Independent Component Analysis
LNT	Low neurological threshold
LRTI	Life Span Risk-Taking Inventory
LTD	Long term depression
LTP	Long term potentiation
NEE	Negative emotional experiences
NMDA	N-methyl-D-aspartate
NT	Neurotypical
PCA	Principal components analysis
rTMS	Repetitive transcranial magnetic stimulation
SES	Socio-economic status
SIT	Sensory Integration Theory
SMD	Sensory Modulation Dysfunction
SNR	Signal-to-noise ratio
SRS-2	Social Responsiveness Scale (2^{nd} edition)
STPI	State-Trait Personality Inventory
SZ	Schizophrenia
TBS	Theta-burst stimulation
TMS	Transcranial magnetic stimulation
TNT	Typical neurological threshold

VEP	Visually evoked potential
VSSR	Visual steady-state response
WASI	Wechsler Abbreviated Scale of Intelligence

Chapter 1: General Introduction

1.1. Introduction

Sensory processing refers to "the way in which the central and peripheral nervous systems manage incoming sensory information from tactile, vestibular, proprioceptive, visual, auditory, olfactory, and gustatory sensory systems" (Mulligan, 2002, p.401). The amount of sensory information available at any one time far exceeds the brain's simultaneous, but limited, processing capabilities (Atick, 1992); therefore, there are specific processes in the brain dedicated to modulating this information. Sensory modulation is the ability to regulate and organize reactions to sensations in a graded and adaptive manner, and represents changes in the levels of habituation and sensitization of the central nervous system (Ayres, 1972; McIntosh, Miller, Shyu, & Hagerman, 1999). Impairments in sensory modulation can lead to under- or over sensory-responsivity, and is often associated with mental health conditions such as schizophrenia (Brown, Cromwell, Filion, Dunn, & Tollefson, 2002; Javitt, 2009), obsessive-compulsive disorder (Rieke & Anderson, 2009), post-traumatic stress disorder (Batya Engel-Yeger, Palgy-Levin, & Lev-Wiesel, 2013), as well as being a feature in developmental disorders such as Asperger's disorder (Dunn, Saiter, & Rinner, 2002; Pfeiffer, Kinnealey, Reed, & Herzberg, 2005), and autism spectrum disorders (Ashburner, Bennett, Rodger, & Ziviani, 2013; De la Marche, Steyaert, & Noens, 2012; Tavassoli, Miller, Schoen, Nielsen, & Baron-Cohen, 2014).

The aim of this chapter is to review the literature on sensory responsivity to date, focusing on sensory processing across development, specifically during adolescence and the transition into adulthood, as well as in the neurodevelopmental disorder autism. First, I will discuss prominent theories of sensory processing, used to model individual differences in sensory responsivity, followed by a review of the literature on sensory processing in adolescence and adulthood, and in autism spectrum conditions. Two of the studies reported in this thesis use electroencephalography (EEG) to examine the neural underpinnings of sensory responsivity; therefore, a background to the EEG methodology and event-related potentials is also covered in this chapter. Finally, the relationship between sensory modulation and neuroplasticity is discussed, concluding with an outline of the research work presented in this doctoral thesis, and the research questions this project aims to answer.

1.2. Theories of sensory processing

The following section will outline two prominent theories of sensory processing, Sensory Integration Theory and Dunn's Model of Sensory Processing, that have both strongly influenced research on sensory responsivity in typical and atypical populations.

1.2.1. Sensory Integration Theory

Widely regarded as a pioneer in sensory research, Jean. A. Ayres was an occupational therapist with extensive knowledge of neuroscience. Her work with children with learning disabilities led her to suggest that there was a biological basis to many of the behavioural and learning problems manifested by her clients. She developed a theory based on sensory integration, which she defines as "the organization of sensory information for use" (Ayres, 1972). It is a neurological process that allows us to make sense of the world by receiving, registering, modulating, organizing, and interpreting sensory information. Impairment in sensory integration would manifest in difficulties observed in purposeful behaviours; for example, children may have problems regulating their attention or learning new skills. Furthermore, Ayres hypothesized that therapies designed to modify the neurobiological bases of behaviours could result in functional improvement. There are five basic assumptions that underlie Ayres's Sensory Integration Theory (1972).

1. *There is plasticity within the central nervous system (CNS); therefore, interventions based on Sensory Integration Theory can produce changes in the brain.*

Plasticity is a fundamental property of the nervous system. Neuroplasticity refers to the brain's ability to change structurally and functionally as a result of input from the environment and perturbations, including injury (Kolb & Teskey, 2012). During most of the 20th century, the consensus among neuroscientists, including Ayres, was that neuroplasticity mostly occurred during childhood, and was immutable after this critical period. We now know that is not the case, with research showing that many aspects of the brain remain plastic well beyond the juvenile period (for a review, see Lillard & Erisir, 2011). For example, Draganski et al. (2004) demonstrated that adults who have been taught to juggle show transient and selective changes in brain areas associated with storage of complex visual motion.

2. *The sensory integrative process occurs in a developmental sequence.*

Ayres (1972) argues that each developmental step is in some way dependent on maturation of previous steps. Complex behaviours cannot be achieved until the simpler 'building block' behaviours are mastered.

3. *The brain functions as an integrated whole but is composed of systems that are hierarchically organized.*

Ayres (1972) asserts that the brain essentially functions as a whole, with no locus of the brain, no nucleus, and no single neuron sufficient unto itself or completely isolated. She states that every area of the brain is dependent on other areas, but not completely dependent. Across the evolutionary development of the human brain, there has been increased localisation of function, however it remains that each part of the brain is dependent on another part. In particular, development and optimal functioning of higher-order structures are dependent on

successful development and functioning of lower-order structures. The opportunity for interaction between areas of the brain allows for a greater adaptive capacity and improved efficiency.

4. *Producing an adaptive response promotes sensory integration, and the ability to produce an adaptive response is based on sensory integration.*

An adaptive response is dependent on continual sensory feedback and adequate interpretation and integration of this information (Ayres, 1972). This feedback is then stored as memories (neuronal models) and later forms the basis for more complex actions.

5. *An inner drive exists to develop sensory integration, which is manifested through participation in sensorimotor activities.*

There are particular developmental stages the CNS goes through, in which "it is sensitive to certain sensory stimuli which are related to motor responses for which there is a drive to emit" (Ayres, 1972, p. 80). For example, it is necessary for survival that a baby learns to master the earth's gravitational force, with the ultimate aim of locomotion. Therefore, because of this innate drive, babies may be especially sensitive to gravity during this period of development, and gradually learn to master gravity through increasingly complex motor responses (e.g. being able to hold up their own head against gravitational forces, to righting themselves so that the sagittal plane of the head is perpendicular to the earth's surface).

These five principles are based on a series of factor analyses conducted by Ayres over 24 years, looking at standardized measures of sensory discrimination, sensory responsivity, fine and gross motor skills, and praxis, through which she was able to identify patterns of sensory integrative dysfunction (for a review see Roley, Mailloux, Miller-Kuhaneck, & Glennon, 2007). Ayres also went on to develop an intervention approach using sensory integration theory founded on the principles of motor learning, the adaptive response, and purposeful activity. Sensory integration therapy is most commonly used by occupational therapists, with the aim of enhancing a child's ability to participate in daily tasks that are meaningful and satisfying for the child in that context. Some of the hallmarks of sensory integration therapy are that it is done in the context of play (activities usually involve large pieces of equipment such as trampolines and balls), that children enjoy the activities, and that the activities are their own reward. There has been more effectiveness research conducted on sensory integration therapy than any other intervention in the field of occupational therapy. However, the evidence so far has been weak due to methodological limitations, including issues relating to inclusion criteria of study samples, adherence to sensory integration principles and limitations in the outcome measures to detect differences (Miller, Schoen, James, & Schaaf, 2007; Miller, Coll, & Schoen, 2007; Parham et al., 2007; Pollock, 2009). Despite the limited evidence for sensory integration therapy, Ayres' work is still regarded as one of the most impressive accomplishments in the

field of occupational therapy, and is considered to have considerably developed our understanding of the contributions of sensation to learning, development, and participation in daily life (Roley et al., 2007).

1.2.2. Dunn's Model of Sensory Processing

Much like Ayres' Sensory Integration Theory, Dunn's Model of Sensory Processing (Dunn & Brown, 1997) was originally developed to explain behavioural responses to sensation in children, but has since been expanded to include responses to sensation in adolescents and adults. The main premise of the model posits that there is a relationship between a person's neurological thresholds and their self-regulation strategies. Neurological threshold refers to the point at which a nerve cell or system receives enough input to cause the cell/system to activate. Thresholds are on a continuum; individuals with low sensory thresholds will notice and respond to stimuli more often than those with high sensory thresholds, because they need less stimulation to activate for sensory events. Thresholds for noticing and responding to sensory events differ amongst individuals and can differ amongst different types of sensory input for the same person. For example, a person may easily notice when someone is touching them (low threshold for touch) but may not notice smells as easily (high threshold for smell). Self-regulation strategies are also on a continuum. At one end of the continuum, individuals have passive strategies, whereby they let things happen to them, and then respond. For example, an individual may continue to shop in a busy shopping centre and become irritated because of overcrowding and noise. At the other end of the continuum, individuals have active strategies, whereby they try to control the amount and type of input that is available to them. For example, the same shopper might choose to do their shopping at a time they know will not be as busy or order their shopping online instead.

Dunn (2007) states that when these two continua intersect, four basic patterns of sensory processing emerge (Figure 1.1). The four patterns that result are (1) Sensation Seeking, which represents high neurological thresholds and active self-regulation strategies, (2) Sensation Avoiding, which represents low neurological thresholds and active self-regulation strategies, (3) Sensory Sensitivity, which includes low neurological thresholds and passive self-regulation strategies, and (4) Low Registration, which represents high neurological thresholds and passive self-regulation strategies. Each of these four sensory processing styles are described in more detail below.

Sensation Seeking. In order to meet their high neurological thresholds, individuals with high sensation seeking sensory processing patterns will actively create additional stimuli or look for environments that provide sensory stimuli. For example, sensation-seeking individuals may listen to music while studying or enjoy eating at restaurants that serve unfamiliar food.

Sensation seeking individuals derive pleasure from sensory experiences; however, they may also become bored more easily in low-stimulus environments.

Sensation Avoiding. Individuals with high sensation avoiding patterns of sensory processing have low neurological thresholds and active self-regulation strategies. Sensation avoiding individuals can often become bothered or overwhelmed by sensory stimuli, and therefore actively aim to reduce sensory stimuli in their environments. For example, sensation-avoiding individuals may use rituals to increase predictability of their sensory environment.

Sensory Sensitivity. People with high sensory sensitivity patterns of sensory processing have low neurological thresholds, causing them to respond readily to sensory stimuli. They have a high level of awareness of the environment and are able to discriminate or attend to detail; however, they can also be easily distracted, and experience discomfort when exposed to intense stimuli.

Low Registration. Individuals with low registration patterns of sensory processing tend to miss or take longer to respond to sensory stimuli that others notice easily. For example, they might not detect smells that others find bothersome; they may also be the last to understand a joke. Whilst these individuals may struggle to respond to certain stimuli, they may also be less easily distracted and more comfortable in a wide range of sensory environments.

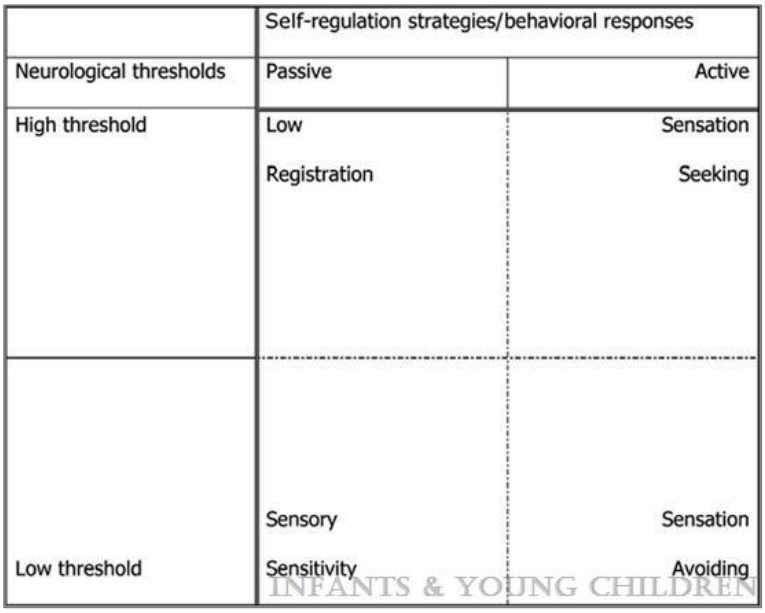


Figure 1.1. Dunn's model of sensory processing. Reprinted with permission from Dunn (1997).

Individuals do not engage in just one type of sensory processing; patterns of sensory processing can differ for different sensory systems. For example, a person might have sensory sensitivity patterns of sensory processing for sounds but have low registration patterns of

sensory processing for touch. Most individuals have moderate responses to sensory stimuli, and their sensory processing patterns aid their everyday lives. However, more extreme responses to sensory stimuli are more likely to interfere with daily life.

Researchers have tested the validity and reliability of Dunn's model of sensory processing by conducting large-scale studies of children and adults with and without disabilities using three age-appropriate questionnaires (the Infant/Toddler Sensory Profile, the Sensory Profile, and the Adolescent/Adult Sensory Profile) that assess the four patterns of sensory processing from Dunn's model. Researchers verified the existence of the four patterns of sensory processing hypothesized in Dunns model in every age group (Brown, Tollefson, Dunn, Cromwell, & Filion, 2001; Brown & Dunn, 2002; Dunn, 2002; Dunn & Westman, 1997; Dunn, 1999, 2007; Dunn & Daniels, 2002). Data from these national samples of children and adults without disabilities had a bell-shaped distribution, indicating that the majority of individuals have moderate responses to sensory stimuli, but some will have intense responses that are similar to cohorts with disabilities. The Sensory Profile questionnaires are the most commonly used questionnaires for assessing sensory processing. They have been used to assess the role of sensory processing in various mental health conditions (Baranek et al., 2002; Crane, Goddard, & Pring, 2009; Engel-Yeger et al., 2016; Ludlow et al., 2014; Mangeot et al., 2001; Rieke & Anderson, 2009; Tomchek & Dunn, 2007), and how different sensory processing styles relate to other psychological or behavioural variables (Ben-Avi, Almagor, & Engel-Yeger, 2012; Batya Engel-Yeger & Shochat, 2012; Hebert, 2015; Jerome & Liss, 2005).

1.3. Sensory responsivity and emotion

The theories discussed above aim to explain why there are individual differences in perceptions of sensory stimuli, but individuals will also differ in their affective response to sensation. In some individuals, such as those with sensory modulation disorder, difficulties regulating their response to sensation are so extreme that it interferes with their ability to participate in daily activities. For example, children with extreme sensory over-responsivity may show negative responses to specific sensory stimuli, in the form of fear, avoidance, distraction, over-vigilance, and/or aggression (Ben-Sasson, Carter, & Briggs-Gowan, 2009; Dunn, 1997; Miller, Anzalone, Lane, Cermak, & Osten, 2007).

Sensory over-responsivity has also been linked to internalizing symptoms (such as anxiety, depression, and withdrawal) in typically developing individuals of all ages. Goldsmith, Van Hulle, Arneson, Schreiber, & Gernsbacher (2006) used a population-based sample of 1394 toddler-aged twins to investigate the relationships between tactile and auditory defensiveness, temperament, and behaviour problems. They reported that the presence of defensive symptoms was common across the sample, with some toddlers in the extreme range, and more girls than boys were included in the extreme tactile defensiveness group. Notably, auditory and tactile

defensiveness were associated with fearful temperament and anxiety but were less related to other measures of dysfunctional childhood behaviour.

Less research on this topic has been carried out in adult samples, but consistent with findings from child samples, studies have shown a link between sensory defensiveness and a tendency towards increased symptoms of anxiety and depression (Kinnealey & Fuiek, 1999). The ability to gain employment and earn money, build and maintain social relationships, and be generally organised may also be more difficult for adults who experience issues with sensory processing (Kinnealey, Koenig, & Smith, 2011). Furthermore, adults may also be more aware that their own sensory processing characteristics are different from the societal norm, which can lead to low self-esteem, limited social participation, and dissatisfaction with quality of life (Kinnealey et al., 1995).

It is also worth noting that even though there is a strong relationship between sensory over-responsivity, social introversion, and emotionality, the presence of one does not necessarily indicate the presence of another. A review by Aron and Aron (1997) found 2 distinct clusters of highly sensitive individuals; the first smaller group reported an unhappy childhood and related variables, whereas the second larger group was similar to individuals with typical sensory responsivity in all other aspects except their sensitivity to sensory stimuli. Together, these results demonstrate that sensory over-responsivity is generally associated with increased anxiety, depression, and withdrawal, which can have an impact on quality of life in many areas.

1.4. Sensory processing across development

Successful motor, cognitive, language, and social skill development in humans depends on successful development of sensory processing abilities. Sensory integration theory is focussed on understanding impairments in sensory processing during childhood; consequently, research has predominantly investigated sensory processing in childhood. However, effective sensory processing is critical for survival at any age; therefore, it is important to understand how sensory-based experiences may change across the life span (Watling, Bodison, Henry, & Miller-Kuhaneck, 2006). In young infants and children, the aim is to learn to process sensory information as quickly as possible, with these early years providing the basis for more complex behavioural responses to sensory stimuli in the future. Initially, environmental sensory information is perceived, modulated and organised, eventually leading to adaptive and more complex responses. However, once we have mastered the basics of processing sensory information, the challenge shifts during adolescence, and into adulthood, to one of being able to effectively, and adaptively balance internal drives and desires with the external pressures of social norms and adult expectations. It is during this transitionary period that the research in this doctoral thesis will focus on. The following sections outline how sensory processing, and sensory responsivity, might play a key role in how well adolescents' manoeuvre through the

complex physical, behavioural, and social changes they experience as they transition into adulthood.

1.4.1. Sensory processing in adolescence

The adolescent period is often defined as starting with the onset of puberty, and completing with the achievement of relative self-sufficiency, thereby beginning with a biological event and ending with a socially defined construct (Blakemore & Mills, 2014). The onset of puberty evokes dramatic changes in hormone levels, and in physical appearance, including growth, changes to the facial structure, appearance of secondary sexual characteristics, as well as a profound effect on brain maturation (Blakemore, Burnett, & Dahl, 2010). Running parallel with these physical changes are numerous changes in an adolescent's social and academic spheres. In adolescence, there is often increased independence from caregivers, and greater susceptibility to peer pressure (although parents do still retain a substantial measure of influence over their adolescent; Brown, Mounts, Lamborn, & Steinberg, 1993). Adolescents also acquire more responsibilities and pressures than they had in childhood and are challenged to effectively and adaptively balance their internal drives and desires with the external pressures of social norms and adult expectations. Some adolescents may find this balance particularly challenging and may find it difficult to 'fit in' with their peers, or struggle to cope with the 'storm and stress' of adolescence (Casey et al., 2010). It has been hypothesized by Watling et al (2006) that some of the difficulties experienced in adolescence may be related to their sensory processing styles, and differing levels of sensory responsivity.

One of those difficulties experienced during adolescence is a greater propensity to engage in risk-taking behaviours. Adolescents, in general, are more likely than any other age group to engage in risk-taking behaviours such as binge drinking, substance abuse, casual sex, criminal or violent activity, driving recklessly, as well as being involved in serious or fatal automobile accidents (Steinberg, 2008). Whilst risk-taking can occur as a result of rational reasoning, when the benefits are perceived as outweighing the risks, risk-taking behaviours can also be driven by the way we feel (Figner, Mackinlay, Wilkening, & Weber, 2009; Figner & Weber, 2011). Affective decision-making theorists suggest that emotional responses to positive and negative consequences of risk-taking guide decisions (Bechara & Damasio, 2005). In addition, impairments in emotion regulation may also increase impulsivity, and in turn increase risk-taking (Donohew et al., 2000; Magar, Phillips, & Hosie, 2008). It is particularly important to consider the relationship between emotional state and risk-taking during adolescence, a time characterized by extreme fluctuations in mood, as well as increased risk-taking (Buchanan, Eccles, & Becker, 1992).

Alongside emotional state, peer influences also significantly affect risk-taking behaviours (Boyer, 2006; Gardner & Steinberg, 2005). It is well documented that adolescents

are more likely to engage in risk-taking behaviours, such as driving recklessly, and using illicit substances, when in the presence of peers (Arnett, 1992). The presence of peers causes adolescents to take more risks, evaluate risky behaviours more positively, and is associated with greater activity in reward-sensitive regions of the brain; findings that are not replicated in adults (Chein, Albert, O'Brien, Uckert, & Steinberg, 2011; Gardner & Steinberg, 2005). Consequently, peer relationships have important influences on risk-taking and are crucial for understanding risk-taking across the life span.

Evaluation of these risk-taking behaviours using a sensory integration framework suggests that these adolescents are engaging in sensory-seeking behaviours that are indicative of high sensory thresholds, which are therefore causing the individual to desire and seek more intense sensory inputs (Zuckerman, 1994). However, this sensation seeking can often put the adolescent in danger – many researchers agree that the biggest threat to adolescent mortality comes from the adolescent themselves (Blum & Nelson-Mmari, 2004; Williams, Holmbeck, & Greenley, 2002). According to the 2007 Youth Risk Behaviour Survey (YRBS; Eaton et al., 2008), the four leading causes of death that account for 72% of adolescent mortality includes motor vehicle accidents, unintentional injury, homicide and suicide – all of which are preventable.

In contrast to the risk-takers, there are also adolescents who have very low sensory thresholds and are therefore very sensitive to sensory information. This increased sensitivity means that typical levels of sensory input are perceived as threatening (Dunn, 1997), and may cause teens to feel overwhelmed with the constant barrage of sensory information, leading to feelings of fear and anxiety. This may manifest behaviourally as withdrawal from social or school events, aggression, irritability, controlling behaviours, or avoidance of certain activities, situations or materials (Lane, 2002). Although there is no research exploring this issue in typically developing adolescents, in adults it has been shown that sensory defensiveness can interfere with job performance, social participation, interpersonal relationships, and employment (Kinnealey, Oliver, & Wilbarger, 1995). In adolescents with Asperger's syndrome (aged 11-17 years), strong positive associations were found between sensory defensiveness and anxiety, as well as a significant relationship between hypo-sensitivity and symptoms of depression (Pfeiffer et al., 2005). It is also possible that changes in sensory sensitivity during the adolescent period could be related to the sharp increase in onset of psychiatric illnesses in adolescence, with the lifetime risk for the emergence of mental illness peaking at 14 years of age (Kessler et al., 2005); however, more work is needed to determine if this is the case.

1.4.2. Gaps in the sensory responsivity literature

My review of the literature revealed a lack of studies examining sensory processing styles or sensory processing difficulties in different age groups, particularly in neurotypical

populations. The majority of sensory processing research so far has focussed on children, with a smaller number of studies looking at adulthood, and no studies (that I am aware of) looking at sensory processing in neurotypical adolescents (discussion of sensory processing research in diagnostic populations is presented in section 1.5). It is possible that the higher frequency of studies focussing on sensory processing in childhood stemmed from the now disproven theory that neuroplasticity mostly occurred during childhood and was immutable after this critical period (Lillard & Erisir, 2011), and therefore priority was given to researching developmental groups where interventions may be most beneficial. Sensory processing difficulties affect social, cognitive and sensorimotor development, and therefore it is important to address these issues early on. However, the current gaps in the literature mean it is unknown whether sensory processing styles or difficulties may arise at different developmental stages beyond childhood, whether they may change across the lifespan, or what effect sensory processing difficulties have on emotions and behaviour at different ages.

As discussed above, there is currently no research exploring the role of sensory processing styles in typically developing adolescents (although there is some research looking at sensory processing difficulties in adolescents with autism spectrum conditions (Pfeiffer et al., 2005)). Furthermore, despite the hypotheses proposed by Watling et al. (2006) that are outlined above, there is currently no empirical research exploring the relationship between difficulties experienced during typical adolescent development and sensory processing. Given that this is a period of significant physical, social, and neural change, associated with increases in negative affect, mental health conditions, and risk-taking behaviours (Casey et al., 2010; Duell et al., 2018; Kessler et al., 2005), it is important to address whether changes in sensory processing may play a part. Consequently, the first aim of this doctoral thesis was to examine the relationships between sensory processing, negative affect, and risk-taking behaviours in typically developing adolescents (Chapter 3). Furthermore, this doctoral thesis also aimed to examine a possible neural mechanism underlying individual differences in sensory responsivity during this developmental stage (Chapter 4), by studying neural plasticity in visual sensory areas in adolescents and adults.

1.5. Sensory processing and mental health

Impairment in sensory processing is a common symptom of various mental health disorders. A large proportion of sensory processing research has been studied within diagnostic populations with the aim of identifying patterns unique to individual diagnoses (Reynolds & Lane, 2008); however, this has proved to be challenging due to the heterogeneity and comorbidity inherent in these diagnostic groups. Impairments in sensory processing have been studied in children and adults with Fragile X Syndrome (Baranek et al., 2002; Baranek et al., 2008; Sinclair, Oranje, Razak, Siegel, & Schmid, 2017), Attention Deficit Hyperactivity

Disorder (ADHD; Dunn & Bennett, 2002; Ghanizadeh, 2011; Mangeot et al., 2001; Parush, Sohmer, Steinberg, & Kaitz, 2007; Reynolds & Lane, 2009), schizophrenia (Brown et al., 2002; Javitt, 2009; Javitt & Freedman, 2015), obsessive compulsive disorder (Dar, Kahn, & Carmeli, 2012; Rieke & Anderson, 2009), and post-traumatic stress disorder (Engel-Yeger, Palgy-Levin, & Lev-Wiesel, 2013). The final study in this doctoral thesis will examine sensory processing in adults with autism spectrum conditions (Chapter 5); therefore, the next section will provide an overview of the sensory processing differences experienced by this population.

1.5.1. Autism spectrum conditions

There are approximately 700,000 people on the autism spectrum in the UK (around 1.1% of the population; Brugha et al., 2012). Five times as many males as females are diagnosed with autism (Fombonne, Quirke, & Hagen, 2011); however, autism is under-diagnosed in females, and therefore the male to female ratio of those on the autism spectrum may be closer than some studies suggest (Gould & Ashton-Smith, 2011). A review into sex/gender differences in autism suggests that differences in presentation of autism symptoms, and gender differences in diagnosis of ASCs may exist for several reasons, including genetic, environmental, and socio-cultural factors (Lai, Lombardo, Auyeung, Chakrabarti, & Baron-Cohen, 2015). Indeed, the etiology of ASC for both sexes is considered to be influenced by a wide range of genetic and environmental factors. Estimates of the heritability of ASC from twin studies range from 38%, to 55%, and even up to 95% (Colvert et al., 2015; Hallmayer et al., 2011; Sandin et al., 2014). Discussion of risk-genes for ASC related to synaptic plasticity is covered in section 1.7.4.2. Environmental risks include neonatal problems such as low birth weight (Ronald, Happé, Dworzynski, Bolton, & Plomin, 2010), exposure to toxic chemicals (Sealey et al., 2016), and vitamin D deficiency during pregnancy or early childhood (Kočovská, Fernell, Billstedt, Minnis, & Gillberg, 2012). Many of these risk factors are thought to have a direct impact on the development of ASD by their effects on gene regulation, and by their effects on the development of the brain.

Autism spectrum conditions (ASCs) are defined clinically by impairment in communication, social interaction and behavioural flexibility (APA, 2013). People with ASCs have difficulties interpreting both verbal and non-verbal language, such as gestures or tone of voice, and may have a very literal understanding of language and not understand jokes or sarcasm. Some autistic people may not speak, or have limited speech, whereas others may have good language skills but will struggle to understand the expectations of others in conversations, for example, by talking at length about their own interests or repeating what the other person has said (National Autistic Society, 2019). Consequently, people with ASCs may find it hard to navigate social interactions and relationships, as their difficulty in reading and interpreting emotions can make them appear insensitive or be socially inappropriate. Another of the

diagnostic criteria for ASCs are restricted and repetitive patterns behaviour and interests. Autistic people often prefer to have a daily routine (e.g. travel the same way to and from school/work, eat the same food for breakfast), and may not be comfortable with changes to this routine. Many autistic people also have highly focused interests, such as art, music, trains, computers, or sometimes more unusual interests, with the pursuit of these interests often reported as being fundamental to their wellbeing and happiness. Of particular relevance to this doctoral thesis, however, is that people with ASCs often experience over- or under-sensitivity to sensory stimuli, for example, finding background noises to be excessively loud and distracting, which can cause anxiety and even physical pain, or they may have a fascination with lights or spinning objects. Sensory hyper- and hypo-responsiveness is present in many other populations with developmental conditions, but appears to be more prevalent in ASC (Leekam, Nieto, Libby, Wing, & Gould, 2007).

1.5.1.1. Sensory processing in Autism Spectrum Conditions

Autism is a particularly heterogeneous condition, which includes individuals with a wide range of intellectual abilities, and phenotypic variation. However, one thing that appears to be common to individuals across the spectrum are atypical behavioural responses to sensory information (Marco, Hinkley, Hill, & Nagarajan, 2011). More than 96% of children with ASC report hyper- and hypo-sensitivities to sensory stimuli with a wide range in sensory behavioural differences (Leekam et al., 2007). Similarly, 94.4% of adults with ASCs reported extreme levels of sensory processing on at least one of the quadrants of the Adolescent and Adult Sensory Profile (Crane et al., 2009). Together these studies demonstrate that atypical responses to sensory stimuli are a common feature of ASCs.

Although there isn't complete agreement across studies, in general, neurophysiological studies of auditory, tactile, and visual processing in autism tend to demonstrate atypical neural activity in response to sensory stimuli (Marco et al., 2011). Studies of auditory processing in ASCs suggests atypical neural activity in the primary and association auditory cortices, as measured by atypical peaks in auditory evoked potentials, although there are discrepancies in the direction of these changes which may reflect the variation in ages, diagnosis, and paradigms used (Bruneau, Bonnet-Brilhault, Gomot, Adrien, & Barthélémy, 2003; Ferri et al., 2003; Martineau, Garreau, Barthelemy, & Lelord, 1984). Tactile sensitivity in ASC has not been studied as much as auditory processing, but studies have shown hypersensitivity to vibro-tactile stimuli at specific frequencies in individuals with ASCs (Blakemore et al., 2006), as well as disrupted cortical representation of their face and hand in a somatosensory mapping study (Coskun et al., 2009). Atypical visual processing in ASC typically includes attempts to avoid visual input (e.g. covering eyes at bright lights) or seeking additional visual stimulation (e.g. twisting fingers in front of eyes). There are inconsistencies in findings in studies of visual

processing, with some studies reporting enhanced detail perception for simple stimuli in ASC (Bertone, Mottron, Jelenic, & Faubert, 2005) and others showing no difference in contrast sensitivity between ASC and neurotypical (NT) individuals (Koh, Milne, & Dobkins, 2010). However, when considered as a whole, these studies suggest that there is disrupted processing of basic unimodal sensory information in ASC, which will undoubtedly affect higher order cortical abilities, such as socialization.

It is of particular importance that we develop our understanding of the neural underpinnings of sensory processing in ASC for several reasons. Firstly, understanding differences in sensory processing in ASC may actually help us to understand the causes of core features of autism, such as language delay (auditory processing) and difficulty reading emotion from faces (visual processing; Marco et al., 2011). Secondly, some individuals may find particular sensory stimuli distressing, which can cause self-injurious and aggressive behaviour in those who are unable to communicate their feelings. Finally, establishing the neural underpinnings of differences in sensory processing in ASC will allow for developments of behavioural intervention trials or psychopharmacologies that may be helpful for individuals who are particularly struggling.

In order to investigate the potential neural underpinnings of sensory differences in individuals with ASC, we need methodological techniques for measuring neural activity. In this doctoral thesis, electroencephalography (EEG) was used to investigate the possible relationship between neural activity and sensory responsivity and in adults with ASCs (Chapter 5). In addition, the same method was also used to examine potential age-dependent changes in sensory sensitivity in adolescents (Chapter 4). Hence, the next section will provide an overview of EEG methodology, and specifically the event-related potentials used to measure response to visual stimulation in the empirical studies presented in this thesis.

1.6. Electroencephalography

Electroencephalography (EEG) is a non-invasive neuroimaging technique, whereby electrical signals generated by populations of cortical pyramidal neurons are detected and measured at the scalp (Luck, 2014). EEG has proven to be a particularly useful tool in both scientific and clinical applications, particularly due to EEG's excellent temporal resolution. In this thesis we focused on visually evoked potentials, as measured using EEG. For details of how EEG data was processed see Chapter 2, section 2.3.1.

Event-related potentials (ERPs) refer to changes in neural activity (or transient electrical potentials) that are time-locked to a specific event. ERPs are presented as waveforms that are described according to latency and amplitude (as in Figure 1.2). The averaged ERP signal consists of various positive and negative peaks that are thought to represent responses to various sensory, cognitive or motor events. Peaks can be labelled according to their position in the

waveform (e.g. P1 is the first positive peak, N2 is the second negative peak), or their latency (the time between stimulus and component). Of particular relevance to this thesis are visual evoked potentials (VEPs), which are ERPs generated by visual stimulation.

The following sections will provide an overview of early visual evoked components (the P1, the N1, and the P2, Figure 1.2), as well as a brief summary of previous research on how VEPs change during development and are affected in individuals with ASCs.

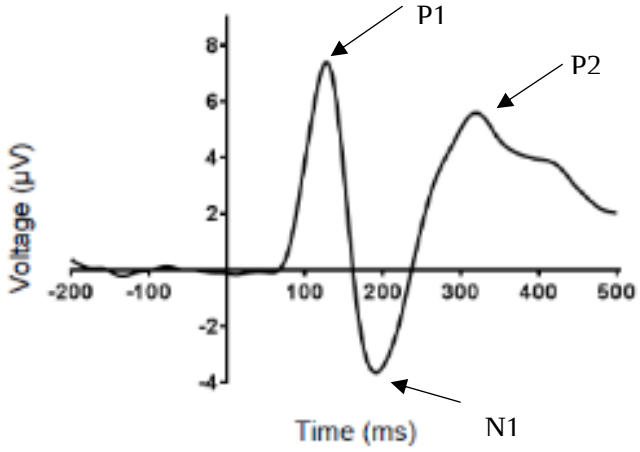


Figure 1.2. An example of a typical ERP waveform in response to a visual cue. Peaks are labelled according to their position in the waveform (P1 is the first positive peak, N2 is the second negative peak), or their latency (the time between stimulus onset and ERP component).

1.6.1. The Visual P1

The visual P1 (also called the P100) is a positive going component that typically begins around 70-90ms, and peaks around 80-130ms post-stimulus onset (Mangun, 1995). Its amplitude is maximal over the lateral occipital scalp, and its neural generators are believed to be localized to the ventral-lateral occipital cortex, within extra-striate area 19 (Clark & Hillyard, 1996; F. Di Russo, Martínez, & Hillyard, 2003). P1 amplitude has repeatedly been shown to be modulated by attention, with participants demonstrating greater P1 amplitudes when shown a stimulus in an area they were attending to (Hillyard, Mangun, Woldorff, & Luck, 1995; Mangun, 1995). This suggests that spatial attention enhances the flow of sensory information in visual pathways, potentially by improving the signal to noise ratio and allowing more information to be extracted from relevant portions of the visual field (Hillyard & Anllo-Vento, 1998). This is supported by research showing associations between enhanced P1 amplitudes and quicker reactions times and improved detectability of target stimuli (Anllo-vento, 1995; Mangun & Hillyard, 1991; Mangun, 1995). The latency and amplitude of the P1 are also significantly affected by pattern luminance, contrast, spatial frequency content (or check size) and stimulus field size (Tobimatsu & Celesia, 2006).

1.6.2. The Visual N1

The visual N1 is a negative going component, with the "1" indicating that it is the first negative-going component in the waveform. The N1 typically peaks between 150-200ms post-stimulus and can be detected at most EEG recording sites, including the occipital, parietal, central and frontal electrode sites (Mangun & Hillyard, 1991). Neural generators of the N1 have been suggested to be within either Brodmann's area 18 or 19, or both (Di Russo, Martínez, Sereno, Pitzalis, & Hillyard, 2002), and to lie outside the primary visual cortex. Like the P1, the N1 is also modulated by selective attention, with attended-location stimuli eliciting larger N1 components than unattended location stimuli (Mangun & Hillyard, 1991; Mangun, 1995). However, P1 attention effects have been observed in the absence of N1 attention effects (and vice versa), suggesting that these effects reflect different attentional mechanisms (Luck, Heinze, Mangun, & Hillyard, 1990). Vogel and Luck (2000) examined the information-processing correlates of the visual N1, by comparing N1 amplitudes for stimuli presented in choice reaction-time tasks, where participants were required to differentiate between two classes of stimuli, and simple reaction-time tasks, in which no discrimination was required. Their results revealed larger N1 amplitudes for choice reaction-time tasks, compared to simple reaction-time tasks, which was also consistent with previous research (Ritter, Simson, & Vaughan, 1983). However, there was no difference in N1 amplitude between colour and form discrimination tasks, suggesting that the N1 discrimination effect reflects a generalized discrimination process, rather than a specific pattern recognition process.

As well as factors influencing N1 amplitude, there are also factors that can affect N1 latency. One of the factors that can influence the latency of the N1 is processing effort, with N1 latency increasing as task complexity or difficulty increases (Callaway & Halliday, 1982). For example, Fort, Besle, Giard & Pernier (2005) showed that the onset, peak, and offset latencies of the N1 occurred significantly earlier in a simple detection task compared to a more difficult identification task. Another factor that can influence N1 latency is stimulus intensity. For example, peak latency of the N1 is shortened as brightness of stimulus flashes is increased (Carrillo-de-la-Pena, Holguin, Corral, & Cadaveira, 1999). Consequently, N1 latency appears to be modulated by stimulus intensity and level of processing effort.

1.6.3. The Visual P2

The visual P2 (or P200) is a positive going component that peaks at approximately 200ms post-stimulus onset but can be anywhere between 150 and 275ms. It can be detected around the centro-frontal and parieto-occipital areas of the scalp. Compared to the P1 and N1, less is known about the neural generators of the P2 in humans. However, it is known that the visual P2 in monkeys is generated by neurons in area V2 of the extra-striate cortex (Mehta, Ulbert, & Schroeder, 2000). There has also been difficulty in establishing the information

processing correlates of the visual P2 because it appears to be modulated by a large and diverse number of cognitive tasks relating to memory, language, and attention. A study by Straube and Fahle (2010) investigated the interaction of orientation and spatial frequency as visual cues in a figure detection task. They reported that P2 amplitude modulation was related to figure saliency, with P2 amplitude decreasing as figure saliency increases. It is suggested that modulation of the P2 could be a correlate of top-down attentional resource allocation, reflecting the notion that highly salient stimuli are perceived effortlessly, whereas the same stimuli embedded in a display with distractors will only be perceived if attention is focussed directly towards it (Nothdurft, 2000). Consequently, more salient stimuli need less attentional resources, and therefore P2 amplitude is reduced.

1.6.4. Age-dependent changes in VEPs

The visual cortex undergoes significant structural changes from early childhood to adulthood, including changes to local connections within the visual cortex (Burkhalter, Bernardo, & Charles, 1993), changes to the composition of the GABAergic signalling system (Pinto, Hornby, Jones, & Murphy, 2010), as well as the glutamatergic signalling system (Siu, Beshara, Jones, & Murphy, 2017). Running alongside these structural changes are significant developmental changes in visual processing, with changes occurring most rapidly during early post-natal development. Behavioural and electrophysiological testing of visual functions in new-born infants indicates that the human visual system is immature at birth, most likely due to immaturities in the visual pathway and visual cortex (Atkinson, 1984; Boothe, Dobson, & Teller, 1985; Burkhalter et al., 1993). The interdependence of structural and functional maturation is neatly demonstrated by research studying the development of binocular vision. Coarse depth discrimination develops at 3.5 months of age, with stereoacuity improving over the ensuing weeks (Birch, Shimojo, & Held, 1985; Birch, Gwiazda, & Held, 1982). This is in synchrony with the gradual segregation of geniculocortical afferents into ocular dominance columns, which reaches maturity at 4-6 months (Hickey & Peduzzi, 1987), and allows for discrimination between inputs from the left and the right eye. Consequently, maturation of structure positively correlates with maturation of functions in the human visual cortex.

Changes to the structure of the visual cortex over development are also reflected in age-related changes in visual evoked potentials. For example, Allison, Hume, Wood, & Goff (1984) studied changes in VEP components in neurologically typical subjects from 4 to 95 years of age, in response to pattern reversal stimulation. They reported that P100 latency decreased in children and approached adult level by about age 20, did not change significantly between 20 and 59 years, and then increased between 60 and 95 years of age. Similarly, P100 amplitude decreased significantly between the ages of 4 to 19 years but showed no significant change beyond that point. A more recent study by Mahajan & McArthur (2012) studied maturation of

VEPs in adolescence. In partial agreement with the findings of Allison et al (1984), Mahajan and McArthur also reported decreases in P100 amplitude from adolescence to adulthood but showed no reliable changes in P100 latency during the developmental period. These findings suggest that even basic visual sensory function is still developing in adolescence. Mahajan & McArthur go on to suggest that decreased metabolic activity (Chugani, 1998), and changes to gonadal steroid levels between 14 and 17 years of age (Oades, Dmittmann-Balcar, & Zerbin, 1997), may alter neurotransmitter activity of visual pathway neurons. This may in turn stimulate the development of both the magnocellular and parvocellular pathways of the striate and extra-striate visual cortex (these pathways are also implicated in visual processing in Autism Spectrum Conditions (see section 1.6.5.)). Consequently, it is important to consider the age of the participant when examining VEPs, especially when comparing age groups that span different developmental periods.

1.6.5. Visual evoked potentials in Autism Spectrum Conditions

As discussed in section 1.5.1.1., disrupted processing of sensory information in ASC is thought to affect higher order cortical abilities, such as socialization. This disrupted processing of sensory information is also reflected in alterations to VEPs in response to specific types of stimuli. Individuals with ASCs often show superior performance in processing fine detail (Happé & Frith, 2006; Jolliffe & Baron-Cohen, 1997), but impaired performance in processing global structure and motion information (Bertone, Mottron, Jelenic, & Faubert, 2003; Milne et al., 2002; Spencer et al., 2000). Fujita and colleagues examined whether differences in visual processing in ASC was related to functional alterations in the parvocellular and magnocellular pathways (Fujita, Yamasaki, Kamio, Hirose, & Tobimatsu, 2011). Using 128-channel EEG, they recorded VEP responses to chromatic (equiluminant red-green sinusoidal gratings) stimuli that would test functioning of the parvocellular pathway, and to achromatic (low contrast black-white sinusoidal gratings) stimuli that would test functioning of the magnocellular pathway. VEP responses to achromatic stimuli were not significantly different between ASC and NT participants; however, ASC participants showed a significantly more prolonged N1 compared to NT participants in response to the chromatic grating. The authors suggest that ASC is associated with impaired parvocellular pathway activity but preserved magnocellular pathway function at the V1 level in ASC.

Individuals with ASC also show altered VEPs in oddball discrimination tasks, whereby the participant responds to infrequent target stimuli presented among more frequent non-target stimuli. For example, Baruth and colleagues demonstrated that individuals with ASC showed abnormally large cortical responses to task irrelevant stimuli over parieto-occipital sites during early stages of visual processing compared to the control group (Baruth, Casanova, Sears, & Sokhadze, 2010). More specifically, individuals with ASC showed larger P50 amplitudes in

response to non-target stimuli compared to the control group. N1 latency was also delayed in participants with ASC, which the authors suggest may be due to sensory hyper-reactivity at earlier stages of visual processing (i.e. P50) that are delaying stimulus discrimination processes associated with the N100. This study also demonstrates how these types of visual tasks are capable of detecting difficulty in filtering irrelevant sensory stimuli in early stages of visual processing, which may be useful when considering potential biomarkers that can aid with diagnosis or assessing outcome measures.

1.6.6. Summary of electroencephalography methodology

EEG is a useful non-invasive technique for studying neural processes with precise temporal resolution. By manipulating stimulus features, and examining resultant event-related potentials, we are able to examine complex neural processes. Participant characteristics are also important to consider when examining ERPs. The next section will look at how EEG is being used to examine neuroplasticity non-invasively – a task that was previously considered impossible but will be employed in two of the studies reported in this doctoral thesis.

1.7. Neuroplasticity

Neuroplasticity is the process by which the CNS adapts its function or organisation based on information coming from a continuously changing internal and external environment, including information provided by the senses. This includes changes in both the electrical and chemical activity of neurons, modulated by changes in hormones and synaptic structure (Miller & Lane, 2000). By examining factors affecting plasticity of sensory systems in the CNS at the molecular level, we gain a deeper understanding of subsequent behaviours and responses to sensory stimuli. Currently, the best-known molecular mechanism of neuroplasticity is long-term-potentiation (LTP). Long-term potentiation refers to a long-lasting experience-dependent change in the efficacy of synaptic transmission (Lüscher & Malenka, 2012). It was first discovered by Bliss and Lømo (1973) when they noticed that brief, high-frequency electrical stimulation of an excitatory pathway to the hippocampus produced a long-lasting enhancement in the strength of the stimulated synapses. There are several mechanistically different forms of LTP (Malenka & Bear, 2004); however, this thesis will focus specifically on *N*-methyl-*D*-aspartate (NMDA) receptor-dependent LTP. This is because NMDA-receptor functioning has been implicated in neuroplasticity processes in typically developing adolescence, as well as in ASCs (see section 1.7.4. for more details).

1.7.1. NMDA receptor dependent LTP

NMDA receptors are ionotropic glutamate receptors that are formed from a tetramer (Figure 1.3). There are seven genes (GluN1, GluN2A, GluN2B, GluN2C, GluN2D, GluN3A, and GluN3B) that code for the polypeptides used to make up an NMDA receptor. Different

combinations of these polypeptides produce NMDA receptors with differing pharmacological and biological properties (Cull-Candy & Leszkiewicz, 2004). Consequently, NMDA receptors in different parts of the brain, or at different stages of development (see section 1.7.4.1 on changes in NMDA receptors over development), may not function in the same way.

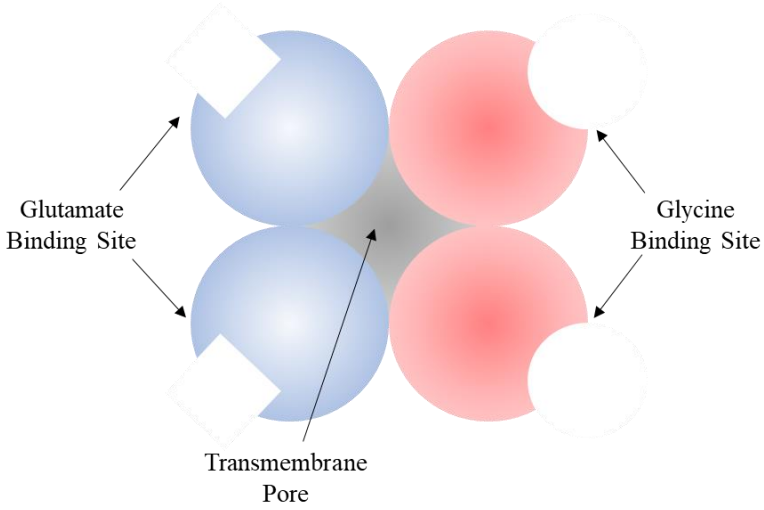


Figure 1.3. *Schematic for the structure of the NMDA receptor complex.*

Unlike other ionotropic glutamate receptors, NMDA receptors require binding of both glutamate *and* glycine (or D-serine) in order for the receptor to function. However, even after binding of glutamate and glycine, NMDA receptors are still inactive at resting membrane potentials, due to a voltage-dependent block of the channel by magnesium (Mg^{2+}) preventing an influx of cations. Only when the cell is sufficiently depolarised (through sustained activation of AMPA receptors) is the magnesium ion released, and the NMDA-receptor channel open for cations (Na^{+} and Ca^{2+}) to cross the cell membrane. In this way, NMDA-receptors function as molecular coincidence detectors – only activating when bound with glutamate and glycine *and* when the cell is sufficiently depolarised, which is essential for synaptic plasticity (Lüscher & Malenka, 2012).

Ca^{2+} influx through open NMDA receptors triggers cascades of second-messenger systems within the cell that are important for inducing long-term changes in synaptic efficacy. Increases in Ca^{2+} concentration in the post-synaptic neuron activates two protein kinases: protein kinase C and calcium-calmodulin-dependent protein kinase II (CaMKII; Lüscher & Malenka, 2012). What happens between activation of protein kinases and a potentiated synapse is less well understood. One possibility is that existing AMPA receptors become more effective as they are phosphorylated by the protein kinases, which increases the ionic conductance of the channel (Liu & Zukin, 2007). Another possibility is that, following CaMKII activation, new AMPA receptors are added to the post-synaptic membrane by fusing with nearby vesicles that are studded with AMPA receptors (Collingridge, Isaac, & Wang, 2004; Isaac, Nicoll, &

Malenka, 1995; Liao, Hessler, & Malinow, 1995; Lüscher, Nicoll, Malenka, & Muller, 2000; Lüscher & Frerking, 2001). There is also evidence to suggest that, following LTP, post-synaptic dendritic spines appear to bud and form new synaptic contacts with axons, which increases the area of responsive post-synaptic surface as well as the likelihood that an action potential in the axon will trigger presynaptic glutamate release (Lüscher & Frerking, 2001; Malinow, 2003; Malinow & Malenka, 2002). A schematic diagram of NMDA receptor dependent LTP is presented below in Figure 1.4.

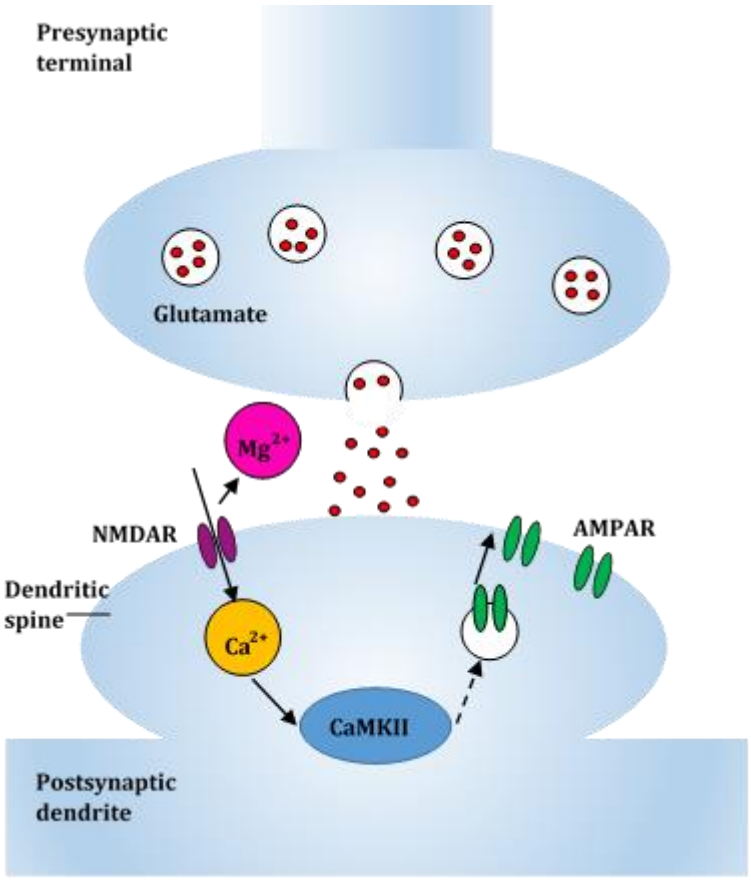


Figure 1.4. Schematic for NMDAR dependent long-term potentiation. Glutamate is released from the presynaptic terminal and binds to NMDA and AMPA receptors. When the post-synaptic cell is sufficiently depolarised, the Mg^{2+} that normally blocks the NMDA receptor channel is removed and allows Ca2+ to enter the post-synaptic cell. This initiates internal signalling molecules, such as calcium/calmodulin-dependent protein-kinase II (CaMKII), and results in the insertion of additional AMPA receptors into the postsynaptic membrane.

Whereas induction of LTP increases the efficacy of synaptic transmission, long-term depression (LTD) decreases the efficacy of synaptic transmission. It is suggested that LTP and LTD result from a phosphorylation and dephosphorylation, respectively, of AMPA receptors (Bear & Malenka, 1994). LTP induction requires the post-synaptic neuron to be *strongly*

depolarised, whereas LTD induction occurs when the post-synaptic neuron is *weakly* depolarised. When the post-synaptic neuron is weakly depolarised, NMDARs are still partially blocked by $Mg^{2+,}$ meaning that only a small trickle of Ca^{2+} will be allowed into the post-synaptic neuron. Consequently, instead of the kinases that are activated by high concentrations of Ca^{2+}, weaker and more prolonged elevations in Ca^{2+} concentration leads to activation of a protein phosphatase cascade (Lee, Kameyama, Huganir, & Bear, 1998). Furthermore, LTD has been shown to be associated with internalization of AMPA receptors at the synapse (Beattie et al., 2000). Essentially, LTP and LTD reflect a bidirectional regulation of both the phosphorylation and number of post-synaptic AMPA receptors (Bear, Connors, & Paradiso, 2007).

1.7.2. Non-human animal studies of long-term potentiation

The biological mechanisms of LTP were first discovered in the early 1970's (Bliss & Gardner-Medwin, 1973; Bliss & Lømo, 1973), and have been studied extensively since, with much progress being made in elucidating the mechanisms underlying its induction and expression. Studies of LTP tend to follow similar steps for inducing and measuring LTP. Typically, LTP is induced by high-frequency electrical stimulation (also known as a tetanus) of afferent fibres. It is deemed that LTP has been successfully induced when immediate and enduring increases in postsynaptic responses are observed at glutamate synapses in cortical neurons. The increased efficiency of synaptic transmission as a result of LTP induction has been shown to last for hours *in* vitro (Bliss & Collingridge, 1993), and even longer *in vivo*, with studies demonstrating effects for days, weeks, and months (Bliss & Gardner-Medwin, 1973; Staubli & Lynch, 1987), and even up to a year (Abraham, Logan, Greenwood, & Dragunow, 2002) depending on the stimulation protocol.

Studies examining the mechanisms of LTP maintenance show that there are at least two stages: early-LTP is often induced with a weaker induction protocol, may only last for a few hours, and does not depend on the synthesis of new proteins, whereas late-LTP can be induced by stronger stimulation protocols, lasts for at least several hours, and requires synthesis of new proteins. However, there are questions surrounding the strength of evidence supporting this theory (see Abbas & Ris (2015) for a detailed review and discussion). LTP effects are maintained by the addition of more post-synaptic AMPA receptors (Isaac et al., 1995; Lang et al., 1995; Park, Penick, Edwards, Kauer, & Ehlers, 2004), neurotrophins (Pang et al., 2004), and synthesis of new proteins (Abraham & Williams, 2003; Reymann & Frey, 2007). LTP can be characterized by several properties: it is long-lasting, frequency dependent (stimulation with higher frequencies induces potentiation, whereas stimulation with lower frequencies can induce depotentiation), input-specific (only inputs that are active during the tetanus will be potentiated;

inputs that are inactive during the tetanus will not be potentiated), dependent on increases in intracellular calcium levels, and is saturable (Cooke & Bliss, 2006).

Until recently, tetanization of afferent fibres could only be achieved by inserting an electrode into the desired brain region and directly applying electrical stimulation. Consequently, the vast majority of LTP research has been conducted using non –human animals, with only a few studies able to investigate LTP processes in human cortical tissue, limited to experiments run with excised cortical tissue from patients undergoing surgery as a treatment for temporal lobe epilepsy. Studies carried out with human cortical tissue taken from the hippocampus (Beck, Goussakov, Lie, Helmstaedter, & Elger, 2000) and the temporal lobe (Chen et al., 1996) found that the LTP properties displayed in the human cortical tissue was identical to that seen in animals. Interestingly, the degree of LTP induced by tetanic stimulation in tissue taken from patients with hippocampal epileptic foci was smaller than in tissue taken from patients with extra-hippocampal epileptic foci. A possible reason for this difference is that synapses in epileptic tissue have become potentiated through epileptic activity, and are near saturation (Cooke & Bliss, 2006). This observation also highlights the difficulty of trying to investigate the mechanisms of LTP in human cortical tissue that is not neuro-typical, but it would be impossible to access cortical tissue from healthy neurotypical human subjects.

Notably, an alternative method of inducing LTP that does not require the application of high-frequency electrical stimulation has been developed. Studies on the visual areas of developing tadpoles (Zhang, Hui-zhong, & Poo, 2000), and of anaesthetized but awake mice (Clapp, Eckert, Teyler, & Abraham, 2006; Cooke & Bear, 2010) have shown that LTP-like changes can be induced by natural sensory stimulation. In these studies, high-frequency electrical stimulation, which is typically used in animal studies of LTP, is replaced with high-frequency visual sensory stimulation. In these studies, the degree of potentiation is measured by examining the evoked potential recorded over the appropriate sensory cortex, relative to pre-HFS baseline values. It has been suggested that high-frequency sensory activity arriving at sensory cortex might induce LTP by exciting neurons in a similar way to the high frequency electrical stimulation that is typically used in animal studies, assuming that a sensory volley arriving at the sensory cortex is analogous to an afferent volley elicited by electrical stimulation (Clapp, Hamm, Kirk, & Teyler, 2012).

1.7.3. Sensory-induced potentiation in humans

LTP-like changes in sensory cortical areas have been observed in human after presentation of visual and auditory HFS (Clapp et al., 2005; McNair et al., 2006; Ross et al., 2008; Spriggs et al., 2019; Sumner et al., 2018; Teyler et al., 2005; Zaehle, Clapp, Hamm, Meyer, & Kirk, 2007). Using a very elegant design, Teyler and colleagues presented healthy participants with a checkerboard stimulus whilst measuring visual evoked potentials (VEP) with

EEG recording electrodes (Teyler et al., 2005). The checkerboard was first presented at a low frequency (1 Hz), with 50% of checkerboards presented in a random order to the left visual field and the other half presented to the right visual field. After obtaining these baseline VEPs, the same checkerboard was then presented either to the left or right visual field for 2 minutes at a high frequency (9 Hz) to induce LTP. In a control condition, participants were asked to focus on a red circular dot for 2 minutes instead of receiving photic tetanic input. To determine if potentiation had been induced, the checkerboard was again presented at the lower baseline frequency (1 Hz) in 7-minute blocks with breaks in between (2-9, 15-21, 30-37, and 45-52 minutes following the end of tetanic stimulation) and VEPs recorded. Analysis of the VEP waveform after HFS found significant potentiation around the negative peak occurring around 170ms post-stimulus onset (termed N1). This effect was long lasting and found only in the hemi-field that received the HFS stimulation, thus supporting the idea that LTP was induced using this non-invasive protocol. There was no change when the photic tetanus was not delivered. The findings of this study have also been replicated in the auditory cortex (using an auditory tetanus; Zaehle et al., 2007), and with fMRI showing increased hemodynamic response in the extra-striate visual cortex (V2) following high frequency visual stimulation (Clapp et al., 2005). Together, these studies demonstrate that it is possible to induce and record LTP-like changes in intact human cortex non-invasively with sensory stimulation.

Signficantly, the ability to examine LTP-like processes in the human brain non-invasively opens the door to examine whether LTP processes are impaired in disorders which affect the glutamatergic system. An example of such a study was conducted by Çavuş et al. (2012), who modified the checkerboard paradigm developed by Teyler et al (2005) and Clapp et al (2005) to investigate deficiencies in visual plasticity in schizophrenia, as it had been suggested that the cognitive and positive symptoms associated with schizophrenia may in part be due to hypofunction of NMDA receptors (Krystal et al., 2003; Stephan, Baldeweg, & Friston, 2006). Consequently, in schizophrenia, hypofunction of NMDA receptors on glutamatergic receptors would result in impaired LTP, whilst hypofunction of NMDA receptors on inhibitory interneurons would result in diminished inhibition. In their study, Çavuş et al. found that whilst healthy controls showed persistent potentiation (20 minutes post-HFS) of both the C1 and N1b components of the VEP waveform, schizophrenic participants showed no potentiation at C1 and only a short-lasting enhancement of the N1b. Çavuş et al. suggest that these results support their hypothesis, proposing that thalamocortical activation of hypofunctioning NMDA receptors on the principal neurons in the primary visual cortex results in impaired C1 potentiation in schizophrenia, whilst activation of hypofunctional NMDA receptors on excitatory and inhibitory neurons in association cortices results in transient local disinhibition and short-lasting N1b enhancement. Although this study did not directly examine the role of NMDA receptors in cortical plasticity in schizophrenia, the results and the known mechanisms of neuroplasticity are

consistent with the NMDA hypofunction model of schizophrenia. Consequently, the Visual Cortical Plasticity Paradigm, developed by Çavuş et al may be suitable for examining NMDAR-dependent LTP in other populations, and for tracking changes in NMDA-dependent LTP over development.

1.7.4. Factors affecting neuroplasticity

1.7.4.1. Developmental stage

One of the main aims of this doctoral thesis was to examine a possible neural mechanism underlying individual differences in sensory responsivity by studying neural plasticity in visual sensory areas. In Chapter 4, I report a study that was designed to examine the relationship between neural plasticity and sensory responsivity in typically developing adolescents. One of the reasons for looking at neural plasticity during adolescence was because of evidence suggesting that the molecular mechanisms used to achieve LTP depend on the developmental stage of the animal. For example, Yasuda, Barth, Stellwagen, and Malenka (2003) examined the role of protein kinase CaMKII in LTP induction in rodents of different ages. Their results indicated that CaMKII becomes more important with development but is not actually required for LTP until approximately P14-20. Similarly, the subunit composition of NMDA receptors is tightly regulated during cortical development. For example, there is a quantitative switch in the dominant synaptic subunit from NR2B to NR2A at both cortical and thalamic synapses in early postnatal development (Liu, Murray, & Jones, 2004; Wang et al., 2011). Furthermore, animal studies have also shown that the ability of synapses to undergo LTP depends on the developmental stage of the animal (Crair & Malenka, 1995; Izumi & Zorumski, 1995). The majority of studies looking at how LTP processes change over development have focussed on early post-natal periods. This thesis, however, is focused more specifically on the adolescent period of development so this next section will examine what is currently known regarding changes in neuroplasticity during the adolescent period. Given that many of the studies discussed in this next section are based on rodent models, it is worth mentioning that rodents are generally considered to be 'adolescents' during postnatal days (PND) 28 to 42 (Spear, 2000).

1.7.4.1.1. Changes in neuroplasticity during adolescence

The child mammalian brain is distinguishable from the adult brain by the presence of connections between brain areas that are not interconnected in the adult brain. This is because overproduction of neurons with ensuing neuronal death in childhood ensures that an appropriate balance of projection and receptive neurons are attained (Williams & Herrup, 1988). During adolescence, brain maturational processes are still ongoing with significant changes including increases in white matter volume and a reduction in grey matter volume and (Giorgio et al., 2010). One of the processes that is thought to lead to reduction in grey matter volume during

this developmental period is 'synaptic pruning'. In the human cortex, peak synaptic density occurs during early childhood, followed by robust synapse elimination during early and mid-adolescence, particularly in the auditory and prefrontal cortex (Huttenlocher, 1979; Huttenlocher & Dabholkar, 1997), then continuing at a lower rate into early adulthood (Petanjek et al., 2011). It has been suggested that NMDA-receptor dependent LTP and long-term depression (a long-lasting reduction in synaptic strength following stimulation; LTD) may constitute the molecular mechanism underpinning synaptic pruning in adolescence, with greater emphasis on LTD and synaptic elimination (Selemon, 2013).

The binding of cortical glutamate to its NMDA receptor sub-type peaks in early-adolescence, and from there declines significantly, with a loss of one third of NMDA receptors by PND60 (Guilarte, 1998; Insel, Miller, & Gelhard, 1990). Interestingly, Schramm and colleagues (2002) showed that NMDAR-dependent LTP is observed more frequently in adolescent mice compared to adult mice. Specifically, they showed that tetanus-evoked NMDA receptor-dependent LTP is more readily induced in the nucleus accumbens of "adolescent" (3weeks old) mice compared to adult mice (6-20 weeks old). In addition, they report that removal of extracellular Mg^{2+} restores LTP in the adult nucleus accumbens, suggesting that it is induction processes (and not maintenance processes) that are developmentally regulated. Together, these studies suggest that glutamate and NMDA receptor systems play a crucial role in the neurochemical remodelling during adolescence. In this thesis, I will use a sensory-induced potentiation paradigm to test whether it's possible to replicate Schramm's findings in humans, by examining whether LTP-like changes are more readily induced in human adolescents compared to adults (Chapter 4).

1.7.4.2. NMDA receptor abnormalities and neuroplasticity

There is increasing evidence suggesting that certain risk genes for various mental health conditions are implicated in the regulation of synaptic plasticity. For example, expression of certain risk genes for schizophrenia in animal models results in NMDAR hypofunction and impaired LTP (Kwon et al, 2008; Tang et al., 2009). Of particular relevance to this thesis is recent evidence suggesting that risk genes associated with ASCs are also implicated in dysfunction of NMDA receptors (for a review see Lee, Choi & Kim, 2015). Specifically, *de novo* mutations in the GRIN2A and GRIN2B genes, that respectively code for the GluN2A and GluN2B subunits, have been linked with ASCs (Kenny et al., 2014; O'Roak et al., 2012; O'Roak et al., 2012; Tarabeux et al., 2011; Yoo, Cho, Park, Yang, & Kim, 2012). It is thought that ASC-related GRIN2A/GRIN2B variants will alter the functional properties of NMDA receptors, and as a result will alter the efficiency of NMDA-receptor dependent plasticity (Lee, Choi, & Kim, 2015). Changes to plasticity in ASC may also be related to ability to respond in a modulated manner, and may therefore help to explain why individuals with ASCs are more

likely to be over- or under-responsive to sensory stimuli (Crane et al., 2009; Horder, Wilson, Mendez, & Murphy, 2014). Furthermore, regulating sensory responsivity is important for adaptive social behaviours because social interactions require flexible responses to multiple, simultaneous, and unpredictable inputs, as well as the ability to notice social cues and respond appropriately (*e.g*. matching the volume of the other speaker, using a light touch if someone is upset or scared) (Ben-Sasson et al., 2009). Consequently, the study outlined in Chapter 5 of this doctoral thesis aimed to examine the relationship between neuroplasticity and sensory responsivity in adults with ASCs and neurotypical matched controls.

1.8. Research questions

The review of the literature included in this chapter has demonstrated that effective sensory processing is critical for survival at any age, so it is important to understand how sensory-based experiences may change across the life span. In early development, the aim is to learn to process sensory information as quickly as possible, so that more complex behavioural responses to sensory stimuli can be developed in the future. Environmental sensory information is simply perceived, modulated and organised, eventually leading to adaptive and more complex responses as we develop. In adolescence, however, it is important to effectively and adaptively balance internal drives and desires with the external pressures of social norms and adult expectations. This period of development is also associated with increases in levels of anxiety and depression, as well as increased risk-taking behaviours, which may in part be due to sensory processing difficulties. The majority of sensory processing research has been carried out with clinical populations, as it is well recognised that many mental health conditions are associated with sensory processing difficulties. The aim of this research has typically been to identify patterns unique to individual diagnoses, although this has proved difficult due to the heterogeneity and comorbidities amongst mental health conditions. There is less research exploring sensory processing difficulties in the neurotypical population; although, these studies often show sensory processing difficulties are present and are associated with negative outcomes even in non-clinical samples.

Both the Sensory Integration Theory and Dunn's Model of Sensory Processing highlight the role of neural response in sensory processing difficulties. For a neural response to sensory stimuli to be adaptive requires flexibility, or plasticity. As far as I am aware, there is currently no research exploring the relationship between sensory responsivity and cortical plasticity. This may in part be due to historic difficulties in measuring cortical plasticity in humans. Traditionally, studies of neuroplasticity required insertion of an electrode into desired brain regions in order to stimulate neurons and measure resultant changes in post-synaptic response. Consequently, the majority of research on neuroplasticity has been carried out on non-human animal subjects, or less often in humans undergoing brain surgery. More recently,

however, paradigms have been developed that allows for non-invasive induction and measurement of LTP-like changes. These non-invasive paradigms substitute high-frequency electrical stimulation for high-frequency visual stimulation, assuming that a sensory volley arriving at the cortex is analogous to an afferent volley elicited by electrical stimulation and measure the resultant changes in electrical activity using EEG. Although it is still a small field of research, there is growing interest in using sensory-tetanic stimulation paradigms to investigate LTP-like changes in humans. Together, these studies suggest that high frequency sensory stimulation induces changes in plasticity that are similar to those induced by high frequency electrical stimulation. These paradigms may also be useful examining factors that affect neuroplasticity, including developmental stage, genetics, and lifestyle factors.

The overall aim of this doctoral thesis is to investigate the role of sensory processing and cortical plasticity in typical and atypical development. Three empirical studies that tackle different aspects of this overall aim are reported in Chapter's 3, 4, and 5. Many of the methodological procedures or instruments are consistent across these three studies. Consequently, Chapter 2 is a methodological chapter and provides information on the various questionnaire measures used throughout this doctoral work, detailed information about the Visual Cortical Plasticity Paradigm, EEG acquisition and processing, and general information about how statistical analyses were conducted in the thesis.

The first empirical study (Chapter 3) focusses on examining whether one can see changes in sensory responsivity in the transition from adolescence into adulthood, and whether sensory responsivity at different ages is related differentially to the individual's well-being. Currently, the literature exhibits a wealth of research examining sensory processing difficulties in childhood, but significantly less is known about sensory processing difficulties during adolescence (particularly in those who are neurotypical), and how this might relate to other difficulties typically experienced by adolescents. This is a critical period of development that has often been overlooked, in the neurotypical population, despite the fact that this age group is synonymous with increased risk-taking behaviours and the onset of many mental health conditions. Research in childhood (and to a lesser degree in adulthood) has demonstrated that extreme sensory responsivity is associated with increased levels of anxiety and depression; however, this has yet to be investigated in typically developing adolescents. Consequently, the questionnaire-based study outlined in Chapter 3 explored the relationships between sensory processing style, negative affect (anxiety, depression, and stress), and risk-taking in a sample of 418 neurotypical adolescents and adults (aged 11-30 years). Research questions for Chapter 3 were:

1) Does degree of sensory responsivity change during the transition from early-adolescence to adulthood?

2) Does degree of sensory responsivity affect risk-taking and level of negative affect in the transition from early-adolescence to adulthood?

3) Is there an interaction effect between sensory responsivity and age on risk-taking and level of negative affect in the transition from early-adolescence to adulthood?

The second empirical study (Chapter 4) was designed to examine the relationship between neuroplasticity and sensory responsivity in neurotypical adolescents and adults. Animal studies have demonstrated that LTP is more readily induced in adolescent rodents, compared to adult rodents (Schramm et al., 2002). However, very little is known about LTP processes in human adolescents. Consequently, the study reported in Chapter 4 utilised the Visual Cortical Plasticity Paradigm to assess developmental differences in LTP-like changes over the visual cortex. Furthermore, this study was also designed to test whether there is a relationship between plasticity changes in a sensory cortical area and an individual's self-reported degree of sensory responsivity. Consequently, this study aimed to investigate whether sensory responsivity was also related to degree of LTP-like changes in the visual cortex. Research questions for Chapter 4 were:

1) Do neurotypical adolescents show greater LTP-like changes in the visual cortex compared to neurotypical adults following sensory tetanic stimulation?

2) Is the magnitude of LTP-like changes related to degree of sensory responsivity in neurotypical adolescents and adults?

The final empirical study reported in this doctoral thesis (Chapter 5) also aimed to examine the relationship between neuroplasticity and sensory responsivity in adults with ASCs and neurotypical matched controls. There is increasing evidence from animal models implicating the role of NMDA receptors and glutamatergic functioning in ASC (as discussed in section 1.7.4.3.); however, relatively little is known about neuroplasticity in humans with ASC. Therefore, this study again utilised the Visual Plasticity Paradigm to examine whether LTP-like changes are reduced in adults with ASCs compared to neurotypical matched controls. Sensory processing difficulties are also more prevalent in individuals with ASC than in the neurotypical population, so this study again aimed to explore the relationship between magnitude of LTP-like changes and sensory responsivity. Research questions for Chapter 5 were:

1) Do adults with ASCs show a smaller magnitude of LTP-like changes (or no LTP-like changes at all) in the visual cortex compared to neurotypical matched controls following sensory tetanic stimulation?

2) Is the magnitude of LTP-like changes related to degree of sensory responsivity in adults with ASCs and neurotypical matched controls?

Following on from the empirical chapters, Chapter 6 summarises the results from this doctoral work, offers a discussion on the findings in relation to past research, describes the key strengths and limitations of the research presented, and concludes with some considerations for future research.

Chapter 2: General Methodology

2.1. Introduction

Many of the methodological procedures or instruments used in this doctoral thesis are consistent across the three empirical studies reported. To save repeating details of procedures or instruments in the following chapters, this chapter will provide general details of the questionnaires, EEG measures and paradigms, and the approach to statistical analysis in this doctoral research.

2.2. Participants

Specific demographic information about participants are presented in the methods section of each empirical chapter; however, there are commonalities between these studies regarding recruitment and ethical approval. Adolescent participants were recruited either through contact with their school, advertisements on social media, or through email invitation. Adult participants were recruited through advertisements on social media, through email invitation, and as part of a University run scheme to encourage undergraduate participants to take part in studies in return for credits. All the studies reported in this doctoral thesis were approved by the University of Sheffield's Department of Psychology ethics committee.

2.3. Materials & Apparatus

2.3.1. Electroencephalography (EEG)

2.3.1.1. EEG Recording

EEG recordings were carried out using Biosemi Active Two 64-channel + CMS / DRL electrode caps and Biosemi 'Pin-Type' Ag-AgCl active electrodes. The electrodes caps were fitted according to the 10/20 electrode system. EEG signals were amplified using the Biosemi Active Two AD-Box. Electrode offsets were stable and kept below ±25 μV. EEG signals were recorded continuously with a sampling rate of 2048 Hz. During recording, the paradigm was delivered using a Viglen Genie Intel Core 15 computer and presented on a 24 inch (61cm) Iiyama G-MASTER 144Hz monitor. The visual stimuli were presented on a white background, and motor responses were recorded using the space bar. During the task, participants were seated approximately 57cm away from the computer monitor in a dark room (only lit by the computer monitor).

2.3.1.2. EEG Processing

All EEG pre-processing was conducted offline. EEG data was down-sampled from 2048 Hz to 512 Hz using Biosemi's decimator tool to make files more manageable. Biosemi's decimator tool applies a fifth order sinc filter to prevent aliasing. Pre-processing of the EEG data was carried out using MATLAB R2014b with in-house scripts that utilised various

functions provided by EEGLAB version 14.1.0 (Delorme & Makeig, 2004). Figure 2.1 illustrates the pre-processing stream for the ERP data analysed in Chapters 4 and 5.

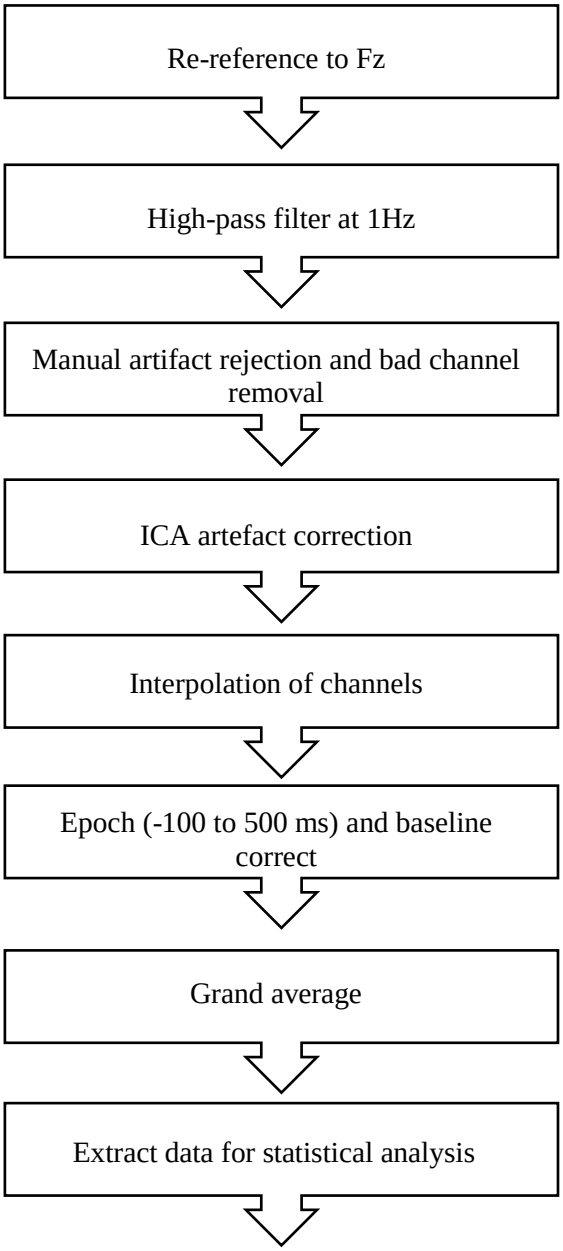


Figure 2.1. Processing stream for EEG data that is analysed in Chapter's 4 and 5.

The aim of the pre-processing stream is to improve the signal-to-noise ratio (SNR) by removing artefacts from the data. Typical EEG artefacts include eye blinks, lateral eye movements, muscle movement, poor electrode impedances and non-neural electrical noise. EEG artefacts can be reduced during data collection by asking participants to sit still, ensuring the electrodes are well connected, and keeping the room cool to minimize slow drifts resulting from sweat; however, it is inevitable that artefacts will occur. When trying to improve the SNR we can either reject the artefact completely by removing that portion of recording from the dataset;

however, this also means that we lose the entire neural signal from that period. Alternatively, we can identify the artefact and use various pieces of software to correct for the artefact, minimizing the amount of noise without the loss of neural signal. The following sections discuss the individual steps of the pre-processing stream used in this doctoral thesis.

2.3.1.2.1. Re-Referencing

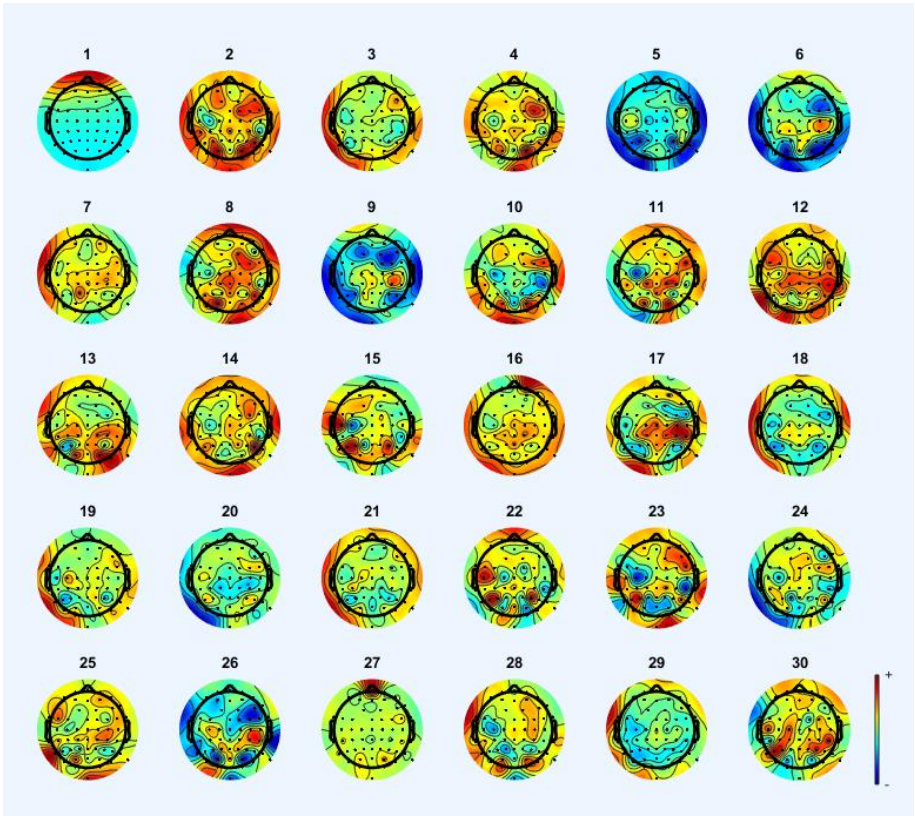
Unlike other EEG recording systems, every electrode or combination of electrodes can be the "reference" in Biosemi systems because the choice is made entirely in software (BioSemi, n.d.). When no reference is selected in the software, EEG signals are displayed with respect to the Common Mode Sense (CMS) electrode. It is recommended that a reference electrode is selected for anything more than a quick check of the electrodes to achieve the full 80 dB common mode rejection ratio (CMRR). To ensure that our results were comparable to that of Çavuş et al. (2012), channel Fz was selected as the reference electrode for both EEG studies in this doctoral thesis.

2.3.1.2.2. High-Pass Filtering

Filtering is a useful and sometimes necessary tool for improving the signal-to-noise ratio in EEG data. Forms of noise that can be removed by applying a high-pass filter (that attenuates low frequency bands) include slow changes in voltage caused by skin potentials, movement artefacts, and other gradual changes in the voltage offset. A high-pass Hamming windowed finite impulse response (FIR) filter with a half-amplitude of 1Hz, with a -6dB (half-amplitude) cut-off was applied to the continuous EEG dataset. A 1Hz high-pass filter was selected as this produced more informative components following independent components analysis (ICA; see 2.3.1.2.4) compared to a high-pass filter of 0.1 Hz (see Figure 2.2). Both types of high-pass filters are equally capable of isolating the blink component (Component 1 in Figure 2.3A and Component 1 in Figure 2.2B), however only with the 1Hz high-pass filter are we also able to distinguish a component for lateral eye movement (Figure 2.2B Component 6), and components for neural activity (Figure 2.2B Components 3, 5 and 7).

High-pass filtering may improve classification of components (Winkler, Debener, Müller, & Tangermann, 2015), but can also lead to distortions in ERPs, including a systematic underestimation of onset latency (VanRullen, 2011), and artificial components (Acunzo, MacKenzie, & van Rossum, 2012). Because of these distortions, it is often recommended that researchers either don't use a high-pass filter or apply very low (≤ 0.1 Hz) cut-off high-pass filters (Acunzo et al., 2012; Luck, 2014). However, others have argued that in studies focussing on differences between groups, filter settings should have the same impact on EEG signal across all experimental groups and leave any potential group difference unaffected (Sinke et al., 2014). Therefore, it is unlikely that use of the 1Hz high-pass filter will influence assessment of group differences explored in this doctoral thesis.

A



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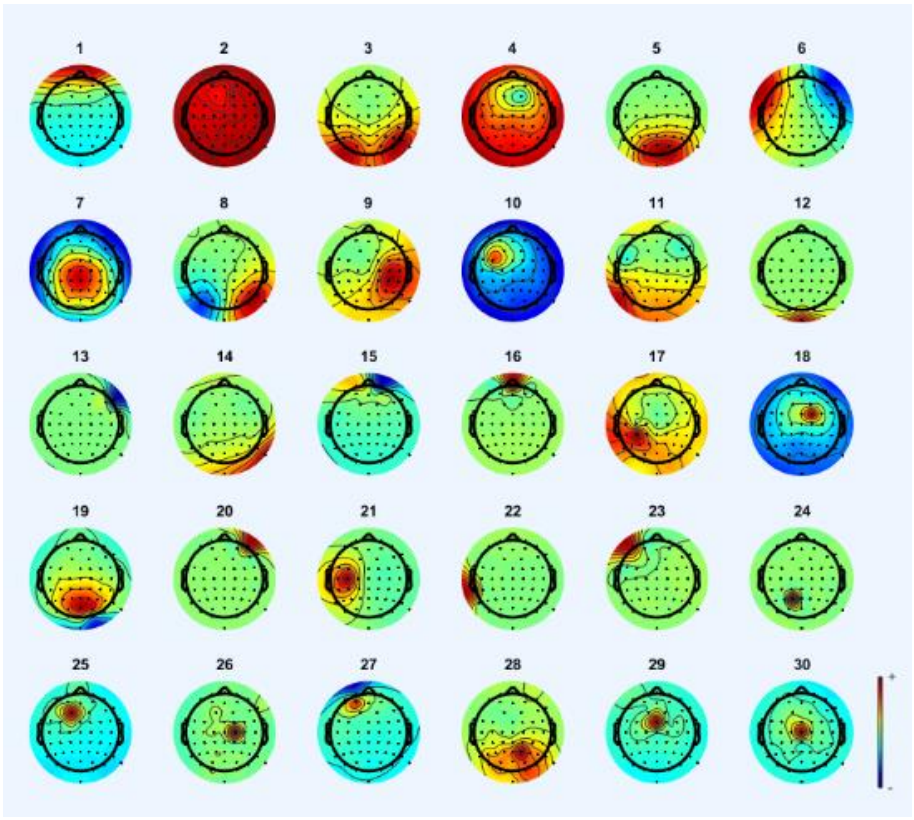


Figure 2.2. ICA component plots for the same participant after applying different high-pass filters. **A**. ICA components after applying a high-pass filter at 0.1Hz. **B**. ICA components after applying a high-pass filter at 1Hz. Only the first 30 components are presented.

2.3.1.2.3. Artefact Rejection and Bad Channel Removal

The next stage in the pre-processing stream was to manually scroll through the EEG recording and remove any sections that showed a high level of noise. Typically, these sections occur when the participant was moving, swallowing, or talking. These periods of very noisy data tend to occur infrequently, and usually during breaks in the paradigm, so removing the entire section of data where this noise occurs does not usually have much effect on the number of trials remaining for statistical analysis. Ocular artefacts (such as eye blinks and lateral eye movements) can occur more frequently throughout the experiment, and therefore removing the entire section of data every time an ocular artefact occurred would also mean removing neural data that is of interest. Trials were removed when participants blinked when the stimulus was onscreen as they would not have seen the stimulus. For all other blinks and ocular artefacts, an alternative method was used and is discussed in the next section (Independent Components Analysis (ICA), section 2.3.1.2.4).

Whilst manually scrolling through the EEG signals, some channels will show excessive amounts of noise. Sometimes this noise is continuous, which may be due to loss of connection during testing or due to bridging with another nearby electrode, which tends to present as a high-frequency signal. Conversely, the noise may be more intermittent and present as occasional large peaks and troughs that are not consistent with activity of other nearby electrode sites. In order to run a successful ICA, the EEG data needs to be as clean as possible; therefore, channels exhibiting continuous high-frequency noise are removed from the dataset. For channels that show intermittent amounts of noise, the decision as to whether or not to remove the channel depends on how often these periods of noise occur and when they occur during the study. If a channel only displayed short bursts (1-2 seconds) of noise a couple of times during the study, then it is more conservative to remove those sections of data and keep the channel, especially if these periods of noise occur during breaks in the paradigm. If, however, the channel repeatedly shows periods of noise throughout the experiment, particularly during trials, then a more conservative approach is to remove that channel, rather than removing the noisy periods of data. When pre-processing EEG data for Chapters 4 and 5, if a channel had infrequent and short (no more than 1 or 2 seconds in length) periods of noise, I would reject the entire noisy portion of data from all channels. If a channel showed frequent and long periods of noise, then I would remove that channel from the dataset.

2.3.1.2.4. Independent Components Analysis (ICA)

Independent Components Analysis (ICA) attempts to decompose an observed multivariate signal into its latent sources of signal, without knowledge of how the signals were mixed. EEG data has multiple independent sources of activity in the brain (including neural activity, ocular activity, muscle activity, and electrical activity from outside the body), that are

linearly summed together at each electrode site. In the case of EEG, we want to isolate these independent sources of activity from the mixtures recorded by each electrode. ICA is increasingly being used to isolate and remove ocular artefacts from EEG data (Jung et al., 2000; Vigário, 1997). ICA is particularly good at identifying and removing blink artefacts because they are large in amplitude, have a discrete source, and reliably produce the same signal from blink to blink. Use of specific electrooculography (EOG) channels is not necessary for detecting ocular artefacts, although they may improve the accuracy of ocular components (Vigário, 1997). Given that the EEG studies in this thesis would be testing young adolescent participants, and autistic participants, who may be more sensitive or uncomfortable with having electrodes placed near their eyes, EOG channels were not used in these studies. It is important to remove ocular artefacts as they are often much larger in magnitude compared to EEG activity, meaning that if ocular artefacts are left in the data, then they can greatly distort the signal.

After running the ICA, the isolated sources of signal are presented as independent components (as in Figure 2.2). These components include neural signals, including those demonstrating neural processing of visual stimuli, as well as signals coming from sources of noise in the data, such as ocular and muscle artefacts. EEGLAB allows you to select particular components and remove the signal associated with that component from the dataset. Consequently, this technique can be used to subtract signals arising from blinking and other unwanted artefacts away from the dataset, thereby improving the signal to noise ratio.

Two types of ocular artefact components are commonly observed after running the ICA. The most commonly observed ocular artefact component represents activity coming from blinking (shown in Figure 2.3A), which is characterised by prominent activity in frontal electrodes that is roughly equal across both sides. Another commonly observed ocular artefact component captures lateral eye movements (Figure 2.3B), which is characterised by prominent activity in frontal electrodes that is positive in polarity on one side, and negative on the other.

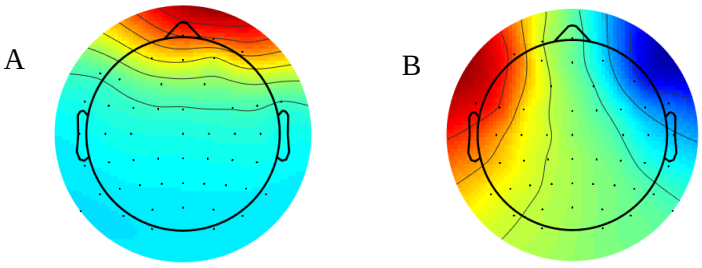


Figure 2.3. Component topographies for ocular artefacts. **A**. Activity relating to eye-blinks. **B**. Activity relating to lateral eye movements**.**

It is important to acknowledge that there are limitations to the ICA method. First of all, ICA can only decompose *N* sources from *N* channels, and it is probable that the recorded EEG activity occurs from more physically separable sources than the number of electrodes used to measure said activity. However, given that we are only using ICA as a means of ocular artefact removal, which is relatively large in magnitude, and not using the components to analyse neural activity, which may be smaller in magnitude, the number of components produced by the ICA is not an issue in this thesis. Secondly, ICA will only be meaningful if a sufficient amount of data is put through the algorithm. In the visual plasticity studies described in this thesis (Chapters 4 and 5), approximately 32 minutes of EEG activity are recorded which, after down-sampling the datasets to 512 Hz, equates to approximately 983,040 data points. The Swartz Centre for Computational Neuroscience (SCCN, n.d.) suggest that to find *N*-stable components (from *N*-channel data) typically requires more than *kN^2* data sample points (at each channel), where *N^2* is the number of weights in the un-mixing matrix and *k* is a multiplier. Therefore, in the studies presented in this doctoral thesis using 64 channels, each EEG dataset has approximately 983,040 data points, that gives 983040/64^2 = 240 pts/weight points, suggesting that there is enough data to decompose stable components. Overall, ICA is the best method for removing ocular artefacts in the EEG data collected for this thesis.

2.3.1.2.5. Interpolation

In order to create grand-averaged waveforms, data files need to have the same number of channels per participant. However, different numbers of channels may have been removed during earlier pre-processing steps. EEGLAB allows the user to interpolate previously removed channels back into the dataset, by creating estimated signals based on the average activity of other close-by channels.

2.3.1.2.6 Epoching and Baseline Removal

Data were epoched into 600ms segments (-100ms to 500ms) time-locked to the onset of the standard circle, and a pre-stimulus baseline correction applied. A maximum of 90 standard circle epochs was possible for each of the 5 VEP assessments.

2.3.1.3. Visual Steady State Response

The visual HFS used to induce potentiation of the visual evoked potentials (VEPs) is similar to stimuli used in studies of visual steady state responses (VSSRs), whereby EEG power and phase synchrony are enhanced at the driving frequency. Unlike transient VEPs, that are responses of the system to sudden changes in input (e.g. an image appearing then disappearing) and are discussed in relation to the time-domain, VSSRs are spectral responses of the system averaged over multiple trials and discussed in the frequency domain (Vialatte, Maurice, Dauwels, & Cichocki, 2010). For example, during visual HFS in the Visual Cortical Plasticity

Paradigm (section 2.4.1.1), the standard circle is presented at ~8.87 Hz for 2 minutes. If the participant is attending to this flickering image, neurons in the visual cortex should also be responding at a corresponding frequency, leading to an observable peak in the frequency spectrum (around 8.87 Hz), as well as harmonic peaks in phase relation with the stimulus (*i.e.* at multiples of 8.87 Hz).

2.3.1.3.1. VSSR Processing

Whilst much of the pre-processing steps of VSSR data is similar to that used to pre-process the VEP data, there are a few differences which are discussed in this section. As in pre-processing of EEG data for VEP analysis, the continuous dataset was first re-referenced to Fz, and a high-pass filter of 1 Hz applied. I removed noisy channels and scrolled through the dataset to remove noisy sections of data. ICA was used to remove ocular artefacts from the data, and missing channels interpolated back in to the dataset. The 2 minute HFS block was then epoched from the rest of the dataset, and dummy triggers inserted every 2 seconds, so that the data from the HFS block was now epoched into 59 continuous two-second epochs. Epochs were then visually inspected, and any epochs containing excessive amounts of noise were rejected.

Following processing of data, self-made MATLAB scripts (utilising functions from EEGLAB) were used to create a power spectrum for each posterior channel, for each participant. Power spectrums were plot for each participant, and visually inspected to assess whether they showed signs of the VSSR, including a peak response at the frequency bin closest to the HFS frequency (9Hz), and harmonics at multiples of this frequency (e.g. 18Hz, and 27Hz). Finally, 9Hz power values (μV^2/Hz), representing the VSSR to HFS, were extracted using self-made MATLAB scripts. Participants who did not show a peak response at 9Hz, or harmonics at multiples of this frequency, were assumed to have not looked at the tetanizing stimulus long-enough to produce a VSSR and were removed from analyses.

2.3.1.4. Stimuli

In the visual cortical plasticity paradigm, discussed in more detail in section 2.4.1.1, two stimuli were presented to participants (Figure 2.4.B). The black and white checkerboard circle, presented centrally on screen, is 8cm in diameter and subtends 8° of visual angle, with each check subtending 0.3° of visual angle. The blue and white checkerboard square is 9 x 9 cm and subtends 9° of visual angle, with each check subtending 0.5° of visual angle. These stimuli are identical to those used in the paradigm described in Çavuş et al. (2012). A red circular fixation point was presented centrally and continuously (so as not to introduce additional onset VEPs for the fixation point coming on screen after the offset of the experimental stimuli) throughout VEP assessment blocks and the HFS block.

2.3.2. Questionnaires

2.3.2.1. The Life Span Risk-Taking Inventory

As outlined in Section 1.4.1, the biggest changes in risk-taking behaviours tend to occur during adolescence. Therefore, many measures of risk-taking are designed specifically for the adolescent population, such as the Adolescent Risk-Taking Questionnaire (Gullone, Moore, Moss, & Boyd, 2000), or the RT-18 (de Haan et al., 2011). Another common feature of risk-taking questionnaires is that they ask invasive questions about specific risky activities, ranging from substance abuse to unsafe sexual behaviour. For example, the Cognitive Appraisal of Risky Events questionnaire (CARE; Fromme, Katz, & Rivet, 1997) asks responders to rate how likely it is they will "have sex without protection against sexually transmitted diseases", and "drive after drinking alcohol" in the next 6 months. In terms of investigating the trajectory of risk-taking behaviours across the life span, using these existing risk-taking questionnaires could be problematic for several reasons. Firstly, questionnaires designed solely for the adolescent period are not suitable for examining risk-taking across the life span. The behaviours and factors associated with risk-taking may change in strength and type as we move through developmental stages; consequently, it is important to study the trajectory of risk-taking behaviours, not just when they are presumed to be at their peak. Secondly, questionnaires that ask about specific risky activities are problematic because (i) not everyone who completes the questionnaire will engage, or even be aware, of each activity, (ii) interpretation of risky activities will vary depending on the respondents' age (e.g. "Leaving a social event with someone I have just met", from the CARE questionnaire may mean something very different to a 11-year old and a 19-year old respondent), and (iii) participants may not answer honestly due to social desirability biases, all of which reduce the validity of the measure. To avoid these problems and examine the trajectory of risk-taking behaviours at different developmental time points, my aim was to develop and validate a new questionnaire, called the Life Span Risk-Taking Inventory (LRTI).

This new questionnaire was designed to retrospectively measure risk-taking across the entire life span, dividing experiences into the developmental stages of childhood, adolescence, and adulthood, whilst also measuring peer influence and emotional experiences at these three developmental time points. Critically, questions in LRTI do not ask about specific risky activities, but rather ask respondents to rate the frequency of their risk-taking behaviours at all three developmental stages (e.g., "How often did you take risks in your childhood?"). This means that the questionnaire would be more suitable to measure risk-taking at all developmental stages, because it is not dependent on lists of specific activities, of which engagement in will vary across the life span, whilst also being less personally invasive which should help respondents to answer more honestly.

2.3.2.1.1 Method

2.3.2.1.1.1. Participants

Participants aged 18-50 years (n = 432) were recruited via email at The University of Sheffield. Participants reporting history of mental/physical illness (n = 156), participants with missing demographic information (n = 17), participants with incomplete responses (n = 34), and extreme statistical outliers (n = 1) were excluded from analyses. To assess test-retest reliability, participants were asked to complete LRTI at time 1 (T1), then again two weeks later at time 2 (T2). Demographic information about the sample included in analyses at both time points is provided in Table 2.1. Participants were primarily of white ethnicity (84.9%), with remaining participants coming from Asian (7.1%), multiple/mixed (4.4%) and African/Caribbean (0.9%) ethnic backgrounds (2.7% ethnicity unknown). Ethical approval was received from the University of Sheffield's Department of Psychology Ethics Committee. Participants were entered into a prize draw for a £20 gift voucher.

Table 2.1

Demographic information

			Age (years)			Current SES			Family SES		
Time	Sample	n	*M*	*SD*	Range	*M*	*SD*	Range	*M*	*SD*	Range
T1	Males	78	24.27	6.97	18-48	5.88	1.37	3-8	5.82	1.82	2-9
	Females	146	23.95	6.98	18-50	5.88	1.43	2-9	5.53	1.90	1-10
	Total	224	24.06	6.96	18-50	5.88	1.41	2-9	5.63	1.88	1-10
T2	Males	27	24.67	7.18	18-42	5.93	1.41	3-8	5.85	1.81	2-9
	Females	51	23.22	6.60	18-50	5.80	1.50	2-9	5.25	2.02	2-10
	Total	78	23.72	6.80	18-50	5.85	1.46	2-9	5.46	1.96	2-10

2.3.2.1.1.2. Questionnaires

As well as completing the LRTI, participants were also asked to complete two other questionnaire measures that could be used to validate the LRTI. The 90 item Cognitive Appraisal of Risky Events questionnaire (CARE; Fromme et al., 1997) assesses an individual's beliefs about the potential costs and benefits of engaging in 30 risky activities (including heavy drinking, illicit drug use, risky sexual activities, aggressive and illegal behaviours, and risky academic/work behaviours), and how likely we are to engage in these activities in the next 6 months. The 80 item State Trait Personality Inventory (STPI; Spielberger et al., 1979) is comprised of eight 10-item scales that assess state and trait levels of anxiety, anger, curiosity and depression. For this study, only trait measures are discussed.

In addition, current socio-economic status (SES) and their family's SES when they were growing up was measure using the Subjective SES Scale (Adler, Epel, Castellazzo, & Ickovics, 2000). This scale shows participants a picture of a ladder with 10 rungs, and asks them to think of the ladder as representing where people stand in society, with people at the top being the best off (best jobs, most money and education), and those at the bottom being the worst off (worst or no jobs, least money and education). In this study, participants were asked to state which rung of the ladder they thought best represented where they are now (current SES), and which rung best represented where their family would have been when the participant was a child (family SES).

2.3.2.1.1.3. Procedure

Development of LRTI focused on capturing the frequency of risk-taking, peer risk-taking, and experience of specific emotions during three developmental stages; childhood, adolescence, and adulthood. Using these components as building blocks, a 33-item questionnaire (see Appendix 1) was developed that asked participants to rate their frequency of risk-taking behaviours, to compare their level of risk-taking with that of their peers, and the frequency with which they experienced various emotional states during their childhood, adolescence, and adulthood. It was an intentional decision to use broad developmental terms rather than specific age ranges to reflect that risk-taking is more influenced by pubertal stage than chronological age (Martin et al., 2002). Questions were formatted using a 5-point Likert scale ranging from 1 ('Never') to 5 ('Always', because it offers greater reliability and validity than scales with fewer points (Krosnick & Fabrigar, 1997). For items asking about participants' and peers' risk-taking, higher scores indicate a higher frequency of risk-taking. For items asking about emotional experiences, positively valenced items have been reverse scored. Therefore, higher scores on emotion items indicate experiencing more negative emotions.

After creating LRTI, all measures were entered into the online survey software, Qualtrics (Qualtrics, n.d.). Email invitations were sent to the University of Sheffield's volunteers list, containing a link that would redirect participants to the Qualtrics survey page. To assess test-retest reliability of LRTI, participants were sent a second email two weeks later inviting them to take part in a follow up questionnaire. LRTI was administered at both time points; however, to minimize participant fatigue, CARE and STPI were only administered once (STPI at T1, and CARE at T2).

2.3.2.1.2. Results

2.3.2.1.2.1. Factor structure of the Life Span Risk-Taking Inventory

Principal components analysis (PCA) was carried out on data collected from the 224 participants who completed the LRTI at T1. Factorability of the correlation matrices was

assessed, with significant results on Bartlett's (1954) test of sphericity ($p < .001$), and an appropriate value achieved on the overall Kaiser-Meyer-Olkin measure of sampling adequacy (KMO = 0.82; Kaiser, 1974). Nine factors met the Keiser-Guttman retention criterion of eigenvalues greater than 1.0 (Kaiser, 1974); however, a scree plot test (Cattell, 1966) suggested a two-component solution (Tabachnick & Fidell, 2013). Solutions for the components were each examined using direct oblimin rotations of the factor loading matrix. The two-component solution was preferred because of its previous theoretical support, 'levelling off' of eigenvalues on the scree plot after two factors, and difficulty of interpreting third and subsequent factors. The two subscales were assessed for reliability by calculating Cronbach's Alpha for component 1 ($\alpha = 0.90$) and component 2 ($\alpha = 0.88$). Cronbach's Alpha indicated a high level of redundancy in component 1, so 3 items with the lowest factor loadings were removed (Cronbach's Alpha remained at $\alpha = 0.90$ after removing these three items, but as all other items loaded highly onto the component, no further items were removed). Communalities for the 30-item scale ranged from .23 to .62 after rotation.

The two components explained 23.64% and 17.53% of the variance respectively, equaling 41.17% of the total variance. Component 1 incorporated all items related to experience of emotions and feelings at different ages, and component 2 incorporated all items relating to risk-taking across the lifespan, including items relating to peers and risk-taking. Names were selected that depicted the distinct components: Risk-Taking (12 items), and Negative Emotional Experience (18 items). Nine items on the Negative Emotional Experience subscale ("During your childhood/adolescence/ adulthood, did you feel happy?", "During your childhood/adolescence/adulthood, did you feel safe?", and "During your childhood/adolescence/adulthood, did you feel confident?") were positively keyed and were therefore reverse scored to fit conceptually with the remaining items. Table 2.2 shows the factor loadings, communalities, and item means and standard deviations for the LRTI.

Table 2.2

Factor loadings, communalities, *M*, *SD*, percentage variance explained, and Cronbach's alpha for the Life Span Risk-Taking Inventory

	PCA factor loadings				
Item	1	2	Communality	*M*	*SD*
How often did you take risks as a child?	.02	-.59	.35	2.58	.95
How often did you take risks as an adolescent?	.04	-.68	.47	2.98	.91
How often do you take risks as an adult?	.00	-.60	.36	2.83	.81
In your childhood, did you feel afraid?	.63	-.16	.45	2.47	.85
In your childhood, did you feel happy?	.61	-.09	.39	1.97	.57

In your childhood, did you feel anxious?	.59	.04	.34	2.52	.88
In your childhood, did you feel depressed?	.51	-.17	.30	1.67	.84
In your childhood, did you feel safe?	.62	-.21	.45	1.61	.73
In your childhood, did you feel confident?	.59	.14	.35	2.91	.95
In your adolescence, did you feel afraid?	.61	-.11	.40	2.60	.81
In your adolescence, did you feel happy?	.66	-.12	.46	2.37	.69
In your adolescence, did you feel anxious?	.69	.14	.48	3.12	.84
In your adolescence, did you feel depressed?	.62	-.17	.44	2.40	1.01
In your adolescence, did you feel safe?	.57	-.21	.39	1.96	.77
In your adolescence, did you feel confident?	.58	.14	.34	3.00	.89
In your adulthood, do you feel afraid?	.58	-.01	.34	2.41	.80
In your adulthood, do you feel happy?	.54	.16	.30	2.15	.60
In your adulthood, do you feel anxious?	.54	.17	.30	3.10	.82
In your adulthood, do you feel depressed?	.48	-.05	.24	2.27	.93
In your adulthood, do you feel confident?	.54	.22	.32	2.48	.84
In your adulthood, do you feel safe?	.57	-.02	.33	2.06	.75
In your childhood, did you take risks with your friends?	-.04	-.66	.44	2.59	.92
In your childhood, did you take more risks than your friends?	-.03	-.74	.55	1.98	.91
In your childhood, did you take more risks than the average child?	.02	-.75	.56	1.90	.90
In your adolescence, did you take risks with your friends?	.02	-.70	.50	2.85	.94
In your adolescence, did you take more risks than your friends?	.02	-.74	.56	2.19	.99
In your adolescence, did you take more risks than the average adolescent?	.03	-.78	.62	2.10	.98
In your adulthood, do you take risks with your friends?	-.08	-.61	.37	2.54	.92
In your adulthood, do you take more risks than your friends?	.04	-.70	.50	2.26	1.00
In your adulthood, do you take more risks than the average adult?	.07	-.71	.51	2.19	.99
Variance explained	23.64%	17.53%			
Cronbach's alpha	.90	.88			

Note. Numbers in bold show the highest factor loadings for each item. Factor 1 = Risk-taking frequency; Factor 2 = Negative Emotional Experiences. N = 224. PCA = principal components analysis.

Based on the PCA, internal subscales were derived for the LRTI. Two subscales, one for risk-taking and another for negative emotional experiences, were made for each developmental stage (childhood, adolescence, adulthood). Higher scores indicate engaging more frequently in risk-taking behaviors and experiencing more negative emotions respectively. To examine the internal reliability of these scoring scales, Cronbach's alpha was calculated for each subscale from data collected at T1 (Table 2.3).

Table 2.3

Cronbach's alpha and descriptive statistics for Life Span Risk-Taking Inventory subscales

LRTI Subscale	Cronbach's α	M (T1)	SD (T1)	M (T2)	SD (T2)
Childhood risk-taking	.87	11.98	3.62	11.25	3.08
Adolescent risk-taking	.87	13.36	3.63	13.32	3.53
Adult risk-taking	.86	12.66	3.55	12.38	3.37
Childhood NEE	.81	13.15	3.48	12.60	3.47
Adolescent NEE	.79	15.45	3.52	15.45	3.93
Adult NEE	.79	14.47	3.34	15.28	3.50

Note. NEE = negative emotional experiences; *M* = mean score. At T1 *N* = 224; At T2 *N* = 78.

2.3.2.1.2.2. Test-retest reliability

Partial correlations were run to compare mean scores for each subscale at T1 and T2, controlling for participants age. Analyses were only run for participants who completed the LRTI at both time points (n = 77; One participant who completed T2 was excluded from T1 analyses as they were an extreme outlier, hence the difference in sample size here). Results showed significant correlations between adolescent (r (75) = .32, p = .005) and adult (r (75) = .23, p = .045) risk-taking scores across T1 and T2, but no significant correlation between childhood risk-taking scores at T1 and T2 (r (75) = .14, p = .233). No significant correlations were found between Negative Emotional Experience scores measured at T1 and T2 for childhood (r (75) = -.21, p = .063), adolescence (r (75) = .00, p = .980), or adulthood (r (75) = .20, p = .081). The same pattern of results was also found in further correlation analyses controlling for participants' gender (not reported for brevity).

The results of these analyses show that there were small correlations between adolescent and adult risk-taking scores across T1 and T2, but no correlations, and consequently poor test-retest reliability, between other scales across T1 and T2. This indicates that the LRTI questionnaire had insufficient test-retest reliability to be considered a viable measure of risk-taking across the lifespan. The following analyses were run to determine what might have led to this lack of reliability.

2.3.2.1.2.3. Validity

To assess the validity of LRTI, participants' responses on LRTI were compared with their responses on existing validated measures of risk-taking (CARE), and emotion (STPI). Means, standard deviations and ranges for LRTI (at T1), CARE, and STPI are presented in Table 2.4.

Table 2.4

Descriptive statistics for LRTI scales, CARE scales, and STPI trait scales

		Males (n = 78)			Females (n = 146)			Total (n = 224)		
Measure	Scale	M	SD	Min-Max	M	SD	Min-Max	M	SD	Min-Max
LRTI-RT (T1)	Childhood	3.33	3.52	6-22	11.27	3.47	5-21	11.99	3.71	5-22
	Adolescent	14.47	3.28	8-24	12.77	3.68	5-23	13.36	3.68	5-24
	Adult	13.97	3.50	6-22	11.96	3.39	5-20	12.66	3.60	5-22
LRTI-NEE (T1)	Childhood	13.40	2.98	8-22	13.02	3.72	6-26	13.15	3.49	6-26
	Adolescent	15.04	3.27	8-23	15.67	3.64	8-25	15.45	3.57	8-25
	Adult	13.96	3.29	7-23	14.74	3.35	8-24	14.47	3.34	7-24
CARE	Expected risk	162.11[a]	22.01[a]	124-203[a]	155.82[b]	28.44[b]	47-198[b]	158.00[c]	26.42[c]	47-203[c]
	Expected benefit	62.26[a]	20.21[a]	30-112[a]	67.53[b]	20.28[b]	30-137[b]	65.71[c]	20.28[c]	30-137[c]
	Expected Involvement	66.11[a]	21.38[a]	30-129	69.12[b]	22.67[b]	30-117[b]	68.08[c]	22.14[c]	30-129[c]
STPI (Trait Scales)	Anxiety	86.26	10.43	68-123	88.29	8.81	68-113	87.58	9.44	68-123
	Depression	85.08	11.33	64-119	86.13	9.90	67-123	85.76	10.41	64-123
	Curiosity	90.00	10.57	68-130	92.16	8.03	65-112	91.41	9.03	65-130
	Anger	87.77	10.61	66-128	89.71	8.47	65-110	89.03	9.29	65-128

Note. LRTI = Lifespan Risk-Taking Inventory; RT = risk-taking; NEE = negative emotional experiences; CARE = Cognitive Appraisal of Risky Events; STPI = State-Trait Personality Inventory. [a] n = 27; [b] n = 51; [c] n = 78.

2.3.2.1.2.3.1. Validity of LRTI Risk-Taking Subscales

To assess the validity of the LRTI risk-taking subscales at each developmental stage, LRTI scores were compared with CARE scores. Prior to analyses, 4 participants were removed from analyses including CARE scales because they were extreme outliers (> 3 SD from mean). Partial correlations were run between CARE Scale scores, and LRTI Risk-Taking scores measured at T1, controlling for participants age. Results revealed significant positive correlations between childhood, and adolescent LRTI risk-taking scores, and the CARE expected involvement scale, with all other correlations being non-significant (see Table 2.5). The same pattern of results was also found in further correlation analyses controlling for participants' gender. This suggests that participants who rated their level of risk-taking during childhood and adolescence as high, rated themselves as being more likely to engage in the risky activities outlined in the CARE questionnaire, compared to those who reported lower levels of risk-taking during childhood and adolescence. Surprisingly, however, there was no significant relationship between self-rated level of risk-taking in adulthood on the LRTI, and expectancy to engage in risk-taking activities on the CARE questionnaire.

Table 2.5

Spearman's rho correlation between Life Span Risk-Taking Inventory's risk-taking subscales and Cognitive Appraisal of Risky Events subscales

LRTI Risk-Taking Scale	CARE Scale					
	Expected Risk		Expected Benefit		Expected Involvement	
	r	*p*	*r*	*p*	*r*	*p*
Childhood	.11	.353	.02	.858	.33	.004
Adolescence	.07	.547	.04	.727	.29	.010
Adulthood	.10	.382	.02	.853	.16	.174

Note. $n = 74$. $df = 72$. LRTI = Lifespan Risk-Taking Inventory; CARE = Cognitive Appraisal of Risky Events.

2.3.2.1.2.3.2. Validity of LRTI Negative Emotional Experiences Subscales

To assess the validity of LRTI's negative emotional experience (NEE) subscale, participants' responses on LRTI were compared with responses on trait measures of the STPI (anxiety, depression, curiosity, and anger). The results of a Pearson's correlation analyses (Table 2.6) show that there are significant, moderate, positive correlations between the NEE scales of LRTI, and the anxiety and depression scales of the STPI. This suggests that individuals who reported feeling more negative emotions on LRTI, at any developmental stage, were likely to have increased anxiety and depression scores in adulthood, as measured by the STPI. This indicates that the NEE subscales of LRTI show good construct validity. There were no

significant correlations between LRTI NEE subscales with curiosity and anger subscales of the STPI.

Table 2.6

Pearson's correlation coefficients between the Lifespan Risk-Taking Inventory and the State-Trait Personality Inventory

STPI Trait Scale	LRTI Negative Emotional Experiences Scale					
	Childhood		Adolescence		Adulthood	
	r	*p*	*r*	*p*	*r*	*p*
Anxiety	.19	.004†	.23	.001†	.32	>.001†
Depression	.30	>.001†	.33	>.001†	.50	>.001†
Curiosity	.01	.929	-.04	.533	-.04	.536
Anger	.04	.601	.02	.777	.04	.548

Note. n = 224; df = 222. † = significant after correcting for multiple comparisons. LRTI = Lifespan Risk-Taking Inventory; STPI = State-Trait Personality Inventory; NEE = negative emotional experiences.

2.3.2.1.2.4. Relationships between LRTI Subscales

Having looked at the reliability and validity of LRTI, the next task was to examine the relationships between LRTI subscales, using data collected at T1. Firstly, Spearman's correlations were run (due to significant skew) to investigate the relationships between NEE scores at different developmental stages. The results (Table 2.7) showed significant positive correlations between the NEE subscales at all developmental stages; those who reported a higher frequency of negative emotional experiences in one developmental stage, were more likely to report having negative emotional experiences in other developmental stages. This relationship was strongest when comparing consecutive developmental stages.

To see if there were any significant differences between mean NEE scores at each developmental stage, a repeated-measures analysis of variance (ANOVA) was run. Mauchly's test indicated that the assumption of sphericity had been violated, χ^2 (2) = 23.79, p <.001, therefore the Huynh-Feldt corrected tests are reported (ε = .90). The results showed that level of negative emotional experience was significantly affected by developmental stage, F (6.21, 325.87) = 54.47, p <.001. Post-hoc tests using the Bonferroni correction revealed that negative emotional experiences significantly increased from childhood to adolescence (p <.001), and from childhood to adulthood (p <.001). However, negative emotional experiences significantly decreased from adolescence to adulthood (p <.001). This suggests that individuals are more likely to experience negative emotional experiences during adolescence, and least likely to experience negative emotional experiences during childhood.

Secondly, we looked at the relationships between risk-taking scores across developmental stages. The results (Table 2.7) of Pearson's correlation analyses showed significant positive correlations between risk-taking subscales at all developmental stages, indicating a high degree of consistency of risk-taking across developmental stages (Table 2.7). Those who engaged in risk-taking more frequently in one developmental stage, were more likely to engage in risk-taking in other developmental stages.

To see if there were any significant differences between mean risk-taking scores at different developmental stages, a repeated-measures ANOVA was run. Mauchly's test indicated that the assumption of sphericity had been violated, χ^2 (2) = 8.63, p = .013, therefore the Huynh-Feldt corrected tests are reported (ε = .96). The results showed that level of risk-taking was significantly affected by developmental stage, F (6.31, 109.00) = 17.26, p <.001. Post-hoc tests using the Bonferroni correction revealed that level of risk-taking significantly increased from childhood to adolescence (p <.001), and from childhood to adulthood (p = .027). In contrast, level of risk-taking significantly decreased from adolescence to adulthood (p = .006). This suggests that individuals are more likely to engage in risky behaviors during adolescence, and least likely to engage in risky behaviors during childhood.

Finally, the relationships between risk-taking and negative emotional experience scores across all developmental stages were analyzed (Table 2.7). Only one significant correlation was found (after controlling for multiple comparisons) between risk-taking and negative emotional experiences in adolescence, suggesting that those who experienced more negative emotions were more likely to engage in risky behaviors. No other significant correlations were found.

Table 2.7

Spearman's correlation coefficients between the Lifespan Risk-Taking Inventory subscales

			LRTI NEE Scale			LRTI Risk-Taking Scale	
LRTI Scale			Childhood	Adolescence	Adulthood	Childhood	Adolescence
NEE	Adolescence	*r*	.66	-			
		p	>.001†	-			
	Adulthood	*r*	.36	.53	-		
		p	>.001†	>.001†	-		
Risk-taking	Childhood	*r*	.09	.12	.01	-	
		p	.194	.067	.840	-	
	Adolescence	*r*	.17	.19	.06	.59	-
		p	.009	.005†	.353	<.001†	-
	Adulthood	*r*	.15	.16	.07	.43	.56
		p	.027	.017	.32	>.001†	>.001†

Note. N = 224; *df* = 222. † = significant after correcting for multiple comparisons. LRTI = Lifespan Risk-Taking Inventory; STPI = State-Trait Personality Inventory; NEE = negative emotional experiences.

2.3.2.1.3. Discussion

This study found that the LRTI was not a reliable or viable measure of risk-taking across the life span. Validation of the questionnaire uncovered two related but independent factors, namely risk-taking and negative emotional experience. However, the questionnaire was found not to be reliable over a two-week period and was therefore considered not suitable for administering. There are several reasons which might explain this lack of reliability.

Firstly, the current structure of LRTI poses difficulties for older participants, as it could be challenging to condense their entire adult experiences of risk-taking and emotion into a few values on a Likert scale. A proposed suggestion is to break adulthood items down into decades of life (e.g., "How often did you engage in risk-taking in your 20s/30s/40s…?"), but this would need to be further validated. Similarly, even for younger participants, issues with ability to accurately recall risk-taking frequency during childhood and adolescence may explain the observed changes in LRTI scores across T1 and T2.

Secondly, whilst LRTI was purposefully developed to not ask about specific risky activities (so that the questionnaire was not invasive, and not affected by developmental changes in types of risk-taking behaviors), this lack of specificity also means that items are more open to participant's interpretation of risk-taking. The lack of any correlation between risk-taking scales on LRTI and CARE suggests that participants may not have been thinking about the same types of risk-taking when completing both questionnaires. It may also be that this lack of specificity

regarding risk-taking in LRTI is responsible for the poor test-retest reliability. The significant positive relationship between LRTI's NEE scales, and anxiety and depression scores (as measured by the STPI) indicated good construct validity for these scales; however, the primary aim of validating this questionnaire was to develop a measure of risk-taking across the lifespan, not emotion across the lifespan, although this may still be a promising avenue of research.

In conclusion, the factors associated with risk-taking may change in strength and type as we move through development; therefore, it is important that we study the trajectory of risk-taking, and not just when it is at its peak. The premise of creating LRTI was to measure risk-taking across the life span in a way that is not dependent on lists of risk-taking activities that reduce its relevance and suitability for certain samples. The non-invasive, non-specific nature and simple structure of LRTI are its greatest strengths, as there is a great need for a risk-taking questionnaire that can be administered to children and adults. Questions that ask about specific risky activities are not appropriate as types of risky behaviors change dramatically from childhood (e.g. climbing trees), to adolescence (e.g. reckless driving), and into adulthood (e.g. financial risks). LRTI aimed to solve this problem by asking about the frequency of, rather than the type, of risk-taking behavior. However, LRTI was found to have poor test-retest reliability and is therefore was deemed not a viable measure of risk-taking across the lifespan, and hence was not used in this thesis for study questions focused on risk-taking.

2.3.2.2. The RT-18

Given that the LRTI was not a reliable instrument to measure risk taking, a suitable measure of risk-taking was still needed to assess the relationship between risk-taking and sensory responsivity. After conducting a search of available risk-taking questionnaires, the RT-18 (de Haan et al., 2011) was considered to be the most suitable measure for adolescent and adult samples in this doctoral work. The RT-18 was specifically designed for use with young adults, and was validated using a sample of young adult social drinkers, recreational drug users, and university students in The Netherlands (N = 7834). This questionnaire asks participants to read through 18 statements and questions, then answer "Yes" or "No" according to how they normally feel or behave. The questionnaire provides a measure of participants' level of risk-taking behaviour, as well as their level of risk assessment (i.e. their level of consideration for the consequences). The minimum possible score for each of the subscales is 0, and the maximum possible score is 9. High scores indicate that the participant is less likely to assess the situation before acting (for the risk-assessment subscale) and will be more likely to take part in risky activities (for the risk-taking behaviour scale). The RT-18 has satisfactory construct validity, a high level of test-retest reliability, and strongly correlates with other measures of impulsivity, venturesomeness, novelty seeking, and impulsive sensation seeking (de Haan et al., 2011). The

RT-18 was considered to be the most suitable risk-taking measure for the following studies for several reasons.

Firstly, the RT-18 is not based on the frequency with which respondents engage in specific risky activities, such as illicit drug or alcohol abuse, or driving recklessly. Opportunity to engage in these types of activities will increase as individuals shift from early to late adolescence and into early adulthood (J. Arnett, 1992; Kilpatrick et al., 2000). Therefore, a questionnaire that is based on frequency of engagement in specific activities is not appropriate for examining risk-taking behaviours across different age groups, as it may be skewed by age-related differences in opportunities to engage in risky activities, and not accurately reflect an individual's propensity for risk-taking behaviours. Items on the RT-18 try to capture the respondent's general attitude towards risk-taking without asking about engagement in specific risky activities (e.g. "I often do things on impulse", "Would you enjoy parachute jumping?"), which makes it suitable for administering to different age groups.

Secondly, not asking about engagement in specific activities may make participants more willing to answer questions honestly, without fear of potential negative consequences of admitting to doing something they know would not be approved of. For example, in CARE (Fromme et al., 1997), participants are asked how likely they are in the next 6 months to engage in activities including driving after drinking alcohol, sex with multiple partners, or trying/using drugs other than marijuana. Even though participants are informed their answers will remain confidential, they may still be reluctant to answer with complete honestly.

Thirdly, there may be ethical concerns with some risk-taking questionnaires around exposing younger participants to risky activities that they may be unaware of, or anything their parents/guardians would be concerned about their children being asked. The RT-18 doesn't ask questions about sexual activities or substance abuse, which are possibly the questions parents/guardians would be most concerned about, thereby avoiding this ethical issue.

Finally, the RT-18 is relatively short compared to existing risk-taking questionnaires, such as the CARE (90 items; Fromme et al., 1997). As participants would also be answering other questionnaires, a shorter questionnaire that can still adequately measure risk-taking behaviour is helpful in staving off participant fatigue and/or boredom, especially with younger participants.

2.3.2.3. The Adolescent/Adult Sensory Profile (AASP)

The Adolescent Adult Sensory Profile (AASP; Dunn, 1999) is a 60-item questionnaire that asks participants to rate the frequency with which they perform certain behaviours in response to sensory stimuli. Items cover sensory stimuli from all modalities, including taste/smell processing, movement processing, visual processing, touch processing, activity

level, and auditory processing. Participants respond on a 5-point scale from "Almost Never" to "Almost Always". Based on Dunn's Model of Sensory Processing (Dunn & Brown, 1997; Dunn, 2007; see Chapter 1.2.2 for discussion of this model), items on the questionnaire can be split into subscales that reflect the 4 quadrants of the model:

1. Sensation Seeking items try to capture whether the respondent is actively seeking out environments or engaging in behaviours that create additional sensory stimuli (e.g. "I go over to smell fresh flowers when I see them").

2. Sensation Avoiding items try to capture whether the respondent is actively seeking out environments or engaging in behaviours that *reduce* sensory stimuli (e.g. "I avoid elevators/escalators because I dislike the movement").

3. Sensory Sensitivity items aim to capture whether the respondent is bothered or uncomfortable with sensory stimuli (e.g. "I'm uncomfortable wearing certain fabrics (for example, wool, silk, corduroy, tags in clothing)").

4. Low Registration items aim to capture whether the respondent misses or takes longer to respond to sensory stimuli that others notice (e.g. "I have trouble following what people are saying when they talk fast or about unfamiliar topics").

The minimum possible score for each subscale is 15, and the maximum possible score is 75. Subscale scores can also be classified into one of 5 categories based on how their score compares to others in the same age group (ages 11-17, 18-64, or 65 and older). This is based on normative data collected by Dunn during the validation of the AASP. Classifications include "Much less than most people", "Less than most people", "Similar to most people", "More than most people", "Much more than most people", with cut-off points varying depending on the age of the participant, and the type of subscale.

Also, in accordance with the model, subscales can be summed together to give scores for neurological threshold and self-regulation strategies/behavioural responses.

1. High neurological threshold = low registration score + sensation seeking score

2. Low neurological threshold = sensory sensitivity score + sensation avoiding score

3. Passive behavioural responses = low registration score + sensory sensitivity score

4. Active behavioural responses = sensation seeking score + sensation avoiding score

The AASP has been used extensively in studies investigating sensory responsivity in adolescents and adults, particularly in relation to mental health conditions, including obsessive compulsive disorder (Rieke & Anderson, 2009), anxiety (Batya Engel-Yeger & Dunn, 2011b),

autism spectrum conditions (Crane et al., 2009; Kern et al., 2007; Pfeiffer et al., 2005), post-traumatic stress (Batya Engel-Yeger et al., 2013), and attention deficit hyperactivity disorder (Dunn & Bennett, 2002).

2.3.2.4 Glasgow Sensory Questionnaire (GSQ)

The Glasgow Sensory Questionnaire (GSQ; Robertson & Simmons, 2013), developed at the University of Glasgow, was initially constructed based on reports of common sensory signs and symptoms associated with ASCs. The 42-item measure has scales that assess both hyper- and hypo-sensitivities in seven modalities (visual, auditory, gustatory, olfactory, tactile, vestibular, and proprioceptive). Items are distributed equally amongst the sensory modalities, with three questions assessing hyper-sensitivity and three questions assessing hypo-sensitivity for each modality. All questions ask how frequently certain sensory events occur (e.g. "Do you find it difficult to concentrate on visual information (for example, reading a book) when there are noises in the background"), to which participants' respond using the scale: "Never – Rarely – Sometimes – Often – Always". Responses are coded on a scale of 0 to 4, with possible scores ranging from 0 to 168.

Scales assessing hyper- or hypo-sensitivity for each modality can be combined to create a total modality score (e.g. hyper-sensitivity to visual stimuli + hypo-sensitivity to visual stimuli = total visual modality score). Similarly, hyper-sensitivity scores across different modalities can be combined to create a general hyper-sensitivity score, and the same for hypo-sensitivity. Furthermore, scores from all 42 items can be summed to create a total GSQ score, with higher scores reflecting more extreme responses to sensory stimuli. The GSQ was designed as a tool for researchers to characterise sensory features in individuals aged 16 years or above. Its authors state that the questionnaire is not restricted to use with individuals with ASC, but that the questionnaire was designed to detect sensory features that are more prevalent in ASC.

In Chapter 4, this questionnaire is used in a neurotypical sample, including early-adolescents (13-14 years). Given that this is not the intended use of this questionnaire, assessments of the questionnaire's reliability (using Cronbach's alpha) and validity (by correlating with other sensory responsivity measures) will be assessed prior to its use in hypothesis testing analyses. Despite its lack of testing in this sample, this questionnaire was selected for use due to its ability to assess sensory responsivity in increasingly specific ways (i.e. from general sensory responsivity, right down to hyper- or hypo-sensitivity of one sensory modality).

2.3.2.5. Depression Anxiety and Stress Scale (short-form version; DASS-21)

The short form of the Depression Anxiety Stress Scale (DASS-21; Henry & Crawford, 2005) consists of three 7-item self-report scales. Participants are asked to read a series of

statements pertaining to feelings of depression, anxiety and stress, then indicate how much the statement applied to them over the past week using a 4-point scale (0 = "Did not apply to me at all", 3 = "Applied to me very much, or most of the time"). In order to compare scores on the DASS-21 item version to the full length 42 item version, scores are multiplied by 2. Therefore, subscale scores range from a minimum score of 0 to a maximum score of 42. Cut-off scores are provided for defining mild/moderate/severe/extremely severe scores for each DASS scale. DASS-21 has been shown to have satisfactory construct validity, and correlate with other measures of negative emotional experiences (Henry & Crawford, 2005).

2.4. Procedure

2.4.1. Tasks

2.4.1.1. Visual Cortical Plasticity Paradigm

Chapters 4 and 5 present an ERP study in which participants completed a visual cortical potentiation task, based on a task previously used by Çavuş et al. (2012). Figure 2.4.A illustrates the timeline of the visual cortical plasticity paradigm.

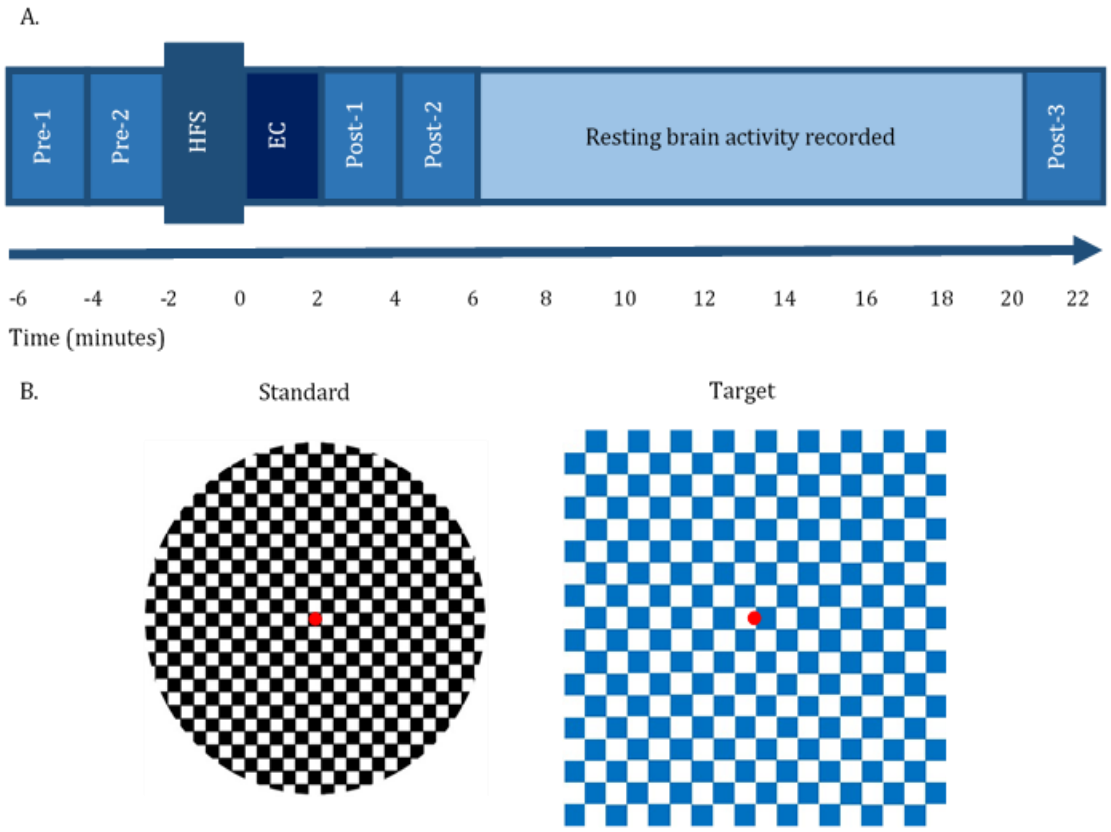


Figure 2.4. Visual Cortical Plasticity Paradigm: timeline and stimuli. **(A)** Timeline of Visual Cortical Plasticity paradigm. VEP assessments were made at Pre-1 (-6 to -4 minutes) and Pre-2 (-4 to -2 minutes), followed by HFS (-2 to 0 minutes). Following HFS, participants were asked to have their eyes closed for 2 minutes. VEP assessments were also made at Post-1 (+2 to +4 minutes), Post-2 (+4 to +6 minutes), and Post-3 (+20 to +22 minutes) after HFS had finished. During the period between Post-2 and Post-3, resting brain activity was recorded whilst the participants eyes were open (EO) or closed (EC). **(B)** Visual stimulus presented in the Visual Cortical Plasticity Paradigm. Left: standard circle presented during high-frequency stimulation (HFS, ~8.83Hz) and visual evoked potential (VEP) assessment blocks (~0.83Hz). Right: target square presented infrequently (10% trials) during VEP assessment blocks.

In blocks assessing visually-evoked potentials (VEPs), participants were asked to complete a visual oddball task in which they were shown a pseudorandom series of standard black and white circular checkerboards (90% of trials) and target blue and white square checkerboards (10% of trials). Participants were asked to press the spacebar on the keyboard in front of them every time they saw a square, but to make no response to the circles. All stimuli

were presented for 33ms with an inter-trial period of 1.17 seconds. A red central fixation dot was presented continuously throughout the block. Each VEP assessment block lasted for 2 minutes. VEP blocks occur before high-frequency stimulation (Pre-1, and Pre-2) in order to obtain a baseline VEP measurement, and after high-frequency stimulation (Post-1, Post-2, and Post-3) to determine if any potentiation has occurred.

During the high-frequency stimulation (HFS) block, participants were asked to fixate on a red central fixation point whilst the standard circle flickered centrally on screen at a frequency of approximately ~8.87Hz for 2 minutes. This block is designed to replicate the tetanus typically delivered via electrode stimulation in traditional studies of LTP and aims to induce LTP in the visual cortex. Directly after the HFS block had finished, participants were asked to close their eyes for 2 minutes before the next VEP block began.

In the interval between the 2nd and 3rd post-HFS VEP assessment blocks, resting brain activity was recorded. Resting activity was recorded whilst the participant had their eyes open (1 minute) and their eyes closed (1 minute) for four repetitions, with 20 second breaks in between to allow the participant to read instructions, or for the researcher to ask the participant to open their eyes. After the four repetitions of eyes open, and eyes closed, there is a short break before the final VEP assessment where participants were asked to rest and await the final part of the task.

2.4.1.2. Resting State EEG

There was a 14 minute gap between Post-2 and Post-3 assessments in the visual cortical plasticity paradigm. In this study, this time was used to collect resting state EEG data to keep the participant occupied (and therefore limit movement artefacts), and also because it should not interfere with the main aim of the paradigm. Based on previous adolescent and adult EEG research (Howsley & Levita, 2018), eight 1 minute intervals of resting state EEG data were recorded. Data was recorded for one minute when the participant's eyes were open, then for a minute when the participant's eyes were closed, with a 15 second buffer in between to allow the participant to read the instructions on screen. This was repeated a further three times, with participants alternating between eye's open for one minute and eye's closed for one minute (EO – EC – EO – EC – EO – EC – EO – EC). Following the resting state data collection, participants had a few minutes before the final VEP assessment (Post-3) where they were asked to relax and wait for further instruction. Given that resting state data is only collected as part of a filler task, resting state data is not analysed in this doctoral thesis.

2.4.2. Statistical analyses

The Visual Cortical Plasticity paradigm was used in two studies reported in this doctoral thesis (Chapter 4 and Chapter 5); consequently, similar analyses are conducted in both

chapters. To save repetition in these chapters, the following sections will outline planned analyses conducted in these chapters, and justifications for why these analyses were conducted. Finally, the approach taken to multiple comparison corrections, and assumptions of statistical tests that were considered across all empirical chapters are discussed. IBM SPSS Statistics for Windows, Version 22.0 was used to carry out all statistical analyses. The significance level was set at $p < .05$ for all tests.

2.4.2.1. Behavioural analyses

2.4.2.1.1. Task performance on Visual Cortical Plasticity Paradigm

During the Visual Cortical Plasticity paradigm, participants are asked to maintain focus on a red central fixation dot whilst the standard circle (90% of trials) or target square (10% of trials) are shown centrally (~0.83Hz). To monitor attention and provide further focus, participants are asked to button press every time the target square appears. To rule out the possibility that group-related differences in VEP amplitude were due to group-related differences in task performance, analyses were conducted to determine if there were group differences on two behavioural measures.

To determine whether attentional vigilance was comparable across groups throughout the paradigm, analyses were run to assess differences in reaction times and response accuracy to the oddball target square. Mean reaction times were calculated for each block, using reaction times for correctly identified oddball targets only. 'Hit rate' scores were calculated for each participant, by totalling the number of target square trials per block where they correctly responded by button press.

2.4.2.2. EEG analyses

2.4.2.2.1. Differences between baseline VEP assessments

To reduce the number of statistical comparisons, a 3-way mixed ANOVA is conducted to determine if there are any differences in mean amplitude between the two pre-HFS blocks (Pre-1 and Pre-2), between the groups at the occipital electrode cluster location for each ERP component (P1, N1, and P2). If there are no significant differences between the two baseline measures, then they would be averaged together for all subsequent analyses. If there are significant differences between the two baseline assessments, rather than including both Pre-HFS blocks in subsequent analyses (which would reduce the tests statistical power), all subsequent analyses will compare Post-HFS blocks to mean amplitudes recorded only during Pre-HFS 2 (which will be known as 'baseline' from hereon). Because this analysis is only concerned with differences in mean amplitude between the two Pre-HFS blocks, only results concerning this difference are reported.

2.4.2.2.2. Validating the Visual Cortical Plasticity Paradigm

The primary aim of both studies reported in Chapter's 4 and 5 was to determine whether or not the Visual Cortical Plasticity paradigm could induce potentiation in the visual cortex, measured by changes in VEPs using EEG. Consequently, it is first important to assess whether visual HFS lead to changes in VEP amplitude by comparing VEP amplitudes measured at baseline and post-HFS assessments. Therefore, a three-way ANOVA was conducted to determine the effect of group, VEP assessment (baseline, Post-1, Post-2, Post-3), and ERP component (P1, N1, and P2) on mean amplitudes observed over the occipital electrode cluster. If a significant three-way interaction was found, the data were then split to determine whether there were statistically significant simple two-way interactions between group and VEP assessment for each ERP component. Follow-up analyses were then run for any significant simple two-way interactions to explore the simple simple main effects of VEP assessment and group on mean amplitude for relevant VEP components.

2.4.2.2.3. Assessing the degree of change in VEP amplitudes following visual HFS

If results showed that visual HFS lead to significant changes in VEP amplitudes for all groups, then further analyses would be conducted to assess whether there were group differences in the degree of change in VEP amplitude. VEP change scores were calculated by subtracting the mean amplitude measured at baseline, from the mean amplitude measured in each Post-HFS block (VEP Change 1 = Post-1 minus baseline; VEP Change 2 = Post-2 minus baseline; VEP Change 3 = Post-3 minus baseline) for each ERP component. A three-way ANOVA was run to compare VEP change scores (VEP Change 1, VEP Change 2, and VEP Change 3) for all groups at each ERP component that previous analyses had shown were significantly altered by visual HFS.

2.4.2.2.4. Assessing the relationship between HFS-driven VSSR power and degree of VEP change

The Çavuş et al. (2012) study found that, in healthy control participants, VSSR correlated significantly with N1b potentiation, suggesting that participants who had greater VSSR power during HFS experienced a greater tetanizing effect. To assess whether HFS-driven VSSR power was related to change in VEP amplitude following HFS in the present study, a linear regression was run for each group for ERP components that previous analyses had shown were significantly affected by visual HFS.

2.4.2.2.6. Assessing group differences in EEG data following processing

Following processing of EEG data, it is important to establish if there are significant group differences in the number of trials and channels removed during processing as this could affect interpretation of other EEG analyses. During VEP assessment blocks, standard circles

were presented for 90 trials per block. To check that there were no significant differences between groups in the number of standard circle trials included in analyses after pre-processing data, a two-way mixed methods ANOVA was conducted between group and block number on number of standard circle trials. One-way ANOVA's were also conducted to assess whether there were significant group differences in the number of channels removed during EEG processing.

2.4.2.3 Questionnaire analyses

2.4.2.3.1. Scale reliability

Prior to use in analyses, scale scores for each questionnaire were calculated according to their respective scoring manuals, and their internal reliability assessed using Cronbach's alpha (Cronbach, 1951). Scales are considered to have good internal reliability if they have Cronbach's alpha values of 0.7 or above (DeVellis, 2003; Kline, 2005).

2.4.2.3.2. Assessing group differences in questionnaire measures

The studies outlined in Chapters 4 and 5 were designed to examine whether self-reported sensory responsivity could be associated with changes in cortical plasticity. Therefore, prior to assessing the relationship between sensory responsivity and cortical plasticity, it was important to determine whether any significant group differences were present in the sensory questionnaire measures, as well as measures previously shown to be related to sensory processing (such as the DASS-21).

2.4.2.3.3. Assessing the Relationship between Sensory Responsivity and VEP Amplitude

One of the research questions this thesis aims to address is if participants with higher levels of responsivity to sensory stimuli might experience stimuli more intensely due to greater activation of neuronal networks in response to sensory stimuli, compared to individuals with lower levels of sensory responsivity. Consequently, two sets of correlation analyses were run to assess the relationship between sensory responsivity and VEP amplitude. The first set of correlations are run to determine if any significant relationships existed between N1 and P2 amplitudes measured at baseline and scores derived from questionnaire measures (AASP: Low Registration, Sensory Sensitivity, Sensation Avoiding; GSQ: total GSQ score) for each age group. The second set of correlation analyses aim to examine whether there are significant relationships between the amount of change in VEP amplitude following HFS for participants and sensory responsivity. Consequently, correlations were run between sensory questionnaire scores and N1 and P2 change scores (post-HFS 3 minus baseline) were run for each age group.

2.4.2.4. Multiple comparison corrections

The significance level for this thesis is set at $p < .05$, which in practice means that if the null hypothesis were true, then there would be a 5% chance of getting our observed result.

However, when you make multiple comparisons, the chance of making a Type 1 error inflates as the number of comparisons you make increases. This is problematic for many reasons, and could mean that significant amounts of time, effort and money could be wasted if important conclusions, or future research directions, were based on these false positives.

Traditionally, the method of choice for correcting for the multiple-comparison problem has been the Bonferroni correction, which aims to control the familywise error rate by altering the *p* value to a more stringent value, making Type 1 Errors less likely. In some cases, however, the Bonferroni correction can be too conservative. For example, if you are conducting a large number of multiple comparisons, the adjusted *p*-value could be very small, and may lead to a high rate of false negatives, especially if you predict that many of the comparisons would be significant. Consequently, by controlling so tightly for Type 1 errors may mean you actually end up missing something of significant interest.

The alternative for controlling for Type 1 Errors is to instead control for Type 2 Errors, known as the false discovery rate (FDR). This refers to the proportion of significant results that are actually false positives. The Benjamini-Hochberg (BH) procedure controls the false discovery rate using the following steps. Firstly, the individual *p*-values are ordered from smallest to largest. The smallest *p*-value has a rank of $i = 1$, with the next smallest *p*-value having a rank of $i = 2$, and so on for every *p*-value. Each individual p-value is then compared to its BH critical value $(i/m)Q$, where i is the rank, m is the total number of tests, and Q is the false discovery rate chosen by the researcher. The largest p value that has $p < (i/m)Q$ is significant, and all other p-values that are ranked as smaller than that are also significant (even if they aren't less than their BH critical value).

Careful consideration needs to be taken when choosing the false discovery rate. A false discovery rate of .05 is considered probably too low for many experiments, except for those where false positive results would be costly to follow up. For exploratory research, such as the studies presented in this thesis, a higher FDR of .10 or .20 is generally recommended (McDonald, 2014). Consequently, an FDR of 0.10 was used in the studies presented in this thesis.

2.4.2.5. Assumptions of Statistical Analyses

Unless otherwise specified in the results sections of the next three chapters, the following assumptions of parametric statistical analyses were met:

- The assumption of normal distribution of variables was met, assessed by graphical and numerical methods, including the Shapiro-Wilk's test ($p > .05$) and visual inspection of Normal Q-Q plots and histograms.

- No extreme outliers were included in analyses, as assessed by visual inspection of a boxplot for values greater than 3 box lengths from a hinge.

- The assumption of homogeneity of variances was met, as assessed by Levene's test for equality of variances ($p > .05$).

- In analyses comparing dependent variable scores for within groups factors, the assumption of sphericity was assessed by Mauchly's test of sphericity and considered to have been met if $p > .05$. If $p < .05$ then Greenhouse-Geisser adjusted values are presented.

Chapter 3: Investigating the relationships between sensory processing, risk-taking, and negative affect in the transition from adolescence to adulthood

Abstract

Whilst there is a wealth of research examining sensory processing difficulties in individuals with psychological conditions, especially in children (and to a lesser extent in adults), there is currently no research examining sensory processing in typically developing adolescents. The present study aimed to establish whether increased risk-taking and mental health issues are related to developmental changes in sensory responsivity, examining the trajectory of these variables during the transition from adolescence to adulthood. Questionnaires measuring sensory processing (Adolescent/Adult Sensory Profile; AASP), negative affect (Depression Anxiety and Stress Scale; DASS-21), and risk-taking (RT-18) were administered to early-adolescents (11-15, n = 51), late-adolescents (16-19, n = 237), young adults (20-24, n = 72) and adults (25-30, n = 58). The results of this study demonstrate that there were no age-related changes in Sensory Sensitivity, Sensation Seeking, or Sensation Avoiding; however, adults had significantly lower Low Registration scores compared to the younger age groups. Furthermore, extreme sensory processing styles were associated with greater levels of negative affect in typically developing adolescents and adults. This study is also the first to show that a propensity to engage in risk-taking behaviours and assess risky situations before acting is associated with sensory processing style. Collectively, these results demonstrate a clear association between sensory responsivity and risk-taking and negative affect in the transition from early-adolescence to adulthood.

3.1. Introduction

Adolescence is a critical period of development, with significant physical, emotional, and social changes, that some adolescents struggle to cope with. It is also the stage of development most typically associated with increased risk-taking behaviours (Arnett, 1992; Duell et al., 2018), and onset of mental health issues (Kessler et al., 2005). The present study aimed to establish whether increased risk-taking and increased negative affect in adolescence is related to developmental changes in sensory responsivity, by examining the trajectory of these variables during the transition from adolescence to adulthood. This chapter begins by outlining research on the emergence and prevalence of mental health issues in adolescence, as well as research examining risk-taking behaviours during this developmental stage, discussing how both of these adolescent phenomenon's may be related to sensory responsivity.

3.1.1. Developmental changes in sensory responsivity

The first aim of this study is to establish whether there are developmental changes in sensory responsivity during the transition from early-adolescence to young adulthood. Several studies have investigated the developmental trajectories of sensory responsivity in individuals with developmental disorders, such as ASC (Ben-Sasson et al., 2009; Talay-Ongan & Wood, 2000), and Fragile X Syndrome (Baranek et al., 2008). However, only a few studies have looked at developmental changes in sensory responsivity in typically developing populations. Again, this research has tended to focus on developmental changes within childhood. For example, using a longitudinal design, Ben-Sasson and colleagues showed that early sensory sensitivities reported at around 18 months of age were associated with sensory responsivity at school-age (Ben-Sasson, Carter, & Briggs-Gowan, 2010). In another longitudinal study, Van Hulle and colleagues (Van Hulle, Lemery-Chalfant, & Goldsmith, 2015) measured tactile and auditory over-responsivity in typically-developing twins (n = 978) and split participants into four trajectory groups based on their risk-status at 2 years and 7 years: low symptom (n = 768), remitted (n = 75), late-onset (n = 112), and chronic (n = 24). A subset of children also took part in a pilot study on sensory over responsivity at 4 years of age. Their results demonstrated that children in the chronic group had more severe sensory over-responsivity at four years of age, and were also more likely to have had a younger gestational age and lower birth weight than the other trajectory groups. Indeed, premature birth and more fearful temperaments were associated with sensory over-responsivity (particularly in the tactile domain) across all ages. This study also points out that extreme sensory over-responsivity tends to be transient in childhood, with only 2.5% of children experiencing elevated symptoms across ages - a finding that would not have been detected in a cross-sectional study. Indeed, a longitudinal design is perhaps the most desired approach to investigating developmental changes in sensory responsivity, but not the

most suitable design for studies that need to be completed in a relatively short-term frame (as is the case in producing a doctoral thesis).

At the time of writing, only one study has examined developmental changes in sensory responsivity in a typically developing sample spanning childhood, adolescence, and adulthood – although this was not the study's primary aim. A cross-sectional study by Kern and colleagues aimed to investigate the development of sensory dysfunction in 104 persons with autism and 104 age-and gender-matched neurotypical controls (Kern et al., 2006). Participants were split into seven age groups (3-7; 8-12; 13-17; 18-22; 23-27; 28-32; 33+), and the Sensory Profile (Dunn, 1999) was completed for each participant, either by a parent or family member. Analysis of sensory responsivity in the control group revealed that there was no significant change with age in auditory, visual, oral and touch processing. Interestingly, abnormalities in sensory processing appeared to decline with age in individuals with autism. Whilst this study has provided some insight into the trajectory of sensory responsivity in typically developing individuals, its broad age range (3-56 years) means that it still doesn't provide specific information about changes in sensory responsivity during the transition from adolescence to early adulthood. Therefore, the present study also examined developmental changes in sensory responsivity from adolescence to adulthood.

The transition between adolescence and adulthood is a critical developmental period, whereby individuals move from the familiar routine of school and peer group, into more independent living situations for further education, to begin careers and full-time employment, or to establish their own home and family (Lenz, 2001). In a biological and evolutionary sense, this transition represents a process whereby the individual secures reproductive success and physiological homeostasis, which are needed for the survival of the species (Rosenfeld & Nicodemus, 2003). With increasing maturity comes an expectation that one will take responsibility for oneself, make independent decisions regarding education, employment and relationships, and become self-sufficient (Arnett, 2000). These changes in social roles and responsibilities can be stressful and test an individual's capacity for adaptation, but can also present opportunities to overcome earlier difficulties and start on a new trajectory (Keller, Cusick, & Courtney, 2007; Masten et al., 2004). Consequently, it is important to further our understanding of factors, such as sensory responsivity, that may alter how successfully an individual transitions from adolescence to adulthood.

3.1.2. Mental health issues in adolescence

Adolescence is a period of profound changes; while most individuals successfully transition into adulthood, for some, these changes can stimulate feelings of uncertainty and anxiety which may develop into more severe mental health problems. It is well documented that mental health issues are common during adolescence, and that the negative consequences of

these problems can continue on into adulthood. In the UK, 20% of adolescents may experience mental health problems in any given year (WHO, 2003). In a U.S. study of over 10,000 adolescents (aged 13-18 years), lifetime prevalence of anxiety disorders was 31.9%, and 14.3% for mood disorders (Merikangas et al., 2010). In the UK, over half of all mental health problems start before the age of 14 years, becoming 75% by 24 years of age (Murphy & Fonagy, 2012). Furthermore, incidences of mental health issues during adolescence are related to poorer outcomes in adulthood (OECD, 2014). In individuals with adolescent onset major depressive disorder, there are significantly higher rates of suicide and suicide attempts, increased rates of psychiatric and medical hospitalizations, psychosocial impairment and lower educational achievement (Weissman et al., 1999). The long-term consequences of poor mental health mean it is important to investigate the possible causes of mental health problems at the age when they are most likely to develop.

The determinants of mental health outcomes in adolescence are varied and complex, but research suggests that there are several risk factors associated with poor mental health during adolescence. One of the most consistent findings from research investigating adolescent mental health problems, particularly those relating to anxiety and depression, is that females often report greater levels of anxiety, depression, and psychological distress compared to male adolescents (Fink et al., 2015; Van Droogenbroeck, Spruyt, & Keppens, 2018; WHO, 2000; Wiklund, Malmgren-Olsson, Öhman, Bergström, & Fjellman-Wiklund, 2012). The causes of gender differences in mental health problems amongst adolescents is still not fully understood, but one possible explanation is that male adolescents have more difficulty in acknowledging the problem, and may also be more likely to act out, possibly resulting in antisocial personality disorders, or substance abuse issues (Patel, Flisher, Hetrick, & McGorry, 2007). Gender differences in mental health problems could also arise from differences in cultural expectations for males and females, with females being expected to be more emotionally sensitive than males (Rosenfield & Mouzon, 2013). Other factors considered to contribute to poorer mental health outcomes in adolescence include delays in reaching more adult levels of autonomy (Patton et al., 2016), social media use (Bell, Bishop, & Przybylski, 2015), and a more highly pressurised school culture (Lessof, Ross, Brind, Bell, & Newton, 2016). On a more positive note, good social connections and support networks are shown to be protective against mental health problems, with adolescents who are satisfied with their social contacts and support reporting lower levels of anxiety depression and psychological distress (Van Droogenbroeck et al., 2018).

To the best of my knowledge, there is no published research exploring the relationship between sensory responsivity and levels of anxiety and depression in typically developing (TD) adolescents. It should be noted that one study did report a positive association between anxiety and sensory sensitivity in children, adolescents, and young adults; however, all participants aged 5-17 years were in treatment for an anxiety or OCD spectrum disorder at a university-based

clinic, and were therefore not considered to be neurotypical (Zickgraf & Elkins, 2018). Instead, the majority of sensory responsivity research in typically developing populations has focussed on children and, to a lesser degree, adults. Interestingly, these studies consistently demonstrate a relationship between sensory over-responsivity and internalizing symptoms (such as anxiety, depression, and withdrawal; see Chapter 1.3). For example, Goldsmith et al. (2006) reported that auditory and tactile defensiveness in toddlers were associated with fearful temperament and anxiety, but were less related to other measures of dysfunctional childhood behaviour. In neurotypical adults, studies have shown a link between sensory defensiveness and a tendency towards increased symptoms of anxiety and depression (Kinnealey & Fuiek, 1999), psychological distress and psychological difficulties (Ben-Avi et al., 2012; Batya Engel-Yeger & Dunn, 2011b), increased negative affect (Batya Engel-Yeger & Dunn, 2011a), poorer sleep quality (Batya Engel-Yeger & Shochat, 2012), and increased relationship anxiety (Jerome & Liss, 2005). Based on the findings of these studies that demonstrate a relationship between sensory processing styles and level of negative affect in children and adults, it is important to determine if sensory processing issues in adolescents are also associated with experiencing more symptoms of depression, anxiety, and stress. To that end, this study aimed to explore the relationship between sensory processing styles and negative affect in the transition from adolescence to adulthood using self-report measures. It was hypothesized that extreme sensory processing styles would be associated with greater levels of depression, anxiety and stress in adolescence.

3.1.3. Risk-taking behaviour in adolescence

As well as increased mental health problems, adolescence is also a period associated with increased risk-taking behaviours. As discussed in Chapter 2.3.2.1, it is largely acknowledged that risky behaviours, including substance abuse, unsafe sexual activity, dangerous driving, and violent and criminal activity will emerge, increase and peak during adolescence (Arnett, 1992; Kilpatrick et al., 2000). Given that many risky activities provide strong sensory inputs (e.g. reckless driving provides strong vestibular inputs and fast-changing visual inputs) or may alter the sensitivity of our sensory processes to make situations feel more pleasurable (as in substance abuse), it is of interest to assess the relationship between sensory processing style and risk-taking behaviours in adolescence.

There is currently little literature exploring the relationship between risk-taking behaviours and sensory responsivity. One study showed that delinquent-prone adolescents (aged 12-18 years) scored lower on praxis and vestibular related tests than non-delinquent prone adolescents, suggesting that low sensory responsivity (at least in terms of praxis and vestibular processing) is associated with greater risk-taking behaviours (Fanchiang, Snyder, Zobel-Lachiusa, Loeffler, & Thompson, 1990). However, it is worth noting that there was a big

difference in the number of delinquent-prone teens (n = 12) and non-delinquent-prone teens (n = 114) included in analyses, so these findings may not be reliable.

Whilst there is limited evidence regarding the relationship between general sensory responsivity and risk-taking, there is a greater wealth of literature concerning the relationship between sensation seeking and risk-taking behaviours. Indeed, positive correlations have been found between sensation seeking and risky behaviours in adolescence, including risky sexual activities (Donohew et al., 2000), greater alcohol use (MacPherson, Magidson, Reynolds, Kahler, & Lejuez, 2010), and even positive risky activities (such as climbing or kayaking; Hansen & Breivik, 2001). Dunn's model of sensory processing (1997) suggests that sensation seeking behaviours are a result of high neurological thresholds and active self-regulation strategies. Furthermore, Dunn posits that individuals who score highly on sensation seeking will experience pleasure from exciting sensory environments and behaviours, will often show risk-taking behaviours that are expressed by a lack of physical boundaries, and may be seen by others as irresponsible, impatient, and lacking in respect (Brown, Tollefson, Dunn, Cromwell, & Filion, 2001; Dunn, 1997). Consequently, and in addition to the aims discussed in section 3.1.1 and 3.1.2, this study also aimed to explore the relationship between sensory processing styles and risk-taking behaviours in the transition from adolescence to adulthood. It was hypothesized that individuals with high sensation seeking scores would be most likely to engage in risk-taking behaviours.

3.1.4. Aims of the present study

The present study aimed to examine the relationships between sensory responsivity, negative affect, and risk-taking in typically developing adolescents and young adults, as well as examining developmental changes in sensory responsivity across this transitional period. It was predicted that individuals with extreme sensory processing scores would be more likely to experience anxiety, depression, and stress. Furthermore, it was predicted that individuals with high sensation seeking scores would be more likely to engage in risk-taking behaviours. Finally, this study also examined whether there is an interaction between age and sensory responsivity on negative affect and risk-taking.

3.2. Method

3.2.1. Participants

In total, 418 participants completed the study (Table 3.1). Participants were split into groups based on their age: early-adolescents (11-15 years), late-adolescents (16-19 years), young adults (20-24 years), and adults (25-30 years). Due to greater accessibility and recruitment of undergraduate students, the sample sizes were not equal amongst the age groups. Participants were entered into a raffle for a £20 voucher. All participants were free of any psychiatric or physical conditions.

Table 3.1

Demographic information

Group		Early-Adolescents	Late-Adolescents	Young Adults	Adults
Age (years)	Range	11-15	16-19	20-24	25-30
	M	13.65	17.84	20.64	26.28
	SD	.74	.92	1.14	1.52
N	Males	14	64	17	20
	Females	37	173	55	38
	Total	51	237	72	58

3.2.2. Questionnaires

Descriptive statistics for all questionnaire measures, and relevant sub-scales are presented in Table 3.2.

3.2.2.1. Adolescent Adult Sensory Profile (AASP)

See Chapter 2.3.2.3 for more information about this questionnaire.

3.2.2.2. Depression Anxiety and Stress Scale (short form version; DASS-21)

See Chapter 2.3.2.5 for more information about this questionnaire.

3.2.2.3. RT-18

See Chapter 2.3.2.2 for more information about this questionnaire.

3.2.3. Procedure

Participants were given a web link (Qualtrics) and completed the questionnaires online. For adolescent participants who completed the questionnaires in school or college, they were asked to remain quiet whilst completing the questionnaires, and not to discuss the questions with their peers whilst they were completing them.

3.2.3.1. Statistical Analysis

The first research question for this study was to examine if there were age-related differences in sensory processing. Consequently, a one-way multivariate analysis of variance (MANOVA) was conducted with age group as the independent factor, and AASP scales as dependent variables. Although it is not a main aim of this study to investigate changes in negative affect and risk-taking during the transition from adolescence to adulthood, it is important to examine whether there were age-related differences in other questionnaire measures collected in this study, as this could affect interpretation of other subsequent analyses assessing the relationships between age, sensory processing, negative affect and risk-taking. Therefore, MANOVA's were also run to assess whether there were significant differences between age groups on DASS-21 and RT-18 measures.

To examine possible interaction effects between age group and sensory processing measures on risk-taking and negative affect measures, a multivariate analysis of covariance (MANCOVA) was run. Age group (early-adolescent, late-adolescent, young adult, and adult) was entered as the between-subjects factor. The four sensory processing measures (Low Registration, Sensation Seeking, Sensory Sensitivity, and Sensation Avoiding) were entered as continuous covariates. Risk-taking measures (risk-taking behaviour, and risk-assessment) and negative affect measures (depression, anxiety, and stress) were all entered as dependent variables. Typically, the aim of this type of analysis is to determine whether there are any statistically significant differences between independent groups on two or more dependent variables, having controlled for a continuous covariate. However, it also allows one to examine interactions between categorical independent variables and continuous covariates on the combined dependent variables, by assessing homogeneity/heterogeneity of regression slopes. If there is significant homogeneity of regression slopes, it is assumed that there is no interaction effect between the independent variable and covariate; however, if there is significant heterogeneity of regression slopes then this suggests that the relationship between covariate and dependent variable changes for each level of the independent variable. Consequently, if there is significant heterogeneity of regression slopes for any covariate, then follow-up analyses will be conducted to statistically compare regression slopes and intercepts. In addition, if the MANCOVA indicates that there is a significant main effect of a covariate variable, follow-up linear regressions will be performed to assess the relationship between the AASP measure and relevant dependent variables.

3.3. Results

Descriptive statistics for all questionnaire scales used in this study are presented in Table 3.2.

Table 3.2
Descriptive statistics and Cronbach's alpha for the AASP, DASS-21 and GSQ questionnaire scales

Age Group	Q-naire	Scale	Mean	*SD*	Min	Max	α
Early-Adolescents	AASP	Low Registration	37.06	10.25	20	69	.85
		Sensation Seeking	44.06	8.30	25	66	.69
		Sensory Sensitivity	38.51	10.63	17	63	.82
		Sensation Avoiding	35.96	9.95	20	58	.82
	DASS-21	Depression	4.69	4.68	0	18	.87
		Anxiety	5.75	4.76	0	19	.84
		Stress	6.94	5.26	0	21	.87
	RT-18	Risk-Taking Behaviour	4.96	2.85	0	9	.83
		Risk Assessment	3.98	2.17	0	8	.62
Late-Adolescents	AASP	Low Registration	35.61	8.15	15	59	.80
		Sensation Seeking	45.14	7.39	26	69	.70
		Sensory Sensitivity	38.57	7.68	20	56	.70
		Sensation Avoiding	34.80	7.50	19	62	.73
	DASS-21	Depression	6.11	4.88	0	19	.89
		Anxiety	5.72	4.12	0	18	.77
		Stress	7.50	4.60	0	21	.85
	RT-18	Risk-Taking Behaviour	5.28	2.87	0	9	.84
		Risk Assessment	3.25	2.20	0	9	.65
Young-Adults	AASP	Low Registration	35.89	7.56	20	55	.77
		Sensation Seeking	45.60	6.70	31	63	.61
		Sensory Sensitivity	39.57	7.30	24	61	.63
		Sensation Avoiding	36.36	8.21	21	58	.77
	DASS-21	Depression	5.72	4.61	0	21	.86
		Anxiety	5.06	4.46	0	21	.84
		Stress	7.69	4.57	0	21	.81
	RT-18	Risk-Taking behaviour	5.15	2.67	0	9	.79
		Risk Assessment	3.49	2.18	0	8	.63
Adults	AASP	Low Registration	31.43	7.63	19	48	.80
		Sensation Seeking	44.45	7.22	28	59	.73
		Sensory Sensitivity	37.93	7.67	22	54	.68
		Sensation Avoiding	36.36	7.97	17	52	.76
	DASS-21	Depression	4.29	4.21	0	16	.88
		Anxiety	3.52	3.30	0	17	.74
		Stress	6.81	4.31	0	18	.83
	RT-18	Risk-Taking behaviour	4.10	2.55	0	9	.78
		Risk Assessment	2.10	2.04	0	7	.70

Note: *SD* = standard deviation; Min = minimum observed score; Max = maximum observed score; AASP = Adolescent-Adult Sensory Profile; DASS-21 = Depression Anxiety Stress Scale (short form version). All values are from untransformed data.

3.3.1. Age-related differences in sensory processing scores

To examine whether there were age-related differences in sensory processing scores, a one-way MANOVA was run with age group (early-adolescent, late-adolescent, young adult, and adult) as the independent factor and Low Registration, Sensation Seeking, Sensory Sensitivity and Sensation Avoiding included as dependent variables. Descriptive statistics for AASP measures are presented in Table 3.2. The differences between the age groups on the combined dependent variables was statistically significant, F (12.00, 1087.70) = 2.61, p = .002, Wilks' Λ = .928, partial η^2 = .025. Follow-up univariate ANOVA's showed that there were significant differences between age groups in Low Registration scores [F (3, 414) = 5.23, p = .001, partial η^2 = .036]. Benjamini-Hochberg corrected pairwise comparisons revealed that adults had significantly lower Low Registration scores than early-adolescents (p < .001), late-adolescents (p = .001), and young adults (p = .002). There were no significant differences in Low Registration scores between the three youngest age groups (p > .258). This suggests that adults are significantly more likely to respond to salient sensory stimuli compared to early-adolescents, late-adolescents, or young adults. There were no significant differences between age groups on scores of Sensation Seeking [F (3, 414) = .57, p = .633, partial η^2 = .004], Sensory Sensitivity [F (3, 414) = .48, p = .695, partial η^2 = .003], or Sensation Avoiding [F (3, 414) = 1.15, p = .329, partial η^2 = .008].

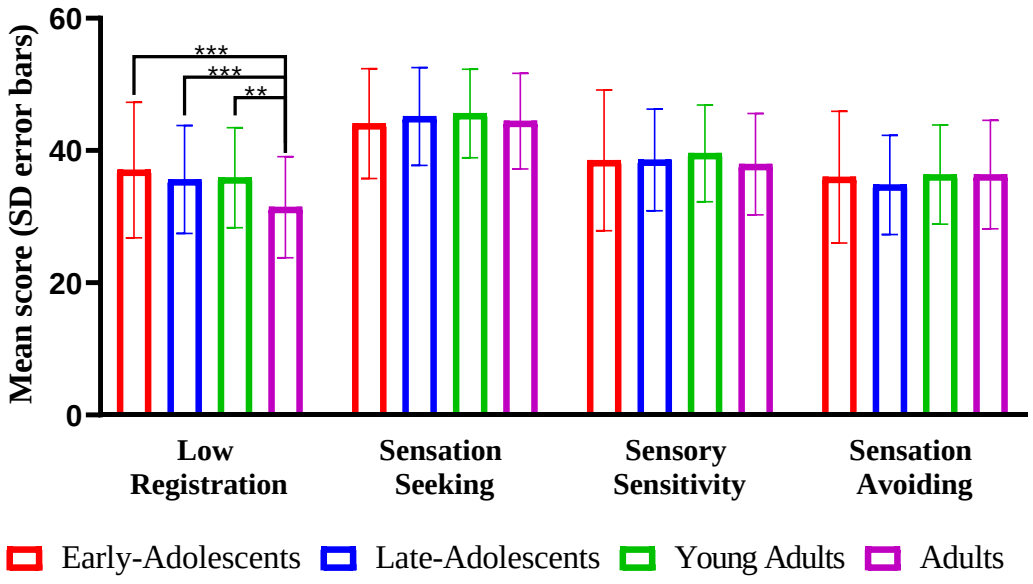


Figure 3.1. Mean AASP scale scores for each age group. Adults had significantly lower Low Registration scores compared to early-adolescents, late-adolescents, and young adults; no other significant age group differences were found. *** p < .001, ** p < .01.

3.3.2. Age-related differences in DASS-21 scores

To examine whether there were age-related differences in DASS-21 scale scores, a one-way MANOVA was run with age group as the independent factor and depression, anxiety and stress scores included as dependent variables. Descriptive statistics for DASS-21 measures are presented in Table 3.2. The differences between the age groups on the combined dependent variables was statistically significant, F (9.00, 1002.85) = 2.61, $p < .001$, Wilks' $\Lambda = .926$, partial $\eta^2 = .025$. Follow-up univariate ANOVA's showed that there were significant differences between age groups in anxiety scores [F (3, 414) = 4.62, $p = .003$, partial $\eta^2 = .032$]. Pairwise comparisons revealed that adults had significantly lower anxiety scores compared to early-adolescents (p =.006), late-adolescents ($p < .001$), and young adults ($p = .037$), but there were no significant differences in anxiety scores between the three youngest age groups (all p's > .238). There were also significant differences between age groups in depression scores [F (3, 414) = 43.05, $p = .029$, partial $\eta^2 = .022$], with pairwise comparisons indicating that late-adolescents had significantly higher depression scores compared to adults ($p = .009$), but all other comparison were not significant (all p's > .052). There were no significant differences between age groups in terms of stress scores [F (3, 414) = .61, $p = .611$, partial $\eta^2 = .004$]. Collectively, these results suggest that adults reported experiencing significantly fewer symptoms of anxiety than adolescents and young adults, and also reported experiencing significantly fewer symptoms of depression compared to late-adolescents. These findings are also presented graphically in Figure 3.2.

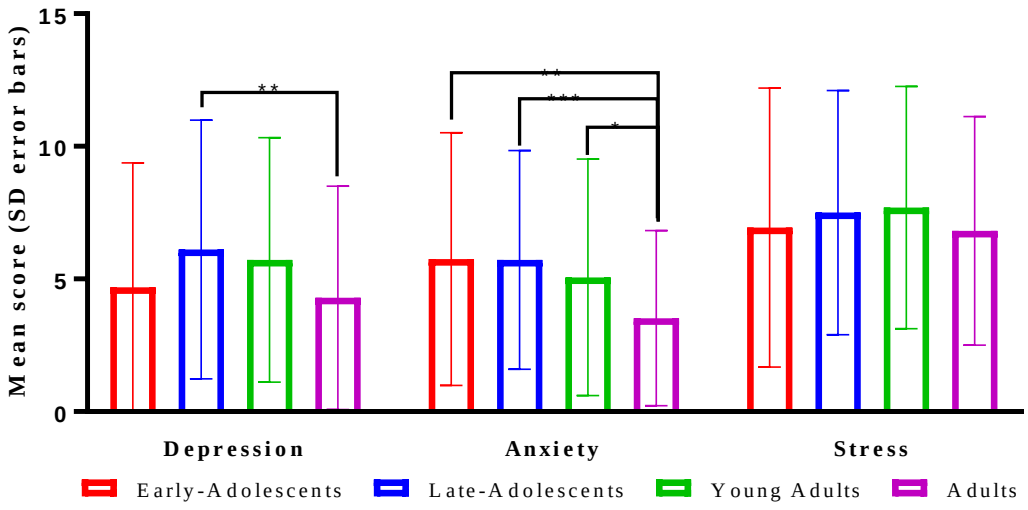


Figure 3.2. Mean DASS-21 scale scores for each age group. Adults had significantly lower depression scores compared to late-adolescents. Adults also had significantly lower anxiety scores than all younger age groups. No other significant age group differences were found. *** $p < .001$, ** $p < .01$, * $p > .05$.

3.3.3. Age-related differences in RT-18 scores

A one-way MANOVA was run with age group as the independent factor and risk-taking behaviour and risk-assessment included as dependent variables. Descriptive statistics for RT-18 measures are presented in Table 3.2. The differences between the age groups on the combined dependent variables was statistically significant, F (6, 826) = 2.61, $p < .001$, Wilks' $\Lambda = .937$, partial $\eta^2 = .032$. Follow-up univariate ANOVA's showed that there were significant differences between age groups in risk-taking behaviour scores [F (3, 414) = 2.83, $p = .038$, partial $\eta^2 = .020$], with pairwise comparisons revealing that late-adolescents and young adults had significantly higher risk-taking behaviour scores compared to adults ($p = .004$ and $p = .034$ respectively), and that all other comparisons were not statistically significant (all p's > .110). There were also significant differences between age groups for risk assessment scores [F (3, 414) = 7.56, $p < .001$, partial $\eta^2 = .052$], with pairwise comparisons revealing that adults had significantly lower risk-assessment scores than early-adolescents, late-adolescents, and young adults (all p's <.001), suggesting that adults were more likely to assess risky situations than the younger age groups. Furthermore, early-adolescents were less likely to risk assess compared to late-adolescents ($p = .031$), but no other comparisons were statistically significant (p's > .215). Collectively, these results suggest that adults were less likely to engage in risk-taking behaviours than late-adolescents and young adults, and more likely to assess risky situations than all younger participants. Early-adolescents were the least likely to assess risky situations before acting. These findings are presented graphically in Figure 3.3.

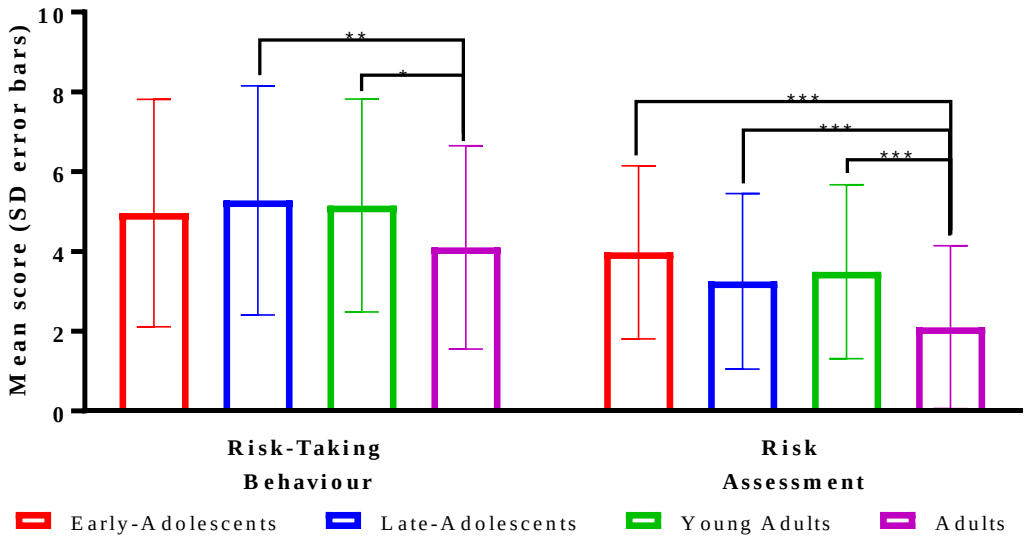


Figure 3.3. Mean RT-18 scale scores for each age group. Adults had significantly lower risk-taking behaviour scores compared to late-adolescents and young adults. Adults also had significantly lower risk assessment scores than all younger age groups. No other significant age group differences were found. *** $p < .001$, ** $p < .01$, * $p > .05$.

3.3.4. The relationship between age and sensory processing on negative affect

A multivariate analysis of covariance (MANCOVA) was run with age group (early-adolescent, late-adolescent, young adult and adult) as the between-subjects factor, three dependent variables (depression, anxiety, and stress scores from the DASS-21), and four covariates (Low Registration, Sensation Seeking, Sensory Sensitivity, and Sensation Avoiding scores from the AASP). There was a linear relationship between each pair of dependent variables for each age group, as assessed by visual inspection of a scatterplot. The correlations between the dependent variables were moderately strong (depression x stress [r (416) = .69, p < .001]; depression x anxiety [r (416) = .63, p <.001]; anxiety x stress [r (416) = .74, p < .001]), which is not ideal in a MANCOVA analysis (Tabachnick & Fidell, 2013, p. 246). However, removing one of the most strongly correlated variables (in this case, stress) did not materially affect the outcome of the results, so was kept in. There was also a linear relationship between each of the covariates and each of dependent variables for each age group, also assessed by visual inspection of a scatterplot. There was homogeneity of regression slopes for three of the covariates, as assessed by their interactions with age group (Sensation Seeking [F (9.00, 963.91) = .92, p = .504]; Sensory Sensitivity [F (9.00, 963.91) = .54, p = .849]; Sensation Avoiding [F (9.00, 963.91) = .88, p = .543]). This suggests that there was no significant interaction effect between age group and these three sensory processing styles on measures of negative affect. However, there was significant heterogeneity of regression slopes for the interaction term between Low Registration and age group, F (9.00, 963.91) = 2.14, p = .024; consequently, Low Registration was removed as a covariate for this analyses and separate moderator analyses was run to examine the interaction between age group and Low Registration scores on the three measures of negative affect (see section 3.3.4.3). There was homogeneity of variances and covariances, as assessed by Box's M test, p > .001. Seven univariate outliers were identified, as assessed by standardized residuals greater than ±3 standard deviations, and two multivariate outliers were identified, as assessed by Mahalanobis distance (p < .001). All outliers were kept in the analysis as they didn't materially affect the outcome of the results, as assessed by comparing analyses with and without the outliers.

The results of the MANCOVA revealed that there were no statistically significant differences between the age groups on the combined dependent variables after controlling for Sensation Seeking, Sensory Sensitivity, and Sensation Avoiding, F (9.00, 973.65) = 1.48, p = .150, Wilks' Λ = .967, partial η^2 = .011. The results also revealed that there was no significant main effect of Sensation Seeking on the combined dependent variables [F (3, 400) = 1.97, p = .118, Wilks' Λ = .985, partial η^2 = .015]; however, there was a statistically significant main effect of Sensory Sensitivity [F (3, 400) = 7.36, p < .001, Wilks' Λ = .948, partial η^2 = .052] and Sensation Avoiding [F (3, 400) = 6.62, p < .001, Wilks' Λ = .948, partial η^2 = .047] on the combined dependent variables. Given that these covariates were continuous variables, follow-up

regression analyses were conducted to examine the relationship between Sensory Sensitivity and Sensation Avoiding on depression, anxiety and stress across the entire sample.

3.3.4.1. The relationship between Sensory Sensitivity and negative affect

Three separate linear regressions were run to examine whether Sensory Sensitivity scores could significantly predict depression, anxiety, and stress scores respectively. The results revealed that Sensory Sensitivity scores could significantly predict depression scores [F (1, 416) = 61.72, $p < .001$, adj. $R^2 = .13$], anxiety scores [F (1, 416) = 112.88, $p < .001$, adj. $R^2 = .21$], and stress scores [F (1, 416) = 146.36, $p < .001$, adj. $R^2 = .26$]. Details of the regression coefficients are presented in Table 3.3.

Table 3.3
Summary of the regression coefficients for DASS-21 variables predicted by Sensory Sensitivity score

DASS-21 Variable	B	SE B	β	95% CI for B
Depression	.21	.03	.359***	.16 to .27
Anxiety	.24	.02	.462***	.20 to .29
Stress	.30	.02	.510***	.25 to .34

Note. *** $p < .001$

Predictions were made to determine mean negative affect scores for Sensory Sensitivity scores that are similar to most people, less than most people, and more than most people based on classifications provided in the AASP scoring manual (see section 2.3.2.3 for more information on AASP scoring). A summary of the predicted scores are presented in Table 3.4. Based on DASS severity ratings (see section 2.3.2.5 for more details on DASS-21 scoring), individuals with Sensory Sensitivity scores that are similar, less than, or much less than most people are predicted to experience normal levels of depression. In contrast, those who have Sensory Sensitivity scores that are more than most people are predicted to experience mild to moderate levels of depression, and individuals with Sensory Sensitivity scores that are much more than most people are predicted to experience moderate to severe levels of depression. Similarly, Sensory Sensitivity scores that are more or much more than most people are also predictive of anxiety scores that range from moderate to extremely severe, and stress scores that are mild to extremely severe, with higher scores predicting more severe experiences of negative affect.

Table 3.4
Predicted range of mean DASS-21 scores [95% confidence intervals] based on Sensory Sensitivity score

DASS-21 Variable	Sensory Sensitivity score				
	Much less than most people	Less than most people	Similar to most people	More than most people	Much more than most people
Depression	.57 [-.76, 1.90] to 1.21 [.03, 1.90]	1.42 [.29, 2.56] to 2.71 [1.86, 3.55]	2.92 [2.12, 3.72] to 6.12 [5.67, 6.57]	6.33 [5.87, 6.80] to 7.61 [6.80, 8.27]	7.83 [7.13, 8.53] to 13.38 [11.39, 15.36]
Anxiety	-.45 [-1.57, .67] to .28 [-.71, 1.28]	.53 [-.43, 1.48] to 1.99 [1.27, 2.70]	2.23 [1.56, 2.90] to 5.87 [5.50, 6.25]	6.12 [5.73, 6.51] to 7.57 [7.02, 8.13]	7.82 [7.23, 8.41] to 14.14 [12.46, 15.81]
Stress	.40 [-.80, 1.59] to 1.28 [.22, 2.34]	1.58 [.56, 2.59] to 3.35 [2.59, 4.10]	3.64 [2.92, 4.36] to 8.07 [7.67, 8.47]	8.36 [7.94, 8.78] to 10.13 [9.54, 10.72]	10.42 [9.80, 11.05] to 18.09 [16.31, 19.88]

3.3.4.2. The relationship between Sensory Avoiding and negative affect

Three separate linear regressions were run to examine whether Sensation Avoiding scores could significantly predict depression, anxiety, and stress scores respectively. The results revealed that Sensation Avoiding scores could significantly predict depression scores [F (1, 416) = 54.48, $p < .001$, adj. $R^2 = .11$], anxiety scores [F (1, 416) = 101.54, $p < .001$, adj. $R^2 = .19$], and stress scores [F (1, 416) = 110.48, $p < .001$, adj. $R^2 = .21$]. Details of the regression coefficients are presented in Table 3.5.

Table 3.5
Summary of the regression coefficients for DASS-21 variables predicted by Sensation Avoiding score

DASS-21 Variable	B	SE B	β	95% CI for B
Depression	.20	.03	.339***	.15 to .26
Anxiety	.23	.02	.443***	.19 to .28
Stress	.27	.03	.458***	.22 to .31

Note. *** $p < .001$

Predictions were made to determine mean negative affect scores for Sensation Avoiding scores that are similar to most people, less than most people, and more than most people based on classifications provided in the AASP scoring manual (see section 2.3.2.3 for more information on AASP scoring). A summary of the predicted scores are presented in Table 3.6. As with predictions based on Sensory Sensitivity scores, individuals with Sensation Avoiding scores that are similar, less than, or much less than most people are predicted to experience normal to mild levels of depression and stress, and normal to moderate levels of anxiety.

Individuals with Sensation Avoiding scores that are more or much more than most people are predicted to experience moderate to severe levels of depression, and moderate to extremely severe levels of anxiety and stress.

Table 3.6
Predicted range of mean DASS-21 scores [95% confidence intervals] based on Sensation Avoiding score

DASS-21 Variable	Sensation Avoiding score				
	Much less than most people	Less than most people	Similar to most people	More than most people	Much more than most people
Depression	1.51 [.33, 2.69] to 2.31 [1.33, 3.29]	2.51 [1.58, 3.45] to 3.72 [3.06, 4.39]	3.92 [3.29, 4.55] to 6.74 [6.21, 7.26]	6.94 [6.38, 7.50] to 8.35 [7.50, 9.20]	8.55 [7.66, 9.45] to 13.58 [11.41, 15.75]
Anxiety	.55 [-.45, 1.54] to 1.48 [.65, 2.31]	1.71 [.92, 2.50] to 3.11 [2.55, 3.67]	3.34 [2.81, 3.87] to 6.60 [6.16, 7.04]	6.83 [6.36, 7.30] to 8.46 [7.75, 9.18]	8.69 [7.94, 9.45] to 14.51 [12.68, 16.34]
Stress	1.97 [.88, 3.05] to 3.03 [2.12, 3.93]	3.29 [2.43, 4.15] to 4.88 [4.27, 5.49]	5.14 [4.57, 5.72] to 8.85 [8.36, 9.33]	9.11 [8.60, 9.62] to 10.96 [10.18, 11.74]	11.23 [10.40, 12.05] to 17.84 [15.84, 19.84]

3.3.4.3. Low Registration as a moderator between age and negative affect

In the above MANCOVA analysis (section 3.3.4), it became apparent that there was significant heterogeneity of regression slopes for the interaction term between Low Registration and age group. Consequently, this analysis aims to examine how Low Registration scores moderate the relationship between age group and measures of negative affect (depression, anxiety and stress). Linear regressions were run to see if Low Registration scores could significantly predict depression, anxiety, and stress scores for each age group (early-adolescent, late-adolescent, young adult, and adult). Additional analyses were run to see if regression slopes were equal; if regression slopes were equal, then analyses were run to test whether intercepts were equal. Analyses to compare regression slopes and intercepts are not available in IBM SPSS; therefore, statistical comparisons of slopes and intercepts were run using GraphPad Prism 7.04. Data are presented as scatter graphs in Figure 3.4.

Firstly, linear regressions were run to see whether Low Registration scores could predict depression scores for each age group. Results of the linear regressions showed that Low Registration scores were significant predictors of depression scores in early-adolescents [F (1, 49) = 19.74, $p < .001$] and late-adolescents [F (1, 234) = 33.66, $p < .001$], but was not a significant predictor for young adults [F (1, 70) = 3.76, $p = .057$] or adults [F (1, 57) = 2.45, $p = .123$]. Analyses to compare the slopes for each age group showed that the slopes were not

significantly different [F (3, 410) = .95, p = .415], and the Y intercepts were also not significantly different [F (3, 413) = 2.54, p = .056].

Second, linear regression analyses were run to see whether Low Registration scores could predict anxiety scores for each age group. Results showed that Low Registration scores were significant predictors of anxiety in all age groups: early-adolescents [F (1, 49) = 10.30, p = .002]; late-adolescents [F (1, 235) = 42.89, p < .001]; young adults [F (1, 70) = 11.66, p = .001]; adults [F (1, 56) =15.24, p < .001]. Analyses to compare the slopes for each age group showed that the slopes were not significantly different [F (3, 410) = .05, p = .984], and the Y intercepts were also not significantly different [F (3, 413) = 2.19, p = .088].

Finally, linear regression analyses were run to see whether Low Registration scores could predict stress scores for each age group. Results showed that Low Registration scores were significant predictors of stress in all age groups: early-adolescents [F (1, 49) = 47.90, p < .001]; late-adolescents [F (1, 235) = 49.91, p < .001]; young adults [F (1, 70) = 5.57, p = .021]; adults [F (1, 56) = 5.49, p = .023]. Analyses to compare the slopes for each age group showed that the slopes were not significantly different [F (3, 410) = 2.24, p = .083], and the Y intercepts were also not significantly different [F (3, 413) = .90, p = .442].

Collectively, these results demonstrate that greater Low Registration scores predict significantly higher levels of depression in early- and late-adolescents, and predict higher anxiety and stress across all the age groups tested in this study. However, none of the analyses reported significant differences in regression slopes or intercepts, suggesting that the relationship between Low Registration and negative affect does not change during the transition from early-adolescence to adulthood.

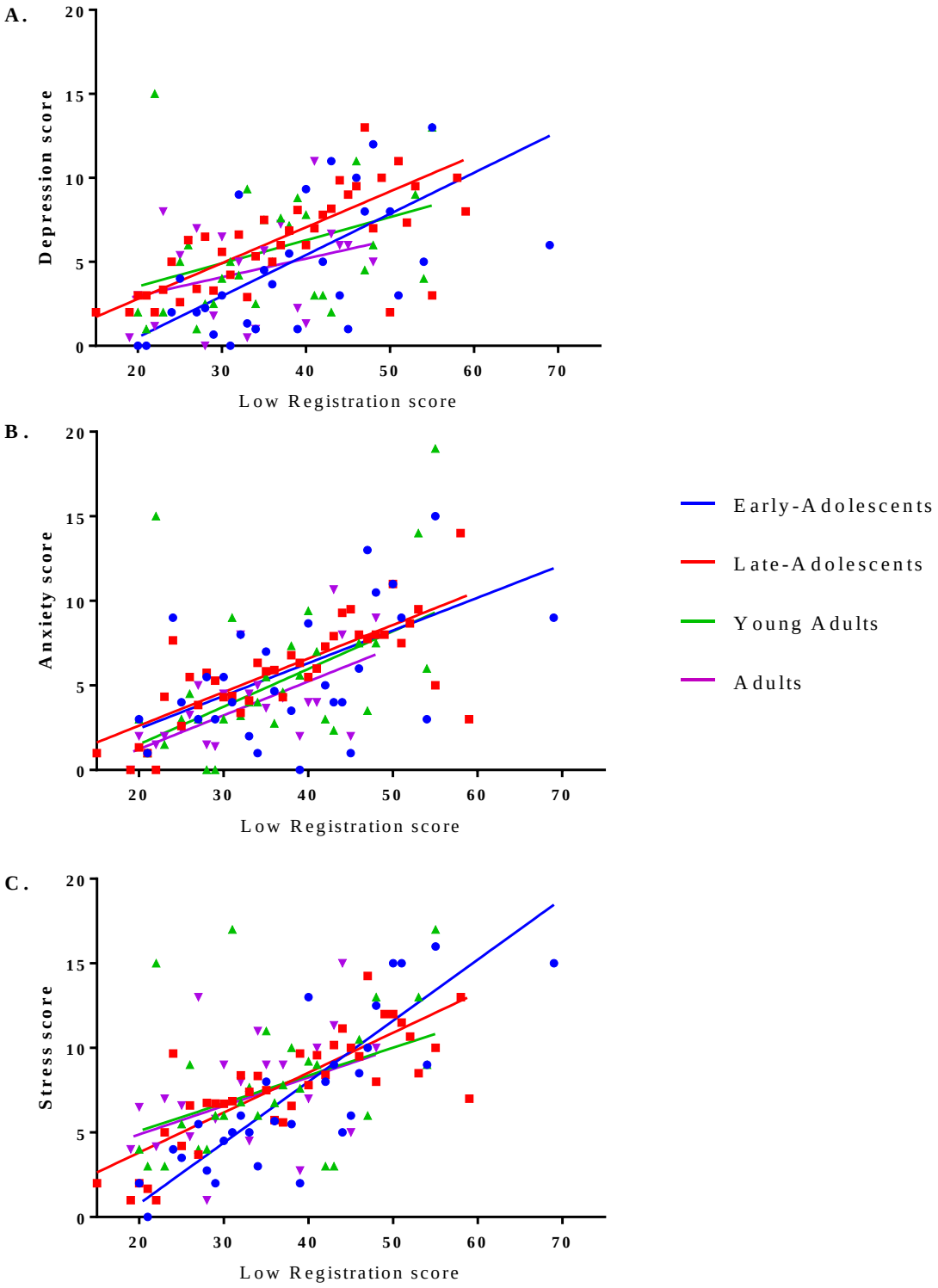


Figure 3.4. Scatter graphs depicting the relationships between Low Registration scores and measures of negative affect (**A**. Low Registration X Depression; **B**. Low Registration X Anxiety; **C**. Low Registration X Stress), with regression lines for each age group.

3.3.5. The relationship between age and sensory processing on risk-taking

A second multivariate analysis of covariance (MANCOVA) was run with age group (early-adolescent, late-adolescent, young adult and adult) as the between-subjects factor, two dependent variables (risk-taking behaviour and risk assessment scores from the RT-18), and four covariates (Low Registration, Sensation Seeking, Sensory Sensitivity, and Sensation Avoiding scores from the AASP). There was a linear relationship between the two dependent variables for each age group, as assessed by visual inspection of a scatterplot. The two dependent variables were weakly correlated, r (416) = .38, $p < .001$. There was also a linear relationship between each of the covariates and each of dependent variables for each age group, also assessed by visual inspection of a scatterplot. There was homogeneity of regression slopes for all four of the covariates, as assessed by their interactions with age group (Low Registration [F (6, 782) = .78, p = .584]; Sensation Seeking [F (6, 782) = 1.38, p = .219]; Sensory Sensitivity [F (6, 782) = 1.00, p = .421]; Sensation Avoiding [F (6, 782) = .8, p = .529]). This suggests that there was no significant interaction effect between age group and sensory processing style on risk-taking measures. There was homogeneity of variances and covariances, as assessed by Box's M test, $p > .001$. One univariate outlier was identified, as assessed by standardized residuals greater than ±3 standard deviations. The same participant was also identified as a multivariate outlier, as assessed by Mahalanobis distance ($p < .001$). The outlier was kept in the analysis as they didn't materially affect the outcome of the results, as assessed by comparing analyses with and without the outlier.

The results of the MANCOVA revealed that there were no statistically significant differences between the age groups on the combined dependent variables after controlling for Low Registration, Sensation Seeking, Sensory Sensitivity, and Sensation Avoiding, F (6, 794) = .82, p = .555, Wilks' Λ = .988, partial η^2 = .006. The results also revealed that there was no significant main effect of Sensation Avoiding on the combined dependent variables [F (2, 397) = 2.44, p = .088, Wilks' Λ = .988, partial η^2 = .012]. However, there was a statistically significant main effect of Low Registration [F (2, 397) = 12.44, $p < .001$, Wilks' Λ = .941, partial η^2 = .059], Sensation Seeking [F (2, 397) = 28.03, $p < .001$, Wilks' Λ = .876, partial η^2 = .124] and Sensory Sensitivity [F (2, 397) = 3.58, p = .029, Wilks' Λ = .982, partial η^2 = .018] on the combined dependent variables. Given that these covariates were continuous variables, follow-up linear regression analyses were conducted to examine the relationship between Low Registration, Sensation Seeking and Sensory Sensitivity on risk-taking behaviour and risk assessment across the entire sample.

3.3.5.1. The relationship between Low Registration and risk taking

Two separate linear regressions were run to examine whether Low Registration scores could significantly predict risk-taking behaviour, and risk-assessment scores respectively. The

results revealed that Low Registration scores could significantly predict risk assessment scores [F (1, 416) = 44.63, p < .001, adj. R^2 = .10], but could not significantly predict risk-taking behaviour scores [F (1, 416) = 1.34, p = .247, adj. R^2 = .00]. Details of the regression coefficients are presented in Table 3.7. These results suggest that individuals who are less likely to respond to salient sensory stimuli (as indicated by high Low Registration scores) are less likely to assess risky situations before acting.

3.3.5.2. The relationship between Sensation Seeking and risk-taking

One outlier was identified with a risk-taking behaviour score of zero (standardized residual = -3.11), and was removed from the analysis. Linear regression analyses revealed that Sensation Seeking scores could significantly predict risk-taking behaviour scores [F (1, 415) = 96.48, p < .001, adj. R^2 = .19], as well as risk assessment scores [F (1, 416) = 16.58, p < .001, adj. R^2 = .04]. Details of regression coefficient are presented in Table 3.7. These results suggest that individuals with high Sensation Seeking scores are more likely to engage in risk-taking behaviours, and also less likely to assess risky situations before acting.

3.3.5.3. The relationship between Sensory Sensitivity and risk-taking

Linear regression analyses revealed that Sensory Sensitivity scores could significantly predict risk-taking behaviour scores [F (1, 416) = 14.65, p < .001, adj. R^2 = .03], but was not a significant predictor of risk assessment scores [F (1, 416) = 2.69, p = .102, adj. R^2 = .00]. Details of regression coefficients are presented in Table 3.7. These results suggest that individuals with high Sensory Sensitivity scores are less likely to engage in risk-taking behaviours.

Table 3.7
Summary of the regression coefficients for RT-18 variables predicted by Low Registration score

RT-18 Variable	AASP Variable	B	SE B	β	95% CI for B
Risk-taking behaviour	Low Registration	.02	.02	.06	-.01 to .05
	Sensation Seeking	.17	.02	.44***	.13 to .20
	Sensory Sensitivity	-.07	.02	-.18***	-.10 to -.03
Risk assessment	Low Registration	.08	.01	.31***	.06 to .11
	Sensation Seeking	.06	.02	.20***	.03 to .09
	Sensory Sensitivity	.02	.01	.08	-.00 to .05

Note. *** p < .001

3.3.6. Assessing Internal Reliability of Questionnaires

Cronbach's alpha values for each scale are presented in Table 3.2. Results suggest that most of the questionnaire scales administered in this study have good internal reliability for

each age group, with a few scales (such as the Risk Assessment scale from the RT-18, and sensation seeking scores for young adults) being slightly below the desired cut-off value of 0.70.

3.4. Discussion

Using a cross-sectional design, this study aimed to examine developmental changes in sensory processing style during the transition from early-adolescence to adulthood in typically-developing individuals. No age-related changes in Sensory Sensitivity, Sensation Seeking, or Sensation Avoiding were found; however, adults had significantly lower Low Registration scores compared to early- and late-adolescents and young adults, suggesting that adults are less likely to miss salient sensory stimuli than the younger age groups. Furthermore, this study examined the relationships between sensory processing styles and negative affect, with results showing that more extreme sensory processing styles are associated with greater levels of negative affect in typically developing adolescents and adults. Interestingly, greater Low Registration scores predicted significantly higher levels of depression in early- and late-adolescents, and predicted higher anxiety and stress across all the age groups tested in this study. However, there were no significant differences in regression slopes or intercepts for these analyses, suggesting that Low Registration might be a better predictor of depression in adolescence than in adulthood, but that the relationship between Low Registration and anxiety is consistent with age.

This study is also the first to show that a propensity to engage in risk-taking behaviours and assess risky situations before acting is associated with sensory processing style. Specifically, increased risk-taking behaviour was positively associated with Sensation Seeking, but negatively associated with Sensory Sensitivity. Similarly, increased risk assessment was negatively associated with Low Registration and Sensory Sensitivity. No significant interactions between age, sensory processing style, and risk-taking were found, suggesting that the relationship between sensory processing style and risk-taking does not change in strength during the transition from early-adolescence to adulthood. The following sections will discuss these results in more detail, explore how the findings presented here relate to previous research, and make suggestions for future research.

3.4.1. Sensory processing style during the transition from early adolescence to adulthood

Given that the transition between adolescence and adulthood is a critical developmental period, associated with significant physical changes, and in terms of emotional regulation and cognition, tied to significant prolonged maturational changes in the brain (Fuhrmann, Knoll, & Blakemore, 2015; Steinberg, 2008), it is possible that this developmental period is associated with changes in sensory processing. Consequently, this study first aimed to assess whether there were developmental changes in sensory processing style during the transition from early-

adolescence to adulthood. Using the Adolescent and Adult Sensory Profile questionnaire (Brown & Dunn, 2002), this study assessed changes in Low Registration, Sensory Sensitivity, Sensation Avoiding and Sensation Seeking with age. Using these questionnaire scales, it was found that adults had significantly lower Low Registration scores compared to the three younger age groups, suggesting that adults are less likely to miss salient sensory stimuli compared to adolescents or young adults. It is not yet clear what mechanisms might explain the age-related difference in Low Registration scores, but one possible explanation may lie in the timing of brain maturation processes. It is now well established that the human brain undergoes a "rewiring" process that is not complete until approximately 25 years of age (Arain et al., 2013). Therefore, adolescents (11-19 years) and young adults (20-24 years) may be more likely than adults (25+ years) to miss salient sensory stimuli because their immature neural networks may not have the optimal performance for perceiving and responding to sensory stimuli; however, more research is needed to establish the relationship between maturity of neural networks and sensory processing abilities.

In contrast to age differences in Low Registration, no age-related changes in measures of Sensory Sensitivity, Sensation Seeking or Sensation Avoiding were found during the transition from early-adolescence to adulthood. At present, there is little in the literature to compare these findings to, but they do appear to be mostly consistent with previous research showing no age-related changes in auditory, visual, oral and touch processing (also measured by the Sensory Profile questionnaire, as used in the study reported here) in neurotypical individuals aged 3-56 years (Kern et al., 2006).

3.4.2. Sensory processing and mental wellbeing

Having established that there were age-related differences in Low Registration scores, it was important to see if there were age-related differences in the relationships between sensory processing styles and mental wellbeing (as assessed by frequency of symptoms of depression, anxiety and stress) in the transition from adolescence to adulthood. Using this approach it was found that greater levels of anxiety, depression, and stress were reported by adolescents and adults who are more likely to be bothered by sensory stimuli (have higher Sensory Sensitivity scores), and more likely to avoid strong sensory stimuli (higher Sensation Avoiding scores). Notably, a greater tendency to miss salient sensory stimuli was also related to increased anxiety and stress in all age groups, but was only related to greater levels of depression in early- and late-adolescents. It is not quite clear why Low Registration scores were only significantly positively associated with depression in adolescence, and not in young adults and adults, but it could be related to our previous finding that Low Registration scores were significantly reduced in adulthood compared to younger age groups. If early- and late-adolescents are more likely to miss salient sensory stimuli (as indicated by greater Low Registration scores), then this could

potentially lead to feelings of being under-stimulated or unfulfilled by their environment, which could develop into depressive symptoms. If, as discussed above, adults are less likely to miss salient sensory stimuli than adolescents, perhaps they are more likely to find their sensory environments sufficiently stimulating and therefore feel more fulfilled. The reverse argument may also be true; adults reported significantly lower levels of depression compared to late-adolescents, so it may be that adults are less likely to experience symptoms of depression, and are therefore more responsive to stimuli in their environment. This would be consistent with research demonstrating that individuals with major depressive disorders have a reduced ability to attend and concentrate (Hasler, Drevets, Manji, & Charney, 2004), and difficulties in differentiating salient stimuli from distractors (Kemp et al., 2010), although more research is needed to establish directional effects of this relationship.

Given that this study is the first to examine the relationship between sensory processing and negative affect in typically developing adolescents, there is little literature to compare these findings to. However, the results presented here are generally in agreement with studies of pre-adolescent children and adults, demonstrating that extreme sensory processing styles are associated with greater levels of negative affect (Batya Engel-Yeger & Dunn, 2011a; Goldsmith et al., 2006; Moya Kinnealey & Fuiek, 1999; Zickgraf & Elkins, 2018). The possible mechanisms underlying the relationship between sensory responsivity and poorer mental wellbeing are still under investigation. Some have suggested that the relationship between sensory over-responsivity and depression might stem from exposure to repeated aversive experiences, and the tendency to become unpleasantly over-aroused by the environment, leading to social withdrawal (Aron & Aron, 1997; Liss, Mailloux, & Erchull, 2008). Green and Ben-Sasson (2010) went even further and proposed three causal mechanisms that may explain the association between sensory over-responsivity and anxiety. Although this paper is particularly interested in the relationship between anxiety and sensory-over-responsivity in individuals with ASCs, their proposals may still help to understand the relationship in typically developing individuals. Their first proposal is that anxiety causes sensory over-responsivity by increasing arousal and vigilance to sensory stimuli, making individuals more likely to notice and react to aversive sensory stimuli. This is supported by studies showing anxious individuals have higher rates of environmental scanning, narrowing of attention once a threat-related stimulus is identified, and difficulty disengaging from that stimulus (Craske et al., 2011; Mobini & Grant, 2007). The second proposal is that sensory responsivity causes anxiety through fear and conditioning, by which unpleasant sensory stimuli (*e.g.* an aversive noise) are associated with objects or situations (*e.g.* balloons) and elicit a conditioned response, such as fear or anxiety. The conditioned response can be elicited by the object even without the presence of the aversive stimuli, and can also shift from being triggered by the object to a location or context in which the aversive stimulus occurred (*e.g.* a birthday party). The final proposal is that sensory

responsivity and anxiety are not directly causally related, but are associated though a third variable, such as amygdala abnormalities. For example, Zald (2003) reviewed studies showing that the amygdala receives sensory input from auditory and visual sensory areas of the cortex, and that the perceived unpleasantness of a stimulus is correlated with the amount of amygdala activation; consequently, Zald proposes that sensory over-responsivity may be due to an over-active amygdala. In practice, these proposals probably over-simplify the relationship between sensory responsivity and negative affect, but they provide a theoretical basis that can be scientifically tested and help to improve our understanding of the association.

3.4.3. Sensory processing and risk-taking

The results of this study are the first to demonstrate relationships between sensory processing styles and risk-taking in typically developing adolescents and adults. Not surprisingly, sensation seeking and risk-taking behaviours were positively related, which is consistent with previous literature demonstrating increased risk-taking in adolescents and adults with greater sensation seeking levels (Greene et al., 2000; Malmberg et al., 2010; Rollison & Scherman, 2002; Scholes-Balog, Francke, & Hemphill, 2016; Zhang, Zhang, & Shang, 2016). This finding also supports Dunn's theory of sensory processing which suggests that individuals who score highly on sensation seeking will experience pleasure from exciting sensory environments and behaviours, will often show risk-taking behaviours that are expressed by a lack of physical boundaries, and may be seen by others as irresponsible, impatient, and lacking in respect (Brown, Tollefson, Dunn, Cromwell, & Filion, 2001; Dunn, 1997). Dunn's model of sensory processing suggests that high levels sensation seeking are associated with high neurological thresholds, so it was also interesting to see a negative relationship between sensory sensitivity (associated with low neurological thresholds) and risk-taking behaviour, whereby individuals who are more likely to be bothered by sensory stimuli are less likely to engage in risk-taking behaviours. Collectively, these results demonstrate a clear association between preference for experiencing sensory stimuli and likelihood of engaging in risk-taking behaviours.

This study is also the first to show an association between sensory processing style and tendency to assess risky situations before acting. More specifically, reduced risk assessment was associated with increased sensation seeking across all age groups. Although more research is needed to establish the direction or possible causal nature of this relationship, one possibility is that sensation seeking individuals may be more influenced by their drive for strong sensory inputs, thus creating a rewards-based bias. Similar proposals have been confirmed when investigating risky decision making in individuals with bipolar disorder. In an ERP study, participants with bipolar disorder and matched controls played a Roulette task in which they won and lost money (Mason, Trujillo-Barreto, Bentall, & El-Deredy, 2016). The results showed

that the bipolar group displayed increased N1 amplitudes, reflecting an early attentional bias to reward. The authors suggest that this attentional bias may drive risk-taking by priming approach behaviour and elevating reward salience in the fronto-striatal pathway. Reduced risk assessment in the present study was also associated with a greater tendency to miss salient sensory stimuli (Low Registration). An increased tendency to miss salient sensory stimuli may mean that individuals are less able to assess risky situations because they are not detecting all the relevant stimuli needed to make an informed decision. Interestingly, findings reported here show that adults are significantly more likely to notice salient sensory stimuli, and also more likely to assess risky situations than adolescents and young adults. However, the relationship between sensory responsivity and risk assessment was not moderated by age, suggesting that the strength of the relationship between sensory responsivity and risk assessment is consistent across this transitional period. Future research should seek to further elucidate the causal mechanisms associated with the relationship between sensory processing and risk-taking behaviours. The following section provides more suggestions for future research, whilst also acknowledging the limitations of the present study.

3.4.4. Study Limitations and Future Directions

The findings of this study should also be considered in light of its limitations. Firstly, grouping participants into categorical age groups rather than using age as a continuous variable can be problematic in developmental research, particularly when it is acknowledged that there are considerable individual differences in the developmental trajectories of adolescents (Steinberg & Morris, 2001). Consequently, it is possible that potentially interesting and important developmental differences may be missed when using categorical age groups. However, categorical age groups also allow for direct examination of discrete changes occurring within and between different developmental stages. Given that the aim of this study was to examine developmental changes in the relationships between sensory processing, negative affect, and risk-taking from early adolescence to young adulthood, using categorical age groups was the preferred approach for this study.

Secondly, there was an uneven split of males and females, with approximately 72% of the total sample being female. It is generally acknowledged that risk-taking behaviours are more frequently observed in male adolescents than in female adolescents, although gender differences can vary according to age, and type of risky activity (Byrnes, Miller, & Schafer, 1999). Gender differences in mental health issues are also observed during adolescence, with female adolescents reporting greater levels of psychological distress, anxiety and depression than males (Van Droogenbroeck et al., 2018). Unfortunately, due to the unequal split of male and female participants in this study, the present study was unable to examine gender differences in the relationships between sensory processing, negative affect, and risk-taking behaviours. Future

studies should seek to establish whether gender differences in sensory processing styles exist during adolescence, and whether these differences may help to explain gender differences in risk-taking and mental health conditions.

Following on from this, one possible direction for future research would be development of interventions targeted at adolescents that aim to reduce risk-taking behaviours. This study found that individuals with high sensation seeking scores were more likely to engage in risk-taking behaviours, and individuals with high sensory sensitivity scores were less likely to engage in risk-taking behaviours. Whilst it is important to remember that not-all risk-taking behaviours are negative experiences (such as kayaking, climbing, and even performing in public), it is widely acknowledged that the biggest causes of adolescent mortality come from self-inflicted causes (e.g. automobile accidents, violence, drug and alcohol abuse; Blum & Nelson-Mmari, 2004; Williams et al., 2002). Intervention programs that are based on educating adolescents about the potential negative consequences of risk-taking activities appear to have been mostly unsuccessful in reducing risk-taking behaviours (Steinberg, 2008). Studies have shown that adolescents are as aware as adults of the potential outcomes of risk-taking behaviours (Beyth-Marom, Austin, Fischhoff, Palmgren, & Jacobs-Quadrel, 1993), with adolescents believing they are more vulnerable to these negative consequences than adults (Millstein & Halpern-Felsher, 2003), but continuing to engage in risky-activities anyway (particularly when in the presence of peers; Gardner & Steinberg, 2005). An alternative intervention that works on reducing neurological thresholds in adolescents prone-to risk-taking behaviours to a more typical level might help to reduce their need for strong sensory stimulation, and in turn reduce their desire to engage in risk-taking activities. In other words, it would reduce the desire for strong sensory input, related to high neurological thresholds in sensation individuals, to a reduced threshold that would make individuals more sensitive to sensory stimulation. Sensory Integration Therapy (based on Jean Ayres Sensory Integration Theory; Ayres, 1972) aims to help individuals with sensory processing issues by exposing them to sensory stimulation in a structured, repetitive way with the hope that over time, neural responses will adapt and process sensory information more efficiently. Consequently, future research could explore sensory integration therapy as an alternative intervention program for adolescents by trying to lower neurological thresholds in teens that might be more prone to risk-taking behaviours.

3.4.5. Conclusion

In conclusion, the transition from early-adolescence to adulthood is a critical period of development, associated with increases in mental health issues, and risk-taking behaviours. This study demonstrated that extreme sensory processing styles are related to greater levels of negative affect in typically developing adolescents and adults, in line with findings from non-

clinical child and adult studies (Ben-Avi et al., 2012; Engel-Yeger & Dunn, 2011b, 2011a; Lane et al., 2012), and from studies of pre-adolescent children with neurodevelopmental conditions (Pfeiffer et al., 2005). Furthermore, this study established a strong link between sensory responsivity and risk-taking behaviours and risk assessment tendencies across all ages, consistent with theories of sensory processing. Future research should seek to explore possible gender differences in sensory processing during adolescence as a possible cause of gender differences in risk-taking and mental health noted during this period, as well as developing sensory-based interventions aimed at reducing risk-taking in adolescence.

Chapter 4: Investigating cortical plasticity in the visual cortex of typically developing adolescents and adults

Abstract

The majority of research investigating long-term potentiation (LTP) has been carried out on animal subjects or brain slice preparations, due to the need to insert an electrode into desired afferent fibres in order to administer tetanisation and induce LTP. However, an alternative non-invasive method of inducing LTP has been developed (Çavuş et al., 2012), whereby presentation of high-frequency visual stimulation has been shown to potentiate visual evoked potentials (VEPs), with many of the hallmarks that are characteristic of LTP (input specific, long-lasting, and frequency dependent). Based on non-human animal research that found greater cortical plasticity in adolescents compared to adults (Schramm et al., 2002), the present study was designed to use this paradigm to assess potential developmental differences in visual cortical plasticity in human adolescents and adults, in addition to exploring whether differences in sensory responsivity may be related to differences in learning dependent changes to sensory processes, studied here using visual HFS to induce LTP. Results found robust changes in VEPs in both adolescents and adults after experiencing visual HFS. Notably, early-adolescents showed greater attenuation of P2 amplitude following visual HFS, compared to late-adolescents and adults, which may reflect greater LTD in adolescence. No significant relationships were found between sensory responsivity and the degree of plasticity observed as a consequence of LTP induction. The results are discussed in relation to previous research utilising sensory-induced tetanization paradigms.

4.1. Introduction

NMDA receptors play a significant role in mediating many of the neural changes associated with the plasticity during development (Haberny et al., 2002). Developmental changes of NMDA receptors have been shown to be involved in activity-dependent changes in the developing brain, such as imprinting in chicks (McCabe & Horn, 1988), olfactory memory formation in rat pups (Lincoln, Coopersmith, Harris, Cotman, & Leon, 1988), the formation of ocular dominance columns in the visual cortex of the kitten (Rauschecker, Egert, & Kossel, 1990), and eye-specific stripes in the tadpole (Cline, Debski, & Constantine-Paton, 1987). The molecular composition of NMDA receptors is also known to change during development (Monyer, Burnashev, Laurie, Sakmann, & Seeburg, 1994; Sheng, Cummings, Roldan, Jan, & Jan, 1994). In the visual cortex of rats, the ratio between NR2B and NR2A subunits changes across early post-natal development, and it is thought that the NR2 subunit composition is involved in the regulation of visual cortical synaptic plasticity (Sheng et al., 1994; Yoshimura et al., 2003; further information regarding NMDA sub-unit composition can be found in Chapter 1.7). Given that there are clear developmental changes in NMDA sub-unit composition, and NMDA receptors play a key role in LTP processes, the next step is to investigate whether there are developmental changes in LTP.

Critically, several animal studies have shown that the ability of synapses to undergo LTP depends on the developmental stage of the animal (Crair & Malenka, 1995; Izumi & Zorumski, 1995). The binding of cortical glutamate to NMDA receptors has been shown to peak early in adolescence, and decline significantly after, with a loss of up to a third of NMDA receptors as a result of synaptic pruning during adolescence in the nucleus accumbens (Insel et al., 1990). Schramm and colleagues (2002) showed that NMDA receptor-dependent LTP is observed more frequently in the nucleus accumbens of adolescent mice (3 weeks old) compared to adult mice (6-20 weeks old). The authors suggest that this developmental decrease is in part due to reduced calcium influx through the NMDA receptor in adult mice. Age-dependent differences in degree of potentiation has its benefits; for a developing organism, extensive experience-dependent refinement is essential for the normal maturation of its neural circuits, whereas for adult organisms, the same level of plasticity may be detrimental unless it is in response to severe alterations of sensory inputs, such as those caused by peripheral lesions (Karmarkar & Dan, 2006).

To date, no research has investigated developmental changes in LTP-like processes in human adolescence. As discussed in Chapter 1.7.3, sensory-induced plasticity is increasingly being used to non-invasively examine LTP-like changes in humans. Several studies have demonstrated that high-frequency visual stimulation is sufficient for inducing LTP-like changes in the visual cortex, as measured by a potentiated N1b relative to a pre-stimulation baseline

(Çavuş et al., 2012; Clapp et al., 2012; Spriggs, Cadwallader, Hamm, Tippett, & Kirk, 2017; Teyler et al., 2005). However, this paradigm has not yet been used to investigate developmental differences in LTP-like changes in the visual cortex of adolescents. Consequently, the first aim of this study is to investigate cortical plasticity in the visual cortex of human adolescents and adults, using high-frequency visual stimulation to induce potentiation and recording changes in VEPs using EEG. Given that animal studies suggest LTP is enhanced in adolescence, and the visual sensory LTP paradigms tend to show potentiation of the N1b following visual HFS, it is predicted that adolescents will show greater potentiation of the N1b compared to adults following visual tetanization. Furthermore, Çavuş et al. also demonstrated that greater HFS-driven VSSR power was also associated with greater N1b potentiation for neurotypical participants. Therefore, this study will also examine developmental changes in the relationship between HFS-driven VSSR power and degree of VEP change following visual tetanization.

The second novel aim of this study is to explore the possible relationship between self-rated sensory responsivity and potentiation of VEPs. Experience-dependent plasticity plays a crucial role in shaping normal brain function and, whilst most evident during development, can shape information processing at any stage in an animals lifespan (Karmarkar & Dan, 2006). For example, Heynen and Bear (2001) investigated the functional consequences of LTP induction in adult rats by monitoring *in vivo* changes in field potentials evoked in the primary visual cortex (Oc1). After applying patterned (theta-burst) stimulation to the dorsal lateral geniculate nucleus, they observed that the cortical visual response to a full field flash was significantly enhanced and that responses to grating stimuli were increased across a range of spatial frequencies. Similarly, in human adults, Clapp et al. (2012) found evidence to suggest that high frequency visual stimulation, achieved by presenting visual checkerboards at a rapid rate, not only resulted in detectable LTP in the visual cortex (as measured by a potentiated N1b ERP component), but also a parallel improvement in visual detection thresholds. These studies demonstrate how past sensory experience and learning shapes future sensory experiences. There is an increasing body of research exploring how our sensory processing style can affect our thoughts, feelings, and perceptions about sensory experiences. Dunn (1999) suggests that, in part, our sensory processing style is determined by neurological thresholds. For example, people who have high levels of sensory responsivity, will have lower neurological thresholds to sensory stimuli, and will therefore respond readily when presented with such a stimulus. It could be argued that these lower neurological thresholds are due to potentiated synapses in sensory cortices, that have been tetanized by previous sensory experiences (as in Heynen & Bear (2001), and Clapp et al. (2012)).

4.1.1. Aims of the present study

In order to test the relationship between developmental stage, plasticity in the visual cortex, and sensory responsivity, a visual HFS paradigm was used (Çavuş et al., 2012). This visual cortical plasticity paradigm involves rapid visual stimulation, analogous to electrical HFS of afferents, and measuring potentiation by observing changes in visual evoked potentials relative to a pre-stimulation baseline. It is hypothesized that adolescent participants will show greater potentiation of the N1b following high-frequency stimulation, compared to adults, in accordance with results from animal studies showing greater binding of glutamate to NMDA receptors (Insel et al., 1990) and greater LTP during adolescence (Schramm et al., 2002) compared to in adulthood. Furthermore, it was predicted that participants with high levels of sensory responsivity would exhibit greater VEPs in response to baseline stimuli, as it is assumed that their previous sensory experiences have induced potentiation of synapses in sensory cortices, in accordance with Dunn's (1999) theory of sensory processing style, and evidence demonstrating tetanization from previous sensory experiences (Clapp, Hamm, Kirk, & Teyler, 2012; Heynen & Bear, 2001). Assuming that participants with higher levels of sensory responsivity show a potentiated response to baseline stimuli, it was also predicted that participants with higher levels of sensory responsivity would show less change in VEP amplitude following HFS, compared to participants with lower levels of sensory responsivity, because they are closer to ceiling effects due to prior tetanization from sensory experiences.

4.2. Method

4.2.1. Participants

In total, 58 participants completed the study. Participants were split into three age groups; early-adolescents (13-14 years), late-adolescents (18-19 years), and adults (25-26 years). One participant (male, early-adolescent) was removed from analyses because the participant's spectral plot showed no peak at the tetanizing frequency (or corresponding harmonics) suggesting they did not adequately observe the tetanizing stimulation from the visual HFS. Table 4.1 presents information about the demographics of the 57 participants included in analyses.

Table 4.1

Demographic Information

Variable	Age Group		
	Early-Adolescents	Late-Adolescents	Adults
N	18	19	20
Percentage female	50%	52.60%	50%
Mean age	14 years and 2 months	18 years and 11 months	25 years and 10 months
Percentage right-handed	100%	100%	90%

Note. All participants were free of any psychiatric or physical conditions.

4.2.2. Experimental paradigm

Participants first completed several questionnaire measures (see section 4.2.3 for more details). Following that, the EEG cap and sensors were set up (see section 2.3.1. for more details). Participants then started the Visual Cortical Plasticity paradigm (Figure 4.1). A more detailed description of this paradigm can be found in Chapter 2.4.1.

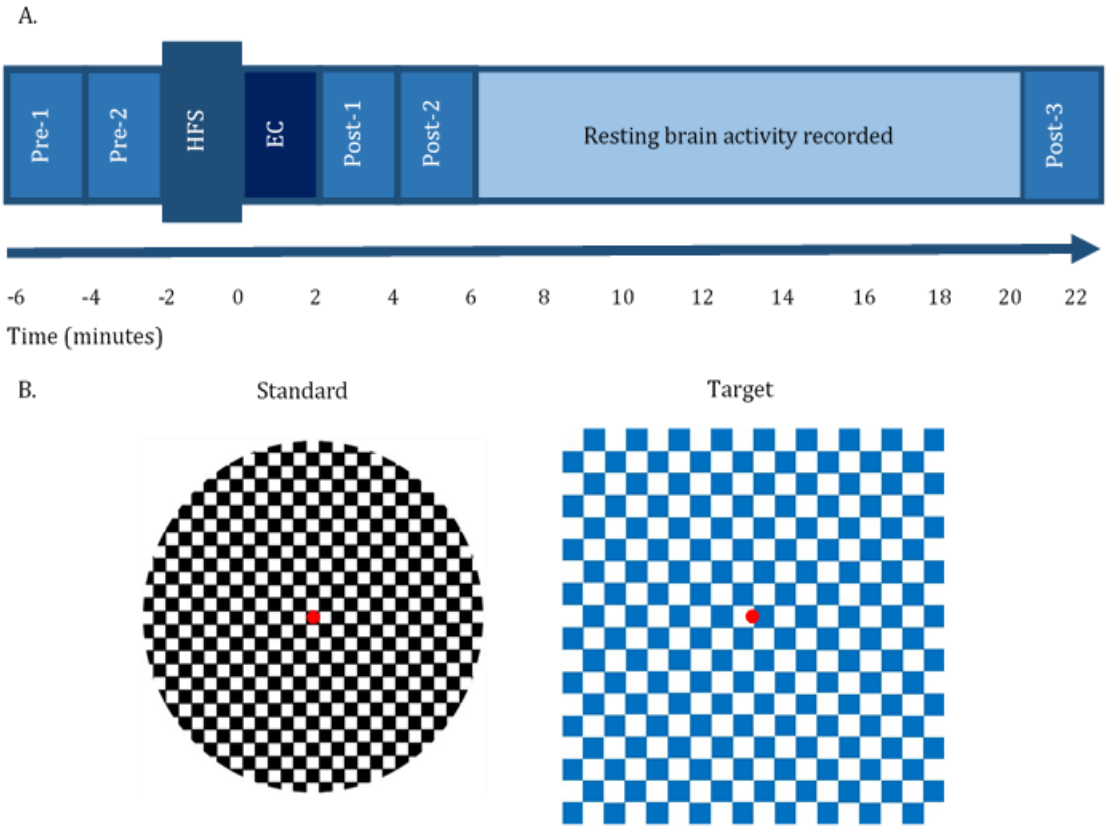


Figure 4.1. Visual Cortical Plasticity Paradigm: timeline and stimuli. During VEP assessment blocks (Pre-1, Pre-2, Post-1, Post-2, and Post-3), participants are asked to maintain focus on a red central fixation dot whilst the frequently presented standard circle (90% of trials; Figure 4.1.B Left) or infrequently presented target square (10% of trials; Figure 4.1.B Right) is shown centrally (~0.83Hz). To monitor attention and provide further focus, participants are asked to press the spacebar every time the target square appears. During the HFS block, designed to induce potentiation, participants are asked to maintain focus on the central fixation dot as the standard circle is repeatedly presented at ~8.87Hz for 2 minutes. Participants closed their eyes for 2 minutes following HFS (EC). Resting data was collected during the interval between Post-2 and Post-3.

4.2.3. EEG Processing and Analysis

4.2.3.1. EEG Processing

See Chapter 2.3.1 for more information about the EEG acquisition and processing.

4.2.3.2. Selecting Time Windows for Analysis

Grand-grand averaged ERPs were calculated by collapsing data across all groups and conditions, and time windows selected based on what best captures each ERP component in the collapsed average. The grand-grand averaged VEPS for posterior electrode sites are presented in Figure 4.3. Based on these collapsed averages, three time windows were selected based around the P1 (50-95ms), the N1 (95-150ms), and the P2 (150-210ms). This method of selecting time

windows for analysis ensures that the ERP component is captured without biasing the selection to the part of the waveform that shows the biggest difference between groups/conditions (Luck, 2014).

4.2.3.3. Selecting Electrodes for Analysis

The grand-averaged waveforms and scalp topographies (Figure 4.2) were visually examined to assess where maximal activity was observed. Both the scalp topographies and grand-averaged ERP waveforms indicate overall maximal activity at occipital sites. Therefore, similar to electrode selection methods used by Teyler et al. (2005a), the four electrodes at the location of the peak amplitude (Oz, Iz, O1, and O2) were selected and averaged together to create an occipital electrode cluster.

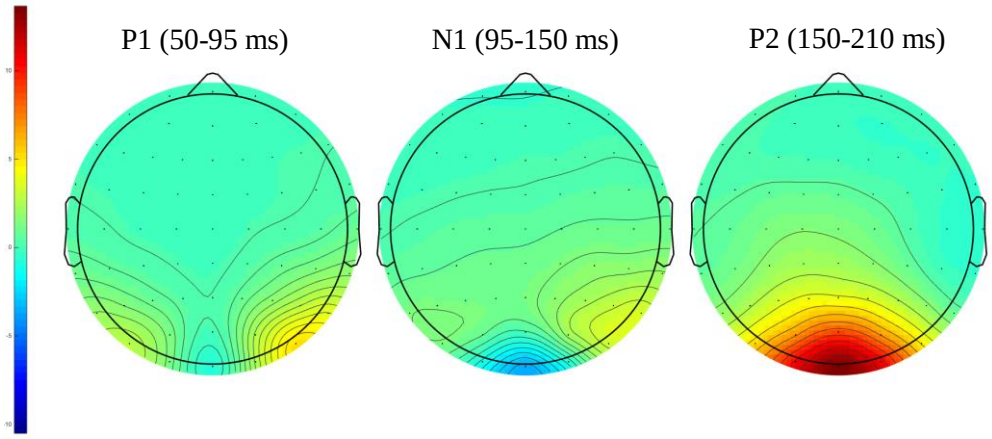


Figure 4.2. Scalp topographies depicting mean amplitude for P1, N1, and P2 time windows. Data is averaged across all participants and all VEP assessment blocks (Pre-1, Pre-2, Post-1, Post-2, and Post-3).

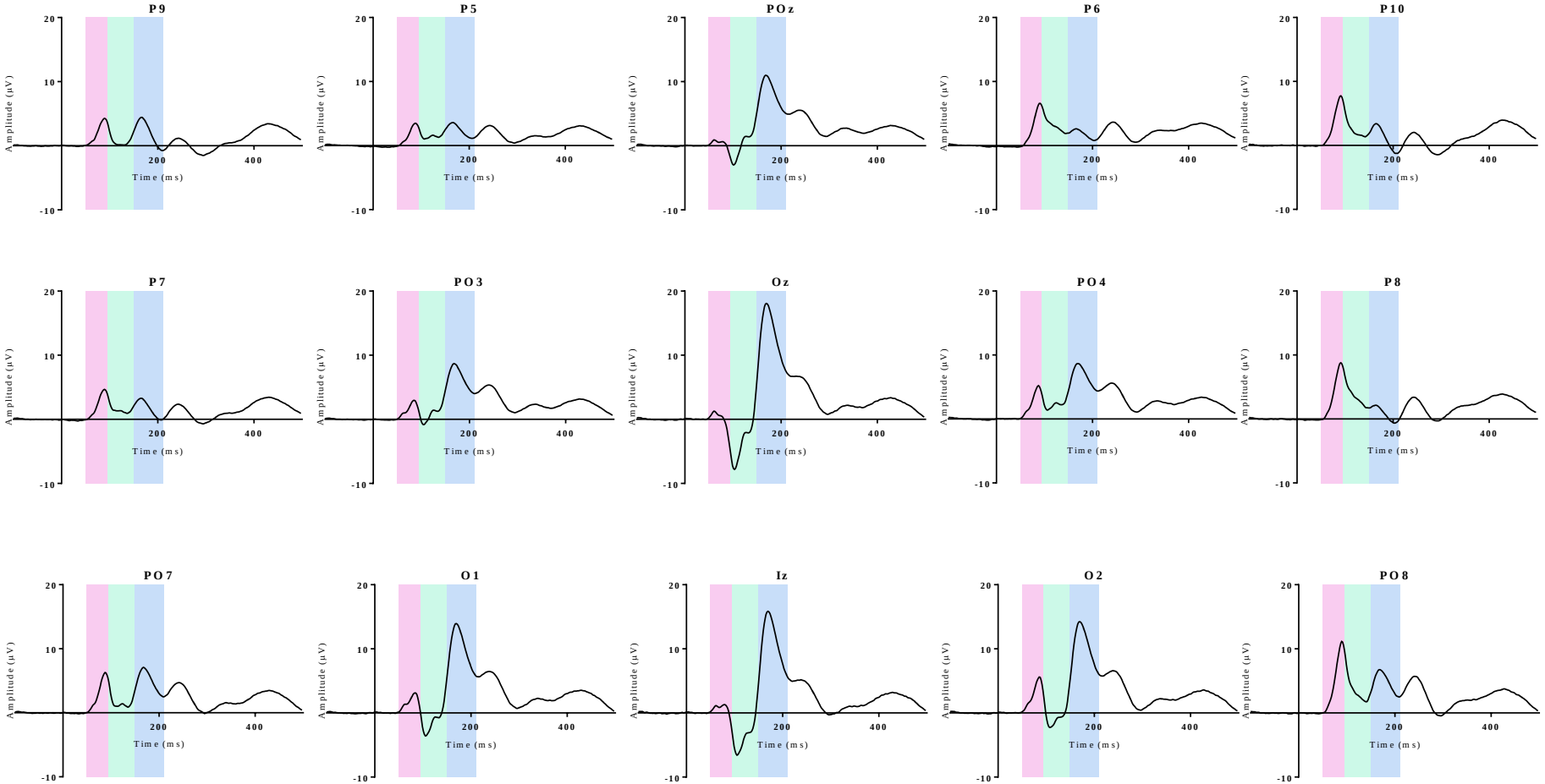


Figure 4.3. *Grand-grand averaged visual evoked potentials (VEPs) from posterior electrodes, used to select time windows used in statistical analyses of VEP components. The pink bar indicates the P1 time window (50-95ms). The green bar indicates the N1 time window (95-150ms). The blue bar indicates the P2 time window (150-210ms).*

4.2.4. Questionnaires

4.2.4.1 Adolescent Adult Sensory Profile (AASP)

See Chapter 2.3.2.3 for more information about this questionnaire.

4.2.4.2 Glasgow Sensory Questionnaire (GSQ)

See Chapter 2.3.2.4 for more information about this questionnaire.

4.2.4.3 Depression Anxiety and Stress Scale (short-form version; DASS-21)

See Chapter 2.3.2.5 for more information about this questionnaire.

4.2.5. Statistical Analyses

Detailed descriptions of planned analyses conducted in this chapter, and justifications for why these analyses were conducted, are provided in Chapter 2.4.2.

4.3. Results

Analyses directly relating to hypotheses outlined in the introduction are clearly indicated by their sub-heading. All other analyses, although not directly related to the hypotheses outlined in the introduction, still assess important group differences that may affect interpretation of other analyses. Summary of the key findings are presented at the end of this results section in Tables 4.12 and 4.13.

4.3.1. Visual Evoked Potential Analyses

4.3.1.1. Assessing differences between baseline VEP assessments

A 3-way mixed ANOVA was conducted to determine if there are any age-group differences in mean amplitude between the two pre-HFS VEP assessment (Pre-1 and Pre-2) at the occipital electrode cluster for each ERP component (P1, N1, and P2). The results revealed that there was no significant 3-way interaction between age group, VEP assessment and ERP component (F (3.94, 106.37) = 1.10, p = .360, η_p^2 = .039). There was also no significant 2-way interaction between VEP assessment and age group (F (2, 54) = .73, p = .485, η_p^2 = .026). However, there was a significant 2-way interaction between VEP assessment and ERP component (F (3.15, 85.05) = 6.05, p = .001, η_p^2 = .183). Benjamini-Hochberg (BH) corrected pairwise comparisons revealed that there were no significant differences in mean amplitude between the two pre-HFS assessments for the P1 component (p = .286) or for the N1 component (p = .381), but that mean P2 amplitude was significantly greater in pre-HFS 2 compared to pre-HFS 1 (p = .021; marginal means are presented in Table 4.2). Consequently, it would be

inappropriate to average both pre-HFS VEP assessments together; therefore, subsequent analyses will only compare post-HFS VEP assessments to mean amplitudes measured during pre-HFS 2 (which will be known as 'baseline' from hereon).

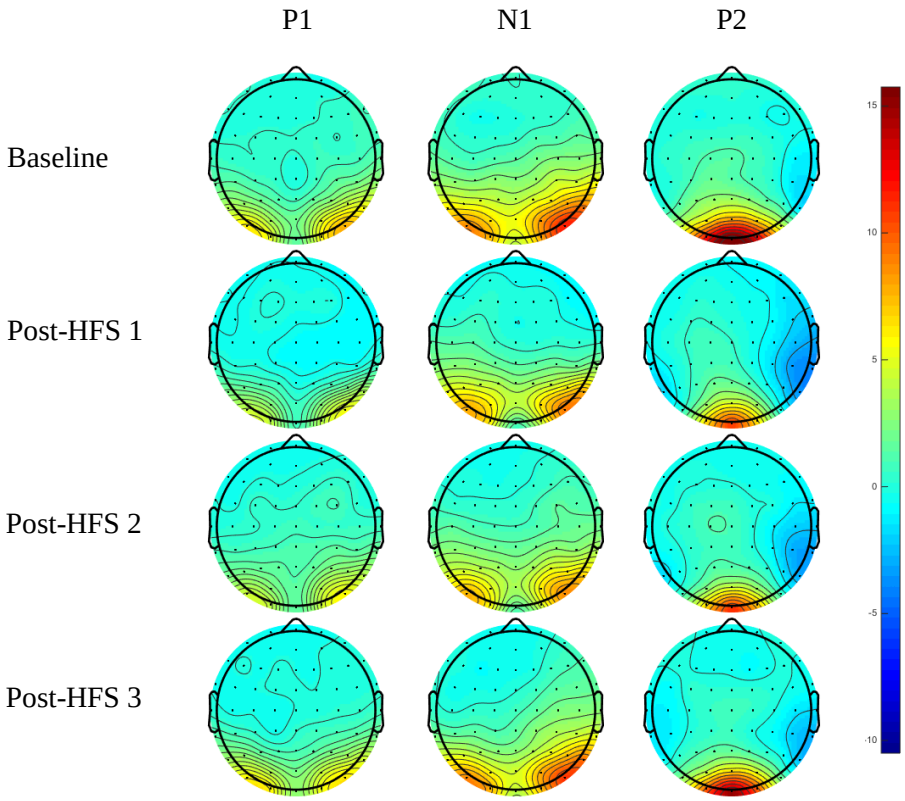
Table 4.2
Marginal means and standard errors for mean ERP amplitudes measured during pre-HFS VEP assessments

	Pre-HFS VEP Assessment			
	Pre-HFS 1		Pre-HFS 2	
ERP Component	*M*	*SE*	*M*	*SE*
P1	.93	.53	.65	.57
N1	-.77	1.06	-1.03	.97
P2	12.48	1.04	13.36	1.01

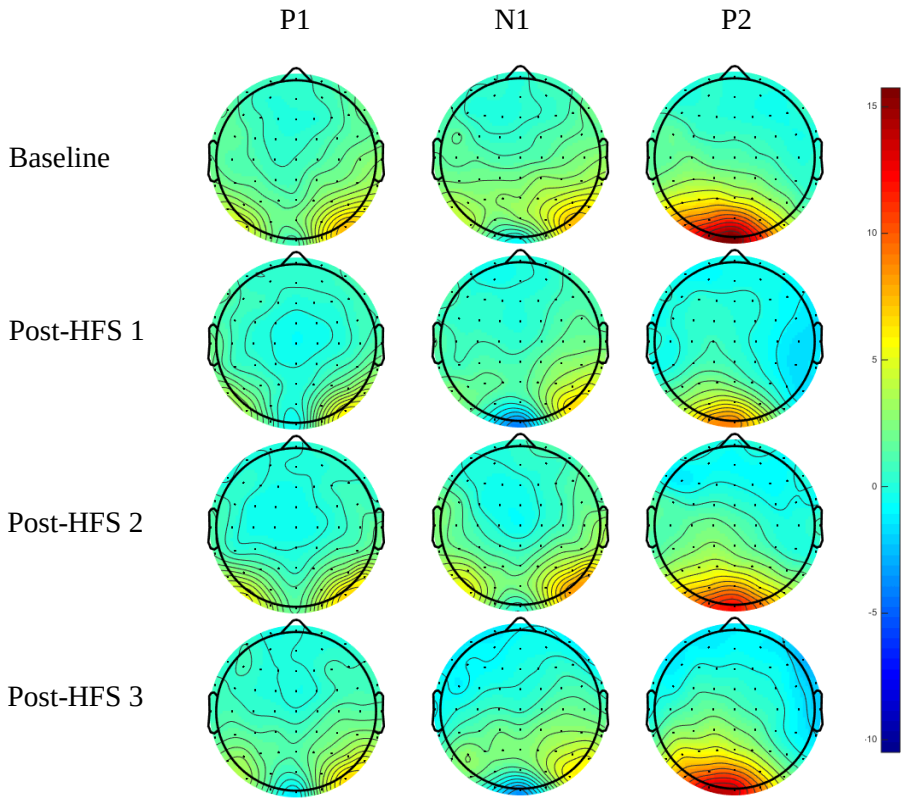
4.3.1.2. Grand-averaged ERPs and scalp topographies

Grand-averaged ERPs for each VEP assessment block (baseline, post-1, post-2, and post-3) and each age group (early-adolescent, late-adolescent, and adult) are presented in Figures 4.5 to 4.7. Grand-averaged scalp topographies for mean amplitude across the ERP components (P1, N1, and P2) for each age group are also presented in Figure 4.4.

Early-Adolescents (13-14 years)



Late-Adolescents (18-19 years)



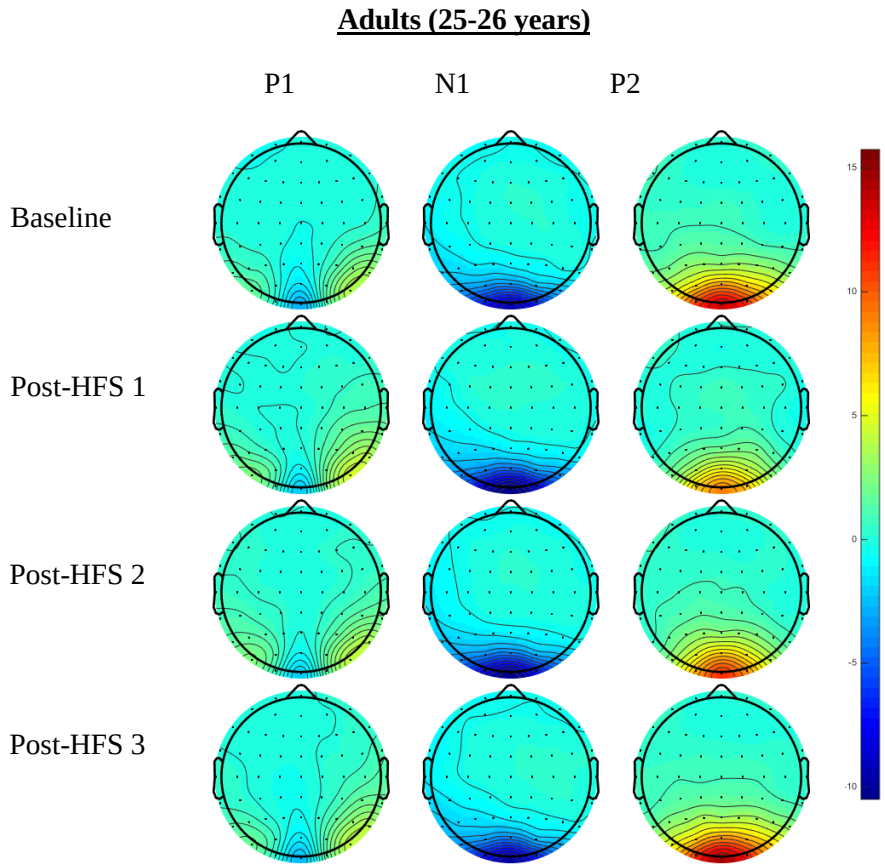


Figure 4.4. Scalp topographies depicting mean amplitude for P1, N1, and P2 time windows for grand-averaged age group data in all VEP assessment blocks (baseline, Post-HFS1, Post-HFS2, and Post-HFS3). Colour scale is standardized across all age groups.

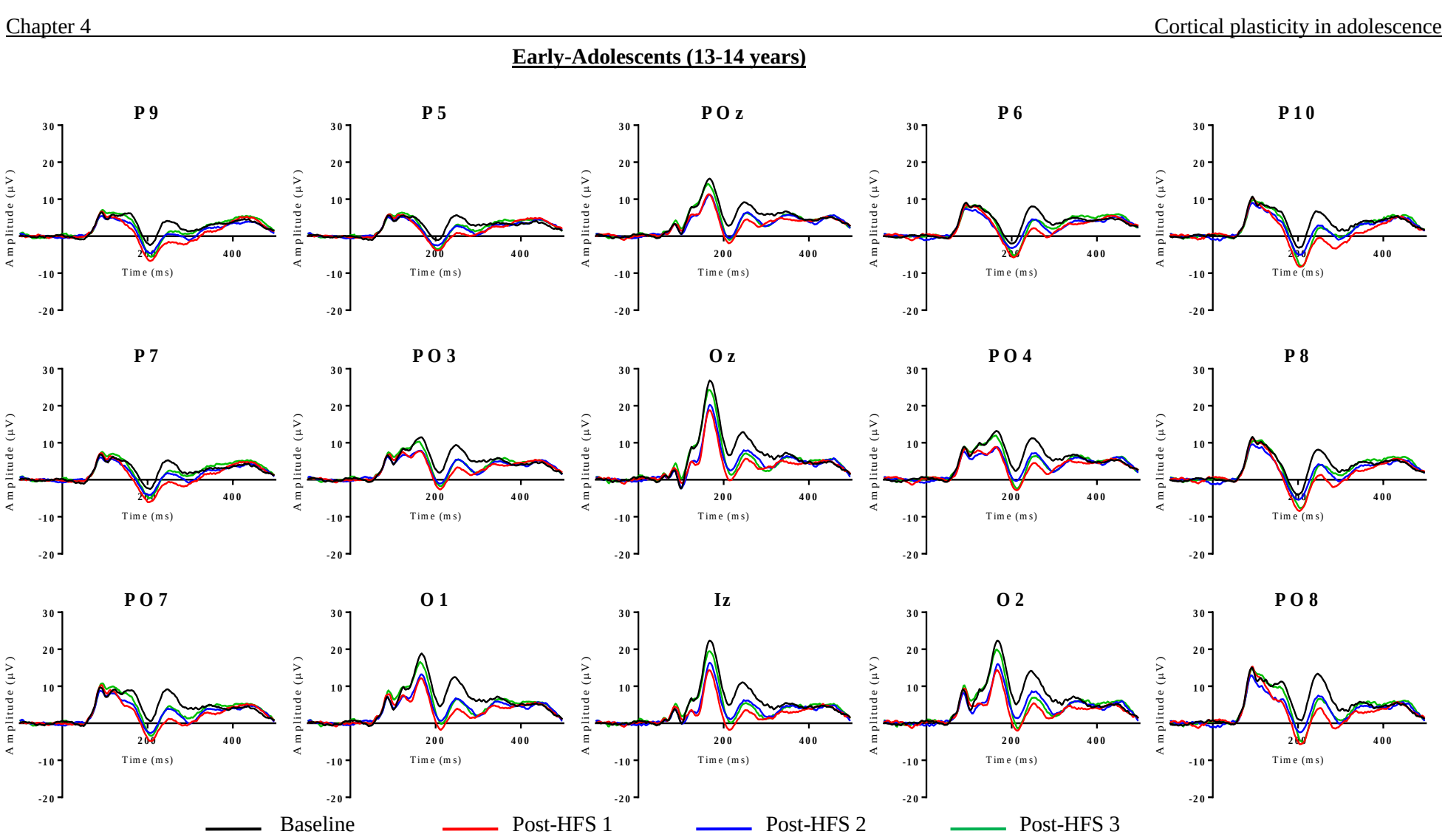


Figure 4.5. Grand average visual evoked potentials (VEP) elicited by the standard circle for early-adolescents (n = 18) across posterior electrode sites and VEP assessment blocks: Baseline (2-4 minutes before HFS; black line), Post-HFS 1 (2-4 minutes post-HFS; red line), Post-HFS 2 (4-6 minutes post-HFS, blue line), and Post-HFS 3 (20-22 minutes post HFS; green line).

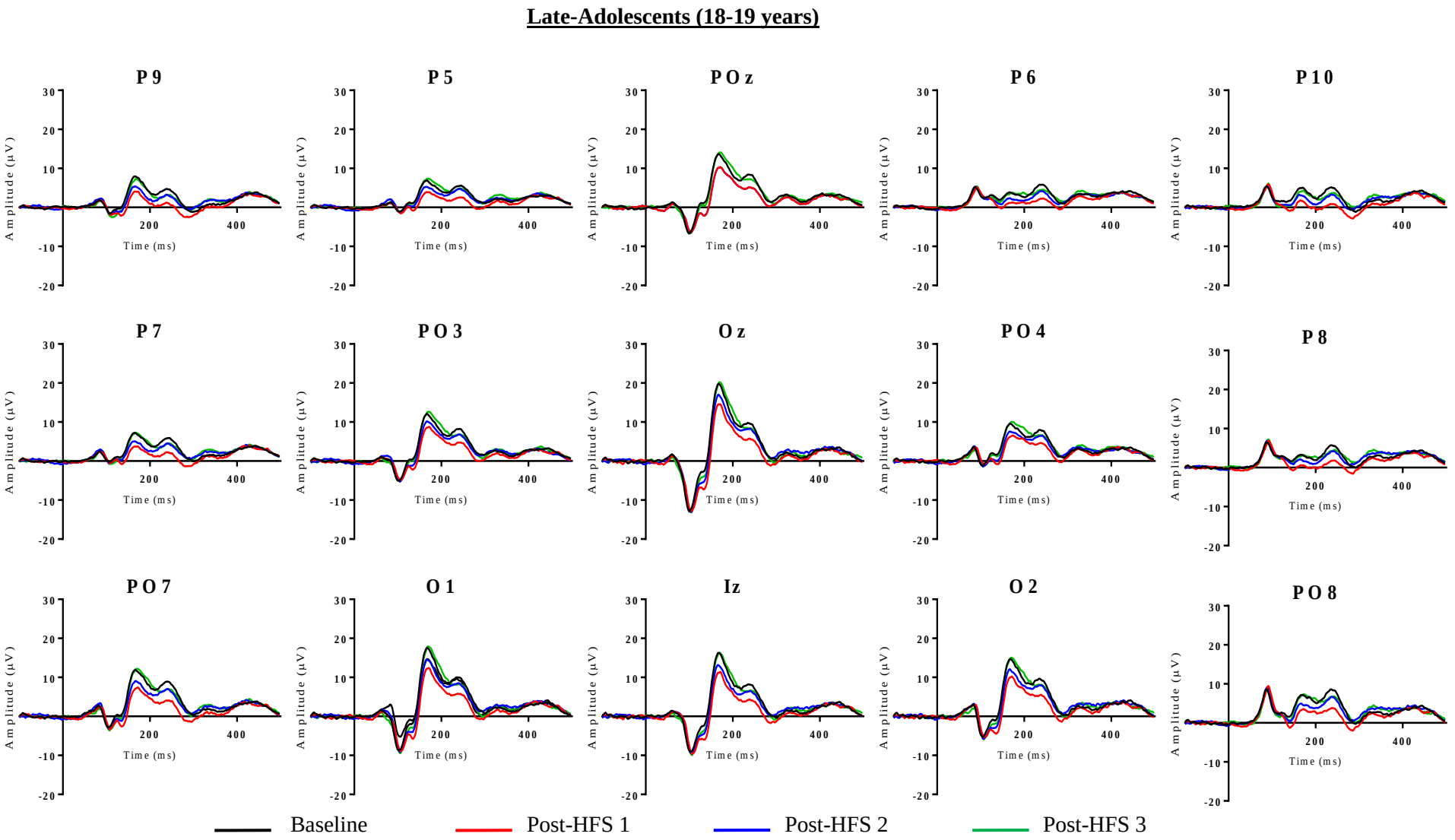


Figure 4.6. Grand average visual evoked potentials (VEP) elicited by the standard circle for late-adolescents (n = 19) across posterior electrode sites and VEP assessment blocks: Baseline (2-4 minutes before HFS; black line), Post-HFS 1 (2-4 minutes post-HFS; red line), Post-HFS 2 (4-6 minutes post-HFS, blue line), and Post-HFS 3 (20-22 minutes post HFS; green line).

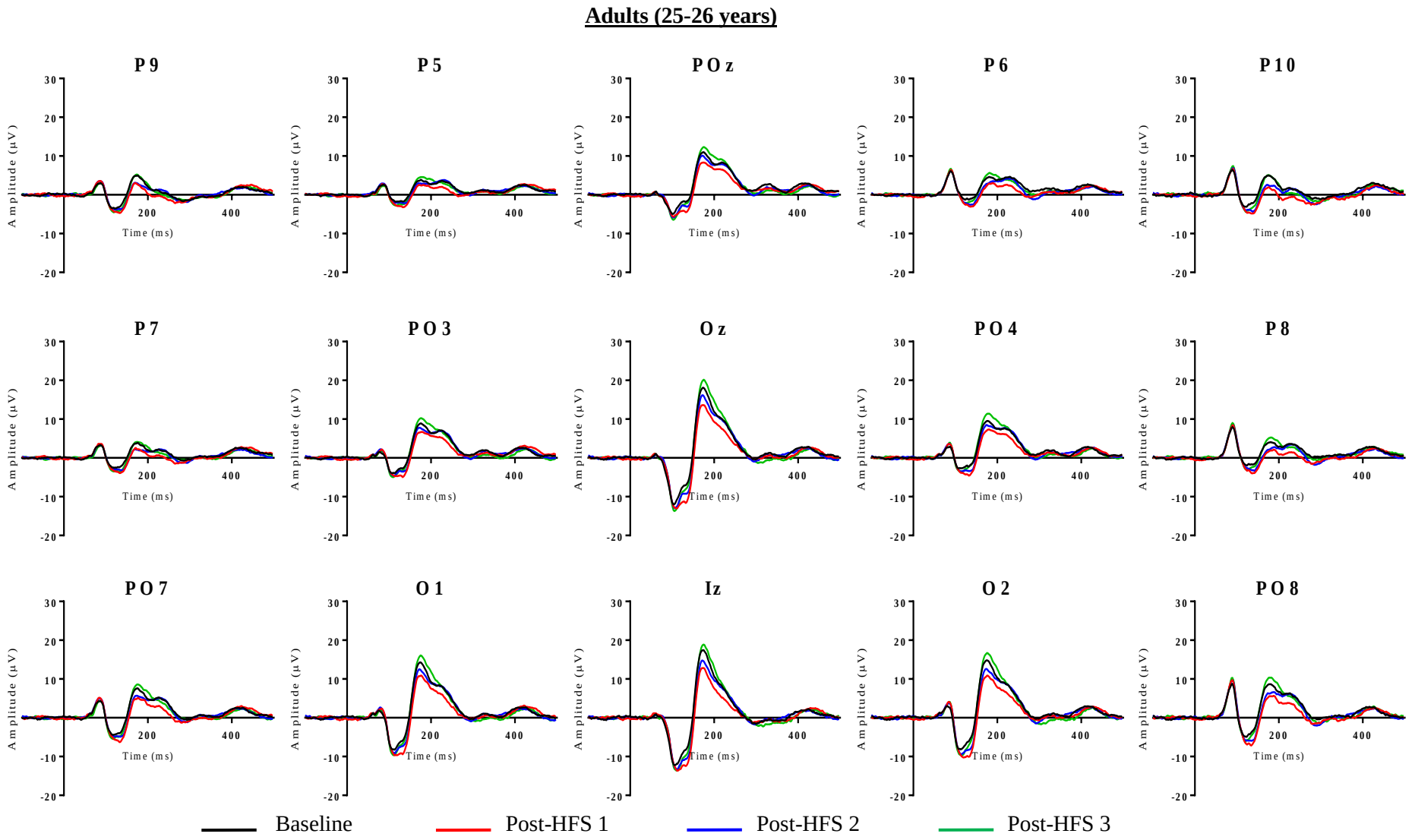


Figure 4.7. Grand average visual evoked potentials (VEP) elicited by the standard circle for adults (n = 20) across posterior electrode sites and VEP assessment blocks: Baseline (2-4 minutes before HFS; black line), Post-HFS 1 (2-4 minutes post-HFS; red line), Post-HFS 2 (4-6 minutes post-HFS, blue line), and Post-HFS 3 (20-22 minutes post HFS; green line).

4.3.1.3. Assessing the effect of visual-HFS on VEP components in adolescents and adults

A three-way ANOVA was conducted to determine the effect of age group (early-adolescent, late-adolescent, adult), VEP assessment (baseline, Post-1, Post-2, Post-3), and ERP component (P1, N1, and P2) on mean amplitudes observed over the occipital electrode cluster. The ANOVA found that there was a significant 3-way interaction between VEP assessment, ERP component and age group, F (9.86, 266.11) = 3.74, $p < .001$, $\eta_p^2 = .122$.

The data were then split to determine whether there were statistically significant simple two-way interactions between age group and VEP assessment for each ERP component. The results showed that there was no statistically significant simple two-way interaction between VEP assessment and age group for the P1 visual component (F (5.64, 152.14) = 1.15, $p = .337$, $\eta_p^2 = .041$). However, there were statistically significant simple two-way interactions between VEP assessment and age group for the N1 visual component (F (5.37, 144.85) = 2.48, $p = .031$, $\eta_p^2 = .084$), and also for the P2 visual component (F (5.91, 159.61) = 3.67, $p = .002$, $\eta_p^2 = .120$). Follow-up analyses were run to further explore the effect of visual HFS on the visual N1 and P2 in each age group. Mean amplitude values (and standard deviations) for visual ERP component at each VEP assessment, for each age group are presented in Table 4.3. The interactions between age group and VEP assessment for the N1 and P2 visual components are also presented graphically in Figure 4.8 respectively. Grand-averaged ERPs for the occipital cluster for each age group are also presented in Figure 4.9.

4.3.1.3.1. N1 analyses

Benjamini-Hochberg (BH) corrected pairwise comparisons revealed that compared to baseline amplitude, early-adolescents showed a significant decrease visual N1 amplitude during post-HFS 1 ($p = .001$) and post-HFS 2 ($p < .001$), but mean amplitude was not significantly different from baseline during post-HFS 3 ($p = .172$). When comparing mean amplitudes measured during post-HFS VEP assessments, the results show that there were no significant differences between mean amplitudes measured during post-HFS 1 and post-HFS 2 ($p = .882$), but amplitudes measured during both of these early post-HFS VEP assessments were significantly reduced compared to those measured during the later post-HFS 3 assessment (post-HFS 1 x post-HFS 3, $p < .001$; post-HFS 2 x post-HFS 3, $p < .001$).

Pairwise comparisons looking at the effect of visual HFS on mean VEP amplitudes for late-adolescents revealed that, compared to baseline, visual N1 amplitude was significantly potentiated during post-HFS 1 ($p = .001$), post-HFS 2 ($p = .007$) and during post-HFS 3 ($p = .019$). For comparisons between post-HFS assessments, results revealed that there were no significant differences between mean amplitudes measured during any of the three post-HFS VEP assessments (post-HFS 1 x post-HFS 2, $p = .209$; post-HFS 1 x post-HFS 3, $p = .057$; post-HFS 2 x post-HFS 3, $p = .486$).

Finally, pairwise comparisons looking at the effect of visual HFS on mean VEP amplitudes for adults revealed that, compared to baseline, visual N1 amplitude was also significantly potentiated during all post-HFS VEP assessments; post-HFS 1 (p = .001); post-HFS 2 (p = .008); post-HFS 3 (p = .033). When comparing mean amplitudes measured during post-HFS VEP assessments, results revealed that mean amplitude was significantly more potentiated in post-HFS 1 compared to post-HFS 3 (p = .026), but there were no statistically significant differences between the other post-HFS comparisons (post-HFS 1 x post-HFS 2, p = .149; post-HFS 2 x post-HFS 3, p = .398).

Collectively, these results suggest that visual HFS lead to significant short-term potentiation of the N1 in early-adolescents, but no significant longer-term changes in N1 (20 minutes post-HFS). In contrast, both late-adolescents and adults showed significant short- and long-term potentiation of the N1 visual component following visual HFS.

See Appendix 2 for pairwise comparisons comparing differences between the age groups for VEP component amplitudes. The grand-averaged VEPs (Figure's 4.5 to 4.7) show that there are developmental differences in VEP pattern, whereby early-adolescent VEPs are generally more positive in polarity (as if they are hanging above the x axis) compared to VEPs from older age groups. This is consistent with what we know about changes in neural structure during adolescence associated with changes in VEPs (see Chapter 1.6.4), and also consistent with previous findings from our lab (Levita, Howsley, Jordan, & Johnston, 2015) which are not related to experimental manipulation. Instead, analyses conducted to assess age-related differences in the degree of VEP change for each VEP component are reported in section 4.3.2.

Table 4.3
Descriptive statistics for mean amplitude across VEP components measured during baseline and Post-HFS assessments for each age group.

		Age Group					
		Early-Adolescent		Late-Adolescent		Adult	
VEP Assessment	ERP Component	*M*	*SD*	*M*	*SD*	*M*	*SD*
Baseline	P1	2.60	4.17	-.35	4.92	-.32	4.37
	N1	6.91	7.43	-3.23	8.69	-6.77	5.61
	P2	15.45	7.99	12.72	6.52	11.91	8.26
Post-HFS 1	P1	3.06	4.37	.00	4.09	.22	3.56
	N1	4.36	8.54	-5.64	9.63	-9.22	5.67
	P2	8.15	8.30	8.59	6.81	8.48	8.04
Post-HFS 2	P1	2.48	4.12	.01	4.14	.16	3.72
	N1	4.26	6.70	-4.80	9.34	-8.29	5.95
	P2	9.93	8.64	10.36	7.36	10.07	8.18
Post-HFS 3	P1	3.22	5.08	-.87	4.48	.01	4.10
	N1	7.59	8.91	-4.38	9.01	-7.79	6.02
	P2	12.68	9.07	13.31	6.92	13.28	8.69

4.3.1.3.2. P2 analyses

Benjamini-Hochberg (BH) corrected pairwise comparisons revealed that compared to baseline amplitude, early-adolescents showed significant attenuation of the visual P2 component during post-HFS 1 ($p < .001$), post-HFS 2 ($p < .001$) and post-HFS 3 ($p = .001$). Comparison of post-HFS VEP assessments revealed that mean VEP amplitude was most attenuated during post-HFS 1, and became significantly more positive in each subsequent post-HFS measure (post-HFS 1 x post-HFS 2, $p = .020$; post-HFS 1 x post-HFS 3, $p < .001$; post-HFS 2 x post-HFS 3, $p = .002$).

Pairwise comparisons looking at the effect of visual HFS on mean VEP amplitudes for late-adolescents revealed that, compared to baseline, visual P2 amplitude was significantly attenuated during post-HFS 1 ($p < .001$) and post-HFS 2 ($p = .003$), but had returned to baseline values by post-HFS 3 ($p = .432$). When comparing mean amplitudes measured during post-HFS VEP assessments, the results show that P2 amplitude was most attenuated during post-HFS 1 and, like with early-adolescents, became significantly more positive in each subsequent post-HFS measure (post-HFS 1 x post-HFS 2, $p = .018$; post-HFS 1 x post-HFS 3, $p < .001$; post-HFS 2 x post-HFS 3, $p = .001$).

Finally, pairwise comparisons looking at the effect of visual HFS on mean VEP amplitudes for adults revealed that, compared to baseline, visual P2 amplitude was also significantly potentiated during post-HFS 1 ($p < .001$) and post-HFS 2 ($p = .015$), but had returned to baseline values by post-HFS 3 ($p = .069$). As with both early- and late-adolescents, P2 amplitude was most attenuated during post-HFS 1 and became significantly more positive in each post-HFS measure (post-HFS 1 x post-HFS 2, $p = .028$; post-HFS 1 x post-HFS 3, $p < .001$; post-HFS 2 x post-HFS 3, $p < .001$).

Together, these results suggest that visual HFS leads to significant long-term attenuation of the visual P2 component for early-adolescents, but only produces short-term attenuation of the P2 in late-adolescents and adults. For all age groups, the attenuating effect of visual HFS on the P2 was strongest immediately after HFS, but the effect significantly reduced in each subsequent VEP assessment.

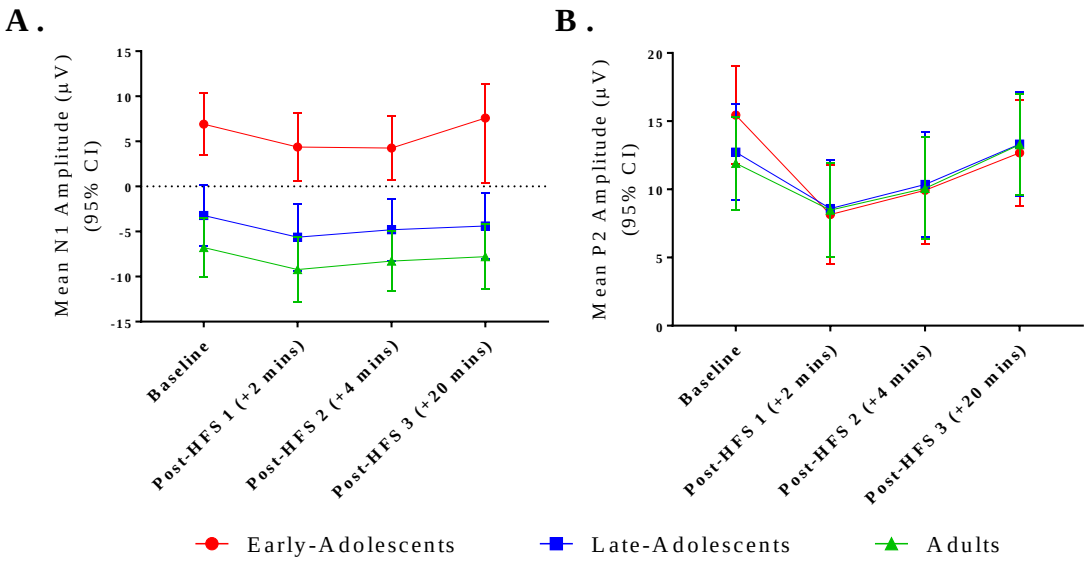


Figure 4.8. **A**: Mean N1 amplitude for each VEP assessment (baseline, post-HFS 1, post-HFS 2, post-HFS 3) and age group (early-adolescents (red); late-adolescents (blue); adults (green)). **B:** Mean P2 amplitude for each VEP assessment and age group. Error bars show 95% confidence intervals.

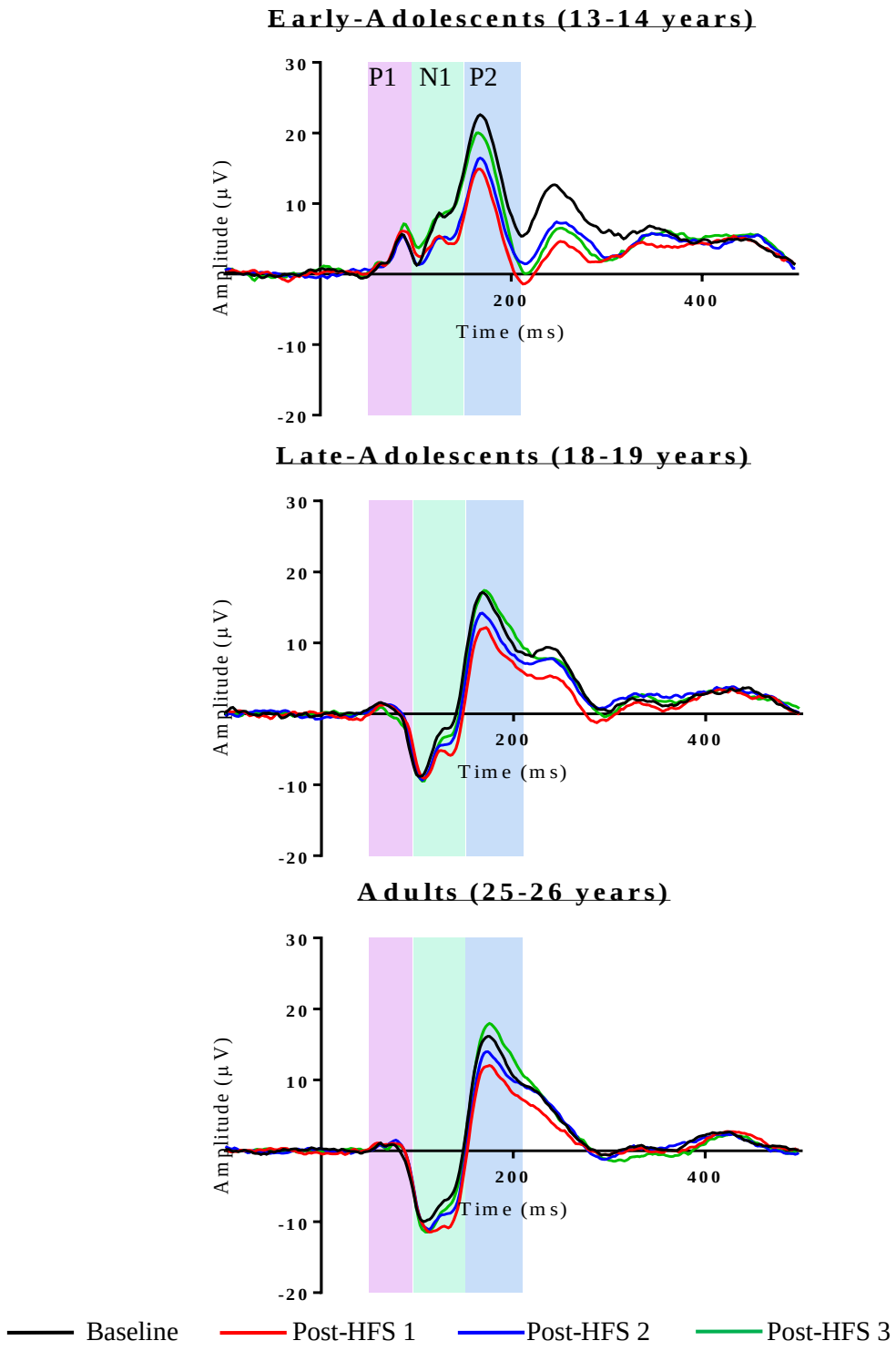


Figure 4.9. Grand average visual evoked potentials (VEPs) elicited by standard circle for early-adolescents (n = 18), late-adolescents (n = 19), and adults (n = 20) for the averaged occipital electrode cluster (Oz, Iz, O1, and O2) for each VEP assessment: Baseline (2-4 minutes before HFS; black line), Post-HFS 1 (2-4 minutes post-HFS; red line), Post-HFS 2 (4-6 minutes post-HFS, blue line), and Post-HFS 3 (20-22 minutes post HFS; green line).The shaded bars perpendicular to the x axis indicate the time windows used to calculate mean amplitude for the P1, N1, and P2 components (P1 50-95ms, pink box; N1 95-150ms, green box; P2 150-210ms, blue box).

4.3.2. Hypothesis: Adolescents will display greater change in VEP amplitude following HFS compared to adults

To assess whether there were age-related differences in the degree of change in VEP amplitude following HFS, a three-way ANOVA was run to compare VEP change scores (VEP Change 1, VEP Change 2, and VEP Change 3) for all age groups (early-adolescent, late-adolescent, and adult) for each ERP component that previous analyses had shown were affected by visual HFS (N1 and P2). Details of how VEP change scores were calculated are presented in Chapter 2.4.2.2.3. The assumption of homogeneity of variances was violated for one cell of the design, as assessed by Levene's test for equality of variances (VEP Change 3 for the P2 visual component [$p = .019$]); however, the three-way ANOVA is considered to be somewhat robust to violations of heterogeneity of variance if group sample sizes are approximately equal, as they are in this study, therefore analysis continued as planned.

The results of the ANOVA indicated that there was a statistically significant three-way interaction between age group, VEP assessment, and ERP component on degree of VEP change (F (3.61, 97.49) = 3.04, $p = .025$, $\eta_p^2 = .101$). Consequently, data were split to see whether there were statistically significant simple two-way interactions between age group and VEP assessment for each ERP component.

4.3.2.1. N1 analyses

The results indicated that there were statistically significant simple two-way interactions between VEP assessment and age group for the N1 visual component (F (3.96, 106.84) = 3.43, $p = .011$, $\eta_p^2 = .113$. Follow-up analyses were run to further explore the interaction between age group and VEP assessment on degree of change of N1 amplitude. Mean N1 amplitude change values (and standard deviations) for each age group are presented in Table 4.4.

BH-corrected pairwise comparisons revealed that there were no significant differences between any of the age groups in the degree of N1 amplitude change during post-HFS 1 (early-adolescent Vs late-adolescent [$p = .888$]; early-adolescent Vs adult [$p = .921$]; late-adolescent Vs adult [$p = .965$]) or during post-HFS 2 (early-adolescent Vs late-adolescent [$p = .190$]; early-adolescent Vs adult [$p = .162$]; late-adolescent Vs adult [$p = .940$]). However, during post-HFS 3, early-adolescents showed a significantly less potentiation of N1 amplitude change to late-adolescents ($p = .010$) and adults ($p = .015$), reflecting the findings of analyses presented earlier (section 4.3.1.2.1). There were no significant differences in degree of N1 amplitude change during post-HFS 3 for late-adolescents and adults ($p = .837$).

When looking at differences in degree of N1 amplitude change between post-HFS measures within one age group, the results for early-adolescents reveal that degree of N1 amplitude change was not statistically different between post-HFS 1 and post-HFS 2 ($p = .882$),

but that degree of change was greater in both these earlier assessments compared to post-HFS 3 (post-HFS 1 [$p < .001$]; post-HFS 2 [$p < .001$]). For late-adolescents, there were no significant differences in degree of N1 amplitude change between any of the post-HFS measures (post-HFS 1 Vs post-HFS 2 [$p = .209$]; post-HFS 1 Vs post-HFS 3 [$p = .057$]; post-HFS 2 Vs post-HFS 3 [$p = .486$]). Finally, for adults, there were no significant differences between post-HFS 1 and post-HFS 2 ($p = .149$), or between post-HFS 2 and post-HFS 3 ($p = .398$) in degree of N1 amplitude change; however, adults showed a significantly greater change in N1 amplitude in post-HFS 1 compared to post-HFS 3 ($p = .026$).

Collectively, these results suggest that all age groups showed a similar degree of N1 potentiation during post-HFS 1 and post-HFS 2. However, by post-HFS 3, early-adolescents showed no significant potentiation of the N1 compared to their baseline VEPs, but this effect was maintained in late-adolescents and adults. These interactions are presented graphically below in Figure 4.10.

Table 4.4
Marginal Means and Standard Errors for VEP change scores

		Age Group					
		Early-Adolescent		Late-Adolescent		Adult	
ERP component	*VEP Change*	*M*	*SD*	*M*	*SD*	*M*	*SD*
N1	Post-1 minus baseline	-2.55	3.91	-2.41	2.33	-2.45	2.67
	Post-2 minus baseline	-2.65	2.94	-1.57	2.46	-1.51	1.95
	Post-3 minus baseline	.68	2.44	-1.15	1.60	-1.01	2.12
P2	Post-1 minus baseline	-7.30	3.56	-4.13	2.87	-3.44	3.41
	Post-2 minus baseline	-5.52	4.08	-2.36	2.62	-1.84	2.97
	Post-3 minus baseline	-2.77	4.78	.60	1.98	-.20	3.70

4.3.2.2. P2 analyses

The results indicated that there were no statistically significant simple two-way interactions between VEP assessment and age group for the P2 visual component [F (3.94, 106.23) = .05, $p = .996$, $\eta_p^2 = .002$]. However, there was a significant main effect of VEP assessment (F (1.97, 106.23) = 56.00, $p < .001$, $\eta_p^2 = .509$). Pairwise comparisons revealed that, compared to baseline, the greatest change in P2 amplitude occurred during post-HFS 1, with degree of change significantly decreasing in each subsequent VEP assessment (post-HFS 1 Vs post-HFS 2 [$p < .001$]; post-HFS 1 Vs post-HFS 3 [$p < .001$]; post-HFS 2 Vs post-HFS 3 [$p < .001$]). There was also a significant main effect of age group on degree of P2 amplitude change (F (2, 54) = 11.61, $p < .001$, $\eta_p^2 = .301$). BH-corrected pairwise comparisons revealed that early-adolescents showed significantly greater attenuation of P2 amplitude compared to late-adolescents ($p < .001$) and adults ($p < .001$); there were no significant differences between late-adolescents and adults ($p = .437$). Together, these results show that the greatest change in P2

amplitude occurred immediately after visual HFS had completed, and was greatest in early-adolescents compared to the older age groups.

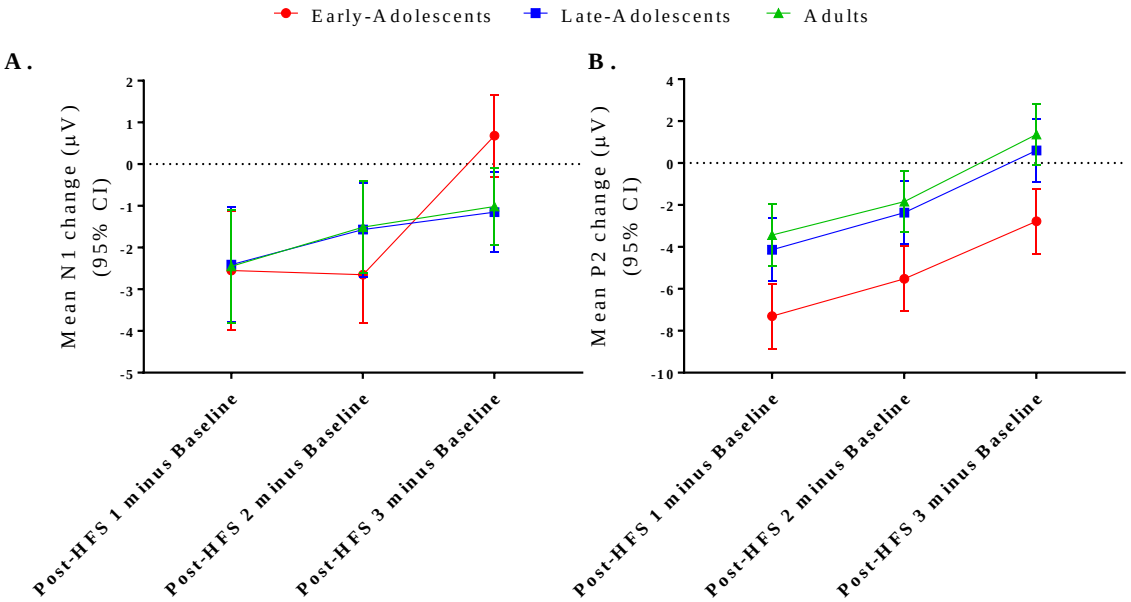


Figure 4.10. Mean VEP change in each VEP assessment for each age group. Values above zero indicate a potentiated VEP following visual HFS, and values below zero indicate an attenuated VEP following visual HFS. **A**: Mean change in N1 amplitude for each VEP assessment (post-HFS 1 minus baseline; post-HFS 2 minus baseline; post-HFS 3 minus baseline) and each age group (early-adolescent (red); late-adolescent (blue); adult (green). **B:** Mean change in P2 amplitude for each VEP assessment and each age group. Error bars show 95% confidence intervals.

4.3.3. Hypothesis: There will be no group differences in HFS-driven VSSR power.

To examine whether there were age-group differences in the tetanizing effect of the visual HFS, power spectra of EEG recorded during HFS were calculated (see section 2.3.1.3 for more detail), and peak power values analysed. A summary VSSR power measure was derived by averaging parieto-occipital channels where the VSSR response was largest (Oz, Iz, O1, O2, POz, PO7, PO8, PO3, PO4). The power spectra for this averaged cluster is presented in Figure 4.11, and demonstrates that HFS-driven VSSR was observed, as evident in the peak power value at 9Hz (the frequency bin closest to the HFS frequency of ~8.87Hz).

The 9Hz VSSR power values (μV^2/Hz) were positively skewed, therefore a non-parametric Kruskall-Wallis H test was run to determine if there were any age-dependent differences in average VSSR power. Inspection of boxplots also indicated one extreme outlier, but they were kept in analyses as they didn't materially affect the results, as assessed by comparison of results with and without the outlier. Results found that average VSSR power scores were not significantly different between early-adolescents (median = 29.71), late-adolescents (median = 26.24) and adults (median = 15.70), $\chi 2$ (2) = 4.22, p = .121.

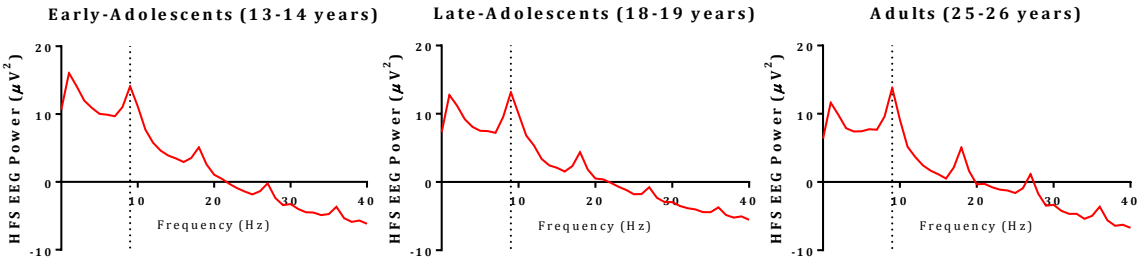


Figure 4.11. *Power spectra of EEG recorded during HFS. These spectra represent data averaged across posterior electrode sites (Oz, Iz, O1, O2, POz, PO7, PO8, PO3, PO4), where VSSR response was largest. The VSSR is evident in these spectra as a peak power value at 9Hz.*

4.3.4. Hypothesis: HFS-driven VSSR power predicts degree of VEP change

Linear regressions were run for each age group and ERP component (N1 and P2) to determine whether HFS-driven VSSR power could significantly predict degree of VEP change in each post-HFS assessment. Results revealed that HFS-driven VSSR power did not significantly predict degree of N1 amplitude change during any post-HFS assessments for any age group. A summary of these regression results are presented in Table 4.5.

Table 4.5.
Summary of regression analyses predicting change in VEP amplitude from HFS-driven VSSR power

Age Group	VEP Component	VEP Change	*F*	*p*	*B*	*SE B*	*β*	Adj. R^2
Early-adolescent	N1	Post-1 minus baseline	.12	.731	.02	.06	.09	-.06
		Post-2 minus baseline	.12	.733	-.02	.05	-.09	-.06
		Post-3 minus baseline	.76	.399	-.03	.04	-.22	-.02
	P2	Post-1 minus baseline	.18	.681	.02	.05	.11	-.05
		Post-2 minus baseline	.31	.583	.03	.06	.14	-.05
		Post-3 minus baseline	1.70	.212	.09	.07	.32	.04
Late-adolescent	N1	Post-1 minus baseline	1.10	.309	-.03	.03	-.25	.01
		Post-2 minus baseline	.16	.695	-.01	.03	-.10	-.05
		Post-3 minus baseline	1.15	.298	-.02	.02	-.25	.06
	P2	Post-1 minus baseline	.78	.391	-.03	.04	-.21	-.01
		Post-2 minus baseline	.01	.944	.00	.04	.017	-.06
		Post-3 minus baseline	.72	.409	.02	.03	.20	-.02
Adult	N1	Post-1 minus baseline	1.34	.262	.02	.02	.26	.07
		Post-2 minus baseline	.93	.347	-.01	.01	-.22	-.00
		Post-3 minus baseline	.14	.715	.01	.01	.09	.01
	P2	Post-1 minus baseline	1.12	.304	.02	.02	.24	.01
		Post-2 minus baseline	.20	.663	.01	.02	.10	-.04
		Post-3 minus baseline	.89	.358	.02	.02	.22	-.01

Note. Early-adolescent, *df* = (1, 15); Late-adolescent, *df* (1, 17); Adult, *df* = (1, 18).

4.3.5. Assessing group differences in number of trials and EEG channels removed during processing of EEG data

4.3.5.1. Number of trials removed during EEG processing

A two-way mixed methods ANOVA was conducted between age group and block number on number of standard circle trials. Data were positively skewed as assessed by inspection of histograms. However, as there is no non-parametric equivalent of a two-way mixed ANOVA, transformation of the data did not improve the distribution of the data, and ANOVAs are robust to deviations from normality, a parametric two-way ANOVA was used to analyse the data. There was a statistically significant interaction between age group and block number on total number of standard circle trials remaining after pre-processing of data, F (5.12, 55.98) = 2.39, p = .039, η_p^2= .081. Descriptive statistics for number of standard circle trials included in each block are included in Table 4.6. Benjamini-Hochberg (BH) adjusted pairwise comparisons found that there were no significant differences between the age groups in number of trials included in analyses during baseline and Post-1 (all p's > .05). However, early-adolescents had significantly fewer trials remaining in Post-2 (p = .001) and Post-3 (p = .005) compared to adults. There were no significant differences between late-adolescents and adults in number of trials included in Post-2 (p = .038) or Post-3 (p = .162). When comparing the number of trials included in blocks for each age group (*e.g.* comparing the number of trials at baseline and Post-1 for early-adolescents), no significant differences were found after BH-corrections were applied.

Overall, these results show that early-adolescents had significantly fewer trials from Post-2 and Post-3 included in analyses compared to adults, with no other significant differences found. This suggests that early-adolescents had more noise in their data towards the end of the experiment compared to adults, which resulted in more trials being removed during pre-processing for this youngest age group.

Table 4.6.
Mean number of standard circle trials included in each VEP assessment for each age group (*SD*)

Block	Early-Adolescents	Late-Adolescents	Adults
Baseline	82.06 (6.64)	84.84 (3.95)	83.75 (5.49)
Post-1	83.61 (6.67)	82.79 (6.28)	84.90 (4.34)
Post-2	81.22 (6.05)	83.68 (5.31)	87.10 (3.43)
Post-3	79.72 (9.40)	83.05 (5.76)	86.15 (4.64)

4.3.5.2. Number of channels removed during EEG processing

A one-way ANOVA revealed no age-group differences in the number of channels removed during pre-processing, F (2, 5) = .091, p = .914. On average, 8 channels per participant were removed during pre-processing of EEG data (min = 0, max = 20).

4.3.6. Analysis of Parieto-Occipital Clusters

Inspection of the grand average VEPs and scalp topographies confirm that the time windows and electrode cluster chosen for analyses are appropriate (section 4.2.3.2. and 4.2.3.3). However, grand-averaged scalp topographies representing the N1 visual component did reveal age-related differences in distribution of activity (see Figure 4.9). Late-adolescents and adults exhibit strong negative activity, dispersed centrally over occipital channels, with maximal activity observed over Oz, Iz, O1 and O2. In contrast, early-adolescents display weak positive activity bilaterally over parieto-occipital channels, with maximal activity observed over PO8 and P8. To ensure that the analysis performed were not biased due to electrode selection over the occipital region, additional analyses were run to examine age-dependent changes in cortical plasticity at 2 corresponding parieto-occipital clusters (right hemisphere: PO8 and P8; left hemisphere: PO7 and P7) for the N1 visual component. Regarding age-dependent differences in cortical plasticity, the conclusions of the findings from analyses run with the parieto-occipital clusters revealed no significant long-term changes to the VEP following HFS, and no interaction between age and VEP assessment following visual HFS. These results are presented in Appendix 3.

4.3.7. Task performance

4.3.7.1. Reaction times to oddball targets

To assess if group differences in VEP amplitude could be due to group differences in attention (as measured by task performance), a two-way ANOVA was run to determine if there were any differences in reaction time across the blocks, and across the age groups. Reaction time data were positively skewed, and therefore data did not meet the assumption of normal distribution. However, ANOVA's are considered to be fairly robust to violations of normality if sample sizes are roughly equal (Schmider et al., 2010), and there is no non-parametric alternative, therefore the two-way ANOVA was deemed to be the most appropriate test. The assumption of homogeneity of variances, as assessed by Levene's test for equality of variances, was violated only for mean reaction times measured during Post-HFS 1 (p = .012).

The results of the ANOVA found that there was no significant two-way interaction between block and age group, F (6, 162) = 1.83, p = .096, η_p^2= .064. There was, however, a significant main effect of block on reaction time to oddball targets, F (3, 162) = 12.25, p < .001, η_p^2= .185. Means and SEs are presented in Table 4.7. BH-adjusted pairwise comparisons found

that reaction times were significantly slower in all post-HFS blocks when compared with reaction times at baseline (Post-1 $p = .019$; Post-2 $p = .001$; Post-3 $p < .001$). Compared to reaction times measured during Post-1, reactions times were also significantly slower during Post-2 ($p = .051$) and Post-3 ($p = .002$). There were no significant differences in reaction times measured during Post-2 and Post-3 ($p = .082$). Overall, these results demonstrate that reaction times for selecting oddball targets were quickest during baseline, and slowest during Post-3. This pattern may be due to participants becoming fatigued during the experiment.

The results of the ANOVA also found that there was a significant main effect of age group on reaction times, F (2, 54) = 7.83, $p = .001$, , $\eta_p^2 = .225$. Pairwise comparisons revealed that early-adolescents had significantly slower reaction times compared to late-adolescents ($p = .023$) and adults ($p < .001$). There were no significant differences in reaction times between late-adolescents and adults ($p = .118$).

Table 4.7.
Marginal means for main effects of VEP assessment and age group

Variable		Mean Reaction Time in seconds (*SE*)
VEP Assessment	Baseline	.357 (.006)
	Post-1	.368 (.007)
	Post-2	.375 (.007)
	Post-3	.382 (.008)
Age Group	Early-Adolescent	.406 (.012)
	Late-Adolescent	.366 (.012)
	Adult	.340 (.012)

4.3.7.2. Response Accuracy to Oddball Targets

A Kruskall-Wallis H test revealed no age group differences in response accuracy between age groups at baseline ([χ^2 (2) = 2.80, $p = .247$]), Post-HFS 1 (+2 mins; [χ^2 (2) = 7.26, $p = .027$] (not significant after adjusting for multiple comparisons)) or during Post-HFS 2 (+4 mins; [χ^2 (2) = 2.91, $p = .233$]). However, significant differences in response accuracy were found between age groups in the final Post-HFS block (+20 mins; [χ^2 (2) = 19.10, $p < .001$]). Pairwise comparisons revealed statistically significant differences in response accuracy to oddball targets between early-adolescents (*Mdn* = 19.69) and late-adolescents (*Mdn* = 32.55, $p = .001$), and early-adolescents and adults (*Mdn* = 34.00, $p < .001$), with early-adolescents missing more targets than older age groups. No significant differences in response accuracy were found between late-adolescents and adults ($p = 1.00$). These results suggest that hit rates, and therefore

attentional vigilance, were comparable across age groups apart from in the final Post-HFS block, where early-adolescents missed significantly more targets than the older age groups.

In addition, a Friedman test was run to determine if there were differences in response accuracy to target squares in different blocks (baseline, Post-HFS 1, Post-HFS 2, Post-HFS 3), but no statistically significant differences were found, χ^2 (3) = 1.03, p < .795. Further descriptive statistics of response accuracy to the target square are in Table 4.8.

Table 4.8.
Response accuracy to target squares (percentage) for all age groups during VEP assessments

	Age Group							
	Early-Adolescents		Late-Adolescents		Adults		Total Sample	
Block	Hit Rate (%)	SD	Hit Rate (%)	SD	Hit Rate (%)	SD	Hit Rate (%)	SD
Baseline	97.22	.46	98.95	.32	99.00	.31	98.42	.37
Post-HFS 1 (+2 min)	96.11	.78	96.32	.60	100.00	.00	97.54	.58
Post-HFS 2 (+4 min)	96.11	.70	98.95	.32	98.50	.49	97.90	.53
Post-HFS 3 (+20 min)	93.89	.70	99.47	.23	100.00	.00	97.90	.49

4.3.7.3. Changes in Target Reaction Time and Absolute VEP Change

To determine if there was any relationship between change in VEP and change in reaction times to target stimuli, associations between VEP change measured at Post-HFS 3 for the N1 and P2 and change in target reaction time were analysed using standard multiple regression. There was independence of residuals, as assessed by a Durbin-Watson statistic of 1.913. There was homoscedasticity, as assessed by visual inspection of a plot of studentized residuals versus unstandardized predicted values. The multiple regression model did not significantly predict target reaction time change scores, F (2, 54) = .1.38, p = .262, adj. R^2 = .01.

Further standard multiple regressions were run to test associations between absolute VEP change and target reaction time change scores for each age group. None of the multiple regression models significantly predicted target reaction time change scores (early-adolescents [F (2, 15) = .55, p = .587, adj. R^2 = -.06]; late-adolescents [F (2, 16) = .23, p = .800, adj. R^2 = -.09]; adults [F (2, 17) = .37, p = .699, adj. R^2 = -.07]). These results suggest that changes in VEP amplitude were not associated with changes in reaction time to target stimuli for any age group.

4.3.8. Questionnaire analyses

4.3.8.1. Assessing Internal Reliability of Questionnaires

Before addressing whether age-dependent changes in cortical plasticity were associated with sensory responsivity, it was first important to examine how reliable the questionnaires used to assess sensory responsivity (and other associated variables) in our sample were. To that end Cronbach's alpha values for each questionnaire scale are presented in Table 4.9. There was great variation in Cronbach's alpha values for scales across the age groups; Cronbach's alpha values were generally higher for questionnaires completed by adult participants, and lower for early-and late-adolescents, suggesting that perhaps these measures are more suited to adult samples. Only three of the scales achieved a Cronbach's alpha value greater than 0.7 for all three age groups; the Low Registration scale from the AASP, the Depression scale from the DASS-21, and the total GSQ summed score. Consequently, subsequent analyses will still use all scales, but additional caution should be applied when interpreting results from scales with poor internal reliability.

Table 4.9.
Descriptive statistics and Cronbach's alpha for AASP, DASS-21 and GSQ questionnaire scales

Age Group	Q-naire	Scale	Mean	SD	Min	Max	α
Early-Adolescents (*n* = 18)	AASP	Low Registration	33.00	8.06	25	54	.79
		Sensation Seeking	42.17	7.59	25	57	.68
		Sensory Sensitivity	33.22	6.39	22	53	.57
		Sensation Avoiding	35.22	7.79	22	53	.75
	DASS-21	Depression	2.61	2.87	0	9	.83
		Anxiety	3.06	2.13	0	7	.48
		Stress	4.06	3.00	0	9	.66
	GSQ	Total GSQ Score	54.61	17.94	29	100	.89
Late-Adolescents (*n* = 19)	AASP	Low Registration	31.58	7.01	15	45	.79
		Sensation Seeking	48.21	6.38	37	56	.54
		Sensory Sensitivity	36.74	7.60	20	50	.70
		Sensation Avoiding	32.42	5.35	22	42	.56
	DASS-21	Depression	3.58	3.25	0	11	.76
		Anxiety	4.53	3.22	0	11	.63
		Stress	6.42	4.75	0	16	.87
	GSQ	Total GSQ Score	47.74	13.00	16	72	.78
Adults (*n* = 20)	AASP	Low Registration	32.65	7.39	19	44	.83
		Sensation Seeking	46.65	6.72	36	59	.72
		Sensory Sensitivity	37.55	6.86	25	50	.70
		Sensation Avoiding	35.80	8.51	17	51	.82
	DASS-21	Depression	2.70	3.32	0	11	.90
		Anxiety	3.50	2.67	0	9	.71
		Stress	6.60	3.84	1	15	.81
	GSQ	Total GSQ Score	52.95	16.78	19	79	.90

Note: *SD* = standard deviation; Min = minimum observed score; Max = maximum observed score; AASP = Adolescent-Adult Sensory Profile; DASS-21 = Depression Anxiety Stress Scale (short form version); GSQ = Glasgow Sensory Questionnaire.

4.3.8.2. Age-related differences in questionnaire measures

4.3.8.2.1. No age group differences in DASS-21 scores

Results revealed that there were no significant differences between the three age groups in terms of depression scores (χ^2 (2) = 1.93, p = .381), anxiety scores (χ^2 (2) = 1.77, p = .413), or stress scores (χ^2 (2) = 4.37, p = .113). For descriptive statistics of DASS-21 scale scores for each age group see Table 4.9.

4.3.8.2.2. Age-group differences in AASP scores

Exploration of the data revealed that the assumption of normality had been met for all but one cell of the design (Low Registration scores for early-adolescents) as assessed by the Shapiro-Wilks test (p = .004). Consequently, a Kruskall-Wallis H test was conducted to explore age group differences in Low Registration scores. Results showed that there were no significant differences in Low Registration scores between the age groups (χ^2 (2) = .11, p = .948). As the rest of the data met the assumptions of a parametric test, three separate one-way ANOVA's were conducted to assess age group differences in Sensory Sensitivity, Sensation Avoiding, and Sensation Seeking scores. The ANOVA's showed that there were no significant age group differences in Sensory Sensitivity scores (F (2, 54) = 2.02, p = .142) or Sensation Avoiding scores (F (2, 54) = 1.16, p = .322). However there was a significant age-group difference in Sensation Seeking scores (F (2, 54) = 3.84, p = .028), whereby early-adolescents (M = 42.17) had significantly lower Sensation Seeking scores compared to late-adolescents (M = 48.21; p = .010) and adults (M = 46.65; p = .049). No significant differences were found between late-adolescents and adults Sensation Seeking scores (p = .481). These results show that there were no age-related differences in Sensory Sensitivity, Low Registration or Sensation Avoiding scores; however, early-adolescents were significantly less likely to seek out sensory stimulation that late-adolescents and adults in this sample. Descriptive statistics of AASP scale scores for each age group can be found in Table 4.9.

4.3.8.2.3. No age-group differences in GSQ scores

A one-way ANOVAs found that there were no significant age group differences in total GSQ score (F (2, 54) = .94, p = .397). Descriptive statistics total GSQ scores for each age group can be found in Table 4.9.

4.3.8.3. Assessing the Relationship between Sensory Responsivity and VEP Amplitude

4.2.8.3.1. Hypothesis: Participants with higher sensory responsivity scores will show larger visual evoked potentials at baseline.

Several of the questionnaire measures in this study violated the assumption of normality, therefore Spearman's rho correlation tests were run. The results of these correlation analyses are presented in Table 4.10. After applying BH-corrections for multiple comparisons,

the results showed that there were no significant correlations between VEP amplitudes at baseline and any of the sensory questionnaire scales for any of the age groups (all *p*'s > .154). These results suggest that perceived intensity of sensory stimuli, as measured by the questionnaires, does not relate to mean N1 or P2 amplitude at baseline for any age group.

Table 4.10.
Spearman's rho correlation coefficients between sensory questionnaire measures and baseline VEP amplitude

			VEP Component			
			N1		P2	
Age Group	Questionnaire	Scale	*r*	*p*	*r*	*p*
Early - Adolescents	GSQ	Total GSQ Score	-.21	.399	.13	.610
	AASP	Low Registration	-.33	.187	-.04	.864
		Sensation Seeking	-.13	.603	.22	.391
		Sensory Sensitivity	-.12	.643	.33	.189
		Sensation Avoiding	.08	.750	.08	.750
Late - Adolescents	GSQ	Total GSQ Score	.04	.886	-.16	.527
	AASP	Low Registration	-.31	.196	-.03	.892
		Sensation Seeking	-.04	.861	-.09	.701
		Sensory Sensitivity	.10	.675	-.08	.742
		Sensation Avoiding	-.05	.840	-.17	.479
Adults	GSQ	Total GSQ Score	.08	.731	-.06	.798
	AASP	Low Registration	-.30	.200	-.09	.719
		Sensation Seeking	-.21	.377	-.05	.823
		Sensory Sensitivity	-.09	.713	-.03	.904
		Sensation Avoiding	.33	.154	.19	.429

4.3.8.2.2. Hypothesis: Participants with higher sensory responsivity scores will show a smaller degree of change in VEP amplitude following high-frequency stimulation

The results of the correlation analyses are presented in Table 4.10. Following BH-corrections for multiple comparisons, no significant correlations were found between any of the sensory questionnaire measures and VEP change scores.

Table 4.11.
Spearman's rho correlation coefficients between sensory questionnaire measures and change in VEP amplitude (Post-3 minus baseline)

			VEP Component			
			N1		P2	
Age Group	Questionnaire	Scale	*r*	*p*	*r*	*p*
Early - Adolescents	GSQ	Total GSQ Score	-.24	.334	.28	.263
	AASP	Low Registration	-.50	.036	.04	.877
		Sensation Seeking	-.14	.591	.29	.238
		Sensory Sensitivity	-.21	.415	.47	.051
		Sensation Avoiding	.00	.977	.27	.288
Late - Adolescents	GSQ	Total GSQ Score	.01	.983	-.20	.404
	AASP	Low Registration	-.38	.114	.07	.771
		Sensation Seeking	-.09	.726	-.09	.712
		Sensory Sensitivity	.08	.744	-.05	.847
		Sensation Avoiding	-.06	.801	-.05	.837
Adults	GSQ	Total GSQ Score	.26	.276	-.13	.593
	AASP	Low Registration	-.16	.513	-.14	.560
		Sensation Seeking	-.33	.159	-.02	.942
		Sensory Sensitivity	.09	.713	.01	.977
		Sensation Avoiding	.36	.120	.19	.427

4.3.9. Summary of results

A summary of the key findings related to hypotheses outlined in the introduction are presented in Table 4.11. In addition, Table 4.12 summarises findings of all other analyses testing for differences between early-adolescents, late-adolescents, and adults that are not directly related to the hypotheses outlined in the introduction but may affect interpretation of these key findings.

Table 4.12.

Summary of key findings

Hypothesis	Finding	Summary
1. Visual HFS will lead to significant long-term changes to VEP components; in particular, long-term potentiation of the N1	✓	Visual HFS lead to long-term potentiation of the N1 for late-adolescents and adults (but only short-term potentiation for early-adolescents). Visual HFS also lead to long-term attenuation of the P2 for early-adolescents (but only short-term attenuation for late-adolescents and adults).
2. Visual plasticity is greater in adolescents compared to adults	✓/×	There were no age-related differences in degree of change in N1 amplitude in early VEP assessments, and early-adolescents actually showed less change in N1 amplitude during post-HFS 3 compared to older age groups. However, early-adolescents did show significantly greater attenuation of the P2 compared to late-adolescents and adults.
3. There will be no group differences in HFS-driven VSSR power	✓	No significant group differences in HFS-driven VSSR power were observed, suggesting that group differences in plasticity are not due to differing levels of tetanization.
4. HFS-driven VSSR power will predict degree of potentiation	×	No significant relationship was found between HFS-driven VSSR power and degree of potentiation
5. Participants with higher sensory responsivity scores will have larger VEPs at baseline	×	No significant relationship was found between sensory responsivity measures and VEP amplitude at baseline at any age
6. Participants with higher sensory responsivity scores will show a smaller degree of potentiation following HFS	×	No significant relationship was found between sensory responsivity measures and degree of potentiation at any age

Table 4.13.

Summary of all other analyses testing differences between early-adolescents, late-adolescents, and adults

Area of Analysis	Were there significant group differences in …?	Result	Summary
Data quality	…the number of epochs used to generate grand-averaged VEPs?	✓	Early-adolescents had significantly fewer trials than adults in Post-2 and Post-3, but no other significant group differences were found
	…the number of channels removed during processing of EEG data?	×	There were no age-group differences in the number of channels removed during pre-processing.
Questionnaire measures	…scores on the Depression Anxiety & Stress Scale (DASS-21)?	×	There were no significant group differences in DASS-21 scale scores.
	…scores on the Adolescent/Adult Sensory Profile (AASP)?	✓ & ×	Early-adolescents scored significantly higher on Sensation Seeking compared to late-adolescents and adults, but there were no significant age-group differences in Low Registration, Sensory Sensitivity, or Sensation Avoiding.
	…scores on the Glasgow Sensory Questionnaire (GSQ)?	×	There were no significant group differences in total GSQ scores.
Task performance	…response accuracy to oddball target squares?	✓	Early-adolescents had significantly lower response accuracy in Post-HFS 3 only, compared to late-adolescents and adults.
	…reaction times when responding to oddball target squares?	✓	Early-adolescents were generally slower to respond to target stimuli compared to late-adolescents and adults across all blocks.

4.4. Discussion

The results of this study demonstrate that exposure to repetitive visual HFS results in long term (lasting at least 20 minutes) changes to visual cortical evoked potentials, consistent with previous studies (Çavuş et al., 2012; Clapp et al., 2012; Teyler et al., 2005). Critically, this is the first study to examine developmental differences in the effect of visual HFS on VEPs in the transition from adolescence to adulthood. The results show that there was no effect of visual HFS on the P1 visual component, suggesting that HFS had no effect at one of the earliest stages of processing visual stimuli. However, significant age-dependent effects of visual HFS were found for later components of the VEP. In terms of changes to the visual N1 components, early-adolescents only showed short term potentiation of the N1 (up to 6 minutes post-HFS), whereas late-adolescents and adults both showed significant longer-term potentiation of the N1 (up to 22 minutes post-HFS). Furthermore, analyses exploring the degree of change in VEP amplitude revealed that all age groups had a similar degree of N1 potentiation in the earliest VEP assessments (post-1 and post-2), and whilst this degree of potentiation was maintained by late-adolescents and adults for 20 minutes following HFS, early-adolescents showed a quick return to baseline N1 amplitudes. When looking at changes to the visual P2 component the reverse pattern was observed, with early-adolescents showing significant long-term attenuation of the P2, but late-adolescents and adults only showing short-term attenuation of the P2. Interestingly, early-adolescents showed a significantly greater degree of attenuation of the P2 compared to the two older age groups, suggesting that plasticity may indeed be greater during adolescence than in adulthood. The following sections will discuss these findings in more detail, including how they relate to existing literature, and how they may guide future research.

4.4.1. Age-dependent differences in changes to the N1 and P2 visual components

Late-adolescents and adults both exhibited long-term potentiation of the N1 visual component. This is similar to previous studies using visual plasticity paradigms that have also demonstrated potentiation of the N1/N1b visual components in participants aged 18-40 years (Çavuş et al., 2012; Clapp et al., 2012; Spriggs et al., 2017). In contrast, early-adolescents only showed shorter-term changes (up to 6 minutes) in the N1 component after HFS, with N1 amplitude returning to pre-stimulation baseline 20 minutes after the HFS. It is not clear why early-adolescents did not also exhibit long-term potentiation of the N1. This interesting age difference could be a result of attentional differences during the task. Amplitude of the visual N1 has been shown to be affected by spatial attention (Hillyard, Vogel, & Luck, 1998; Mangun, 1995), and is thought to reflect some sort of discriminative processing (Luck, 2014). Interestingly, early-adolescents had significantly lower response accuracy scores in the final VEP assessment (post-HFS 3) compared to late-adolescents and adults. Therefore, it is possible that long-term potentiation of the N1 component was not observed for early-adolescents due to

poorer attention and/or greater fatigue during the final block, which was reflected in their task performance and (possibly) their VEP. Given that the aim of the visual plasticity paradigm is to assess long-term changes in visual plasticity, shortening the paradigm for younger participants is not really an option. However, it may be beneficial to test whether having a more stimulating task to complete during the interval between Post-HFS 2 and Post-HFS 3 (as opposed to collecting resting state data in the present study) could help to sustain attention levels for younger participants.

An alternative explanation is that what we are seeing is not a result of differential attention, but actually due to age-related differences in glutamatergic function. This argument is supported by the finding that early-adolescents did show long-term changes to P2 amplitude. This demonstrates that early-adolescents did show long-term changes to the VEP, but not in the N1 where we expected to see the most change based on findings from previous studies (Çavuş et al., 2012; Clapp et al., 2012; Teyler et al., 2005). Where early-adolescents exhibited significant long-term attenuation of the P2, late-adolescents and adults only exhibited short-term attenuation of the P2. As reported in Chapter 1.6.3, P2 amplitude is thought to be modulated in relation to figure saliency, with more salient stimuli needing fewer attentional resources, such that P2 amplitude decreases as figure saliency increases (Nothdurft, 2000; Straube & Fahle, 2010). However, very few studies have examined the effect of visual HFS on the P2 component.

Most of the previous research using the visual plasticity paradigm has not looked at the effect of HFS on visual evoked components beyond the N1, which is not too surprising given that majority of the literature consistently shows that visual HFS leads to potentiation of the N1 (Çavuş et al., 2012; Clapp et al., 2012; McNair et al., 2006). However, one study looking at the effects of aging on sensory-induced LTP-like effects examined changes to both the N1 and P2 following visual HFS. Spriggs and colleagues wanted to examine LTP-like modulation of the N1b component in young (18-35 years) and older (68-91 years) participants (Spriggs et al., 2017). They found that young adult participants showed the expected LTP-like potentiation of the N1b in response to visual tetanization, whereas the older adult participants did not. Interestingly, both groups showed significant potentiation of the P2a (the first part of the P2 component) in response to tetanized and non-tetanized stimuli, which the authors suggest indicates an active depotentiation (or LTD) of the VEP, resulting from repeated presentations of stimuli at a low frequency (~ 1Hz). Consequently, alterations to the P2 component may be more reflective of LTD-like changes induced by low-frequency presentation of stimuli in VEP assessments, rather than due to changes induced by high-frequency visual stimuli.

However, the direction of changes in P2 amplitude in Spriggs' study differ from the findings reported in the present study, which show significant attenuation of the P2. Although the results reported here show no significant potentiation of the P2 for any age group, visual

inspection of adult VEPs in Figure 4.9 does show that P2 amplitudes were potentiated during Post-HFS 3 compared to baseline – although it is important to emphasize that this difference is not statistically significant. It is possible that inconsistency in the findings of the two studies are due to methodological differences. Spriggs' study differed from the present study in that they present a sinusoidal grating flash stimulus, rather than the checkerboard stimulus presented in this study, as well as using a higher density electrode array (128 channels); therefore, it is difficult to make a direct comparison between the two studies. Ultimately, the findings of two studies are not sufficient to establish the effect of repeated presentation of visual stimuli (at either high or low frequencies) on P2 amplitude, and more research is needed to determine the developmental nature of these changes.

4.4.2. Degree of VEP change following visual-HFS

After confirming that there were age-dependent differences in VEP changes following HFS, the next step was to determine whether there were also developmental differences in the amount of change to VEP components following HFS. The results suggest that all age groups showed a similar degree of N1 potentiation during post-HFS 1 and post-HFS 2. However, by post-HFS 3, early-adolescents showed no significant potentiation of the N1 compared to their baseline VEPs, whilst this potentiating effect was maintained in late-adolescents and adults. Notably, early-adolescents did show significantly greater attenuation of the P2 component, compared to late-adolescents and adults. If Spriggs' (2017) suggestion that low-frequency presentation of stimuli in VEP assessments is responsible for alterations to P2 amplitude is correct, then it is possible that the findings presented in this study demonstrate greater LTD processes in early-adolescence, compared to late-adolescence and adulthood. This might seem contrary to our prediction that adolescents would show greater potentiation of VEPs compared to adults, which was based on the rodent literature demonstrating greater LTP in adolescence than in adulthood (Insel et al., 1990; Schramm et al., 2002). The authors of these rodent studies suggest that LTP is greater in adolescence because of a greater number, and improved functioning of NMDA receptors; however, NMDA receptors also play a key role in LTD processes. Therefore, the greater number, and improved functioning of NMDA receptors in adolescence may also mean that LTD is more easily induced by low-frequency stimulation, which is reflected by greater attenuation of the P2 in early-adolescents.

Greater LTD in adolescence is biologically advantageous, given that this developmental period is associated with significant neural restructuring. As discussed in section 1.7.4.1.1, in the human cortex, peak synaptic density occurs during early childhood, followed by robust synapse elimination during early and mid-adolescence, particularly in the auditory and prefrontal cortex (Huttenlocher, 1979; Huttenlocher & Dabholkar, 1997), then continuing at a lower rate into early adulthood (Petanjek et al., 2011). It is suggested that NMDA-receptor

dependent LTD (and LTP) may constitute the molecular mechanism underpinning synaptic pruning in adolescence, with greater emphasis on LTD and synaptic elimination (Selemon, 2013), so it is possible that LTD processes are enhanced during adolescence although more research is needed to confirm this.

4.4.3. HFS-Driven Visual Steady State Response

Developmental differences in VEP change cannot be attributed to age-related differences in response to the HFS. All age groups had comparable HFS-driven VSSR power, suggesting that participants attended to the tetanizing stimulus equally well, regardless of age, and exhibited comparable neuro-oscillatory entrainment to the HFS. However, unlike in previous studies, no significant correlation was found between HFS-driven VSSR power and degree of change in VEP amplitude, following HFS. This is surprising, given that a preliminary analysis of this dataset (for a poster presentation) found that greater VSSR power measured at Oz was significantly predicted greater potentiation of N1 amplitude at Post-3. The correlation analysis in this chapter looked at the VSSR power averaged over several parietal and occipital electrodes, so that findings were more comparable to those of Çavuş et al. (2012), who also used an averaged VSSR power. Consequently, it may be that the averaged VSSR power diluted the effect that was present at Oz so that the relationship was no longer significant.

4.4.4. Sensory Responsivity and Visual Cortical Plasticity

As well as exploring developmental differences in visual cortical plasticity, this study also aimed to explore the possible relationship between sensory responsivity and visual cortical plasticity. It was predicted that participants with high levels of sensory responsivity will exhibit greater VEPs in response to baseline stimuli, and will also show less change in VEP amplitude following HFS, compared to participants with lower levels of sensory responsivity. However, the results of this study found no significant correlations between the sensory questionnaire measures and VEPs measured at baseline, or amount of change in VEP amplitude following visual HFS. Therefore, the hypothesis that a significant relationship exists between sensory perception and VEP amplitude must be rejected.

One possible reason that this prediction was not substantiated could be that changes in plasticity resulting from visual HFS do not reflect shared mechanisms with sensory responsivity. However, evidence from sensory gating paradigms suggests that sensory responsivity is associated with adaptive responses to sensory stimuli. For example, in P50 suppression sensory gating paradigms, two stimuli are presented in close succession so that response to the first stimulus (conditioning stimulus) induces an adaptive suppression of response to the second stimulus (test stimulus), thereby avoiding excessive activation of the CNS. Children with sensory processing difficulties show impaired sensory gating compared to typically developing children in P50 suppression (Davies & Gavin, 2007); a finding that has

also been observed in adults with schizophrenia (for review and meta-analysis see Patterson et al., 2008; Freedman et al., 1987). Furthermore, sensory gating performance on pre-pulse inhibition tasks (whereby a weak first stimulus is followed by a strong second stimulus, and the amount of reduction in startle response is indicative of the amount of sensorimotor gating) has been shown to be affected by blockade of NMDA-receptors, in animal models of schizophrenia (for a review see Geyer, Krebs-Thomson, Braff, & Swerdlow, 2001). These findings suggest that a relationship between sensory responsivity and cortical plasticity is very plausible.

The more likely explanation for why this study did not see any association between cortical plasticity and sensory responsivity is due to issues with using questionnaire measures of sensory responsivity. Many of the scales had poor internal reliability (as assessed by Cronbach's alpha; see Table 4.9). This may in part be because some of the questionnaires, such as the GSQ, were not designed for use with adolescents as young as 13-14 years. However, even scales from the AASP, which is specifically designed to be administered to adolescents as young as 11 years of age, had Cronbach's alpha values that were below an acceptable level. Similarly, Cronbach's alpha scores were also poor for some of the scales even in the older age groups that they were designed for use with. Furthermore, sensory responsivity questionnaires may not be the best method for assessing an individual's threshold for sensory stimulation, as they assume that an observable reaction accurately captures the complexity of processing sensory input (Schauder & Bennetto, 2016). Questionnaire measures of sensory responsivity were selected in this doctoral work for mostly for their practicality, in that they could be administered easily to all participants, and would not be too tiring to complete before the EEG task; however, future studies should seek to assess sensory responsivity using physiological measures.

4.4.5. Study Limitations and Future Directions

There are some limitations to this study, which should be considered. Firstly, significant differences were found between the two baseline measures of mean VEP amplitude, which is problematic because no experimental manipulation had taken place at that point (the visual HFS) so it would be expected that VEPs should remain consistent. However, mean P2 amplitude was significantly larger in pre-HFS 2 compared to pre-HFS 1. As discussed earlier, Spriggs et al (2017) found significant potentiation of the P2 component in response to non-tetanized stimuli, which is thought to reflect LTD-like changes to the VEP induced by repeated low-frequency presentations of visual stimuli. This could potentially explain the baseline differences in P2 amplitude observed in the present study. Unfortunately, Spriggs' study was published after data collection for the present study (and the study reported in Chapter 5) had almost been completed; therefore, it was not possible to alter the paradigm to also assess the effect of low-frequency stimulation on VEPs in response to non-tetanized stimuli in this study,

although it should be recommended to include in future studies using sensory-induced tetanization paradigms.

A second limitation is that the age ranges used in this study did not entirely cover the adolescent period, and therefore may have failed to detect further developmental differences in visual plasticity (for example, before the age of 13, or between the ages of 15-17 and 20-24 years). However, this study is the first to utilise this paradigm in an adolescent sample; therefore, it was important to assess its suitability first, before possibly replicating with a larger, more representative sample. Using narrow age ranges in this instance meant that the study could explore distinct developmental stages, which is often an issue with developmental studies that use broad age ranges (Williams et al., 2012). Interestingly, few differences were observed between the late-adolescent (aged 18-19 years) and adult group (aged 25-26 years); future studies should explore developmental differences in visual cortical plasticity in the ages between our early-adolescent (aged 13-14 years) and late-adolescent groups (18-19 years), to determine the age when visual cortical plasticity becomes adult-like.

Finally, this study did not look at changes in VEP amplitude beyond 20 minutes after visual HFS. This is mostly due to practical reasons, and issues with increasing fatigue, particularly amongst younger participants. However, the results of our adult sample were consistent with findings of other non-invasive HFS paradigms (using adult samples), that have shown effects lasting for over an hour (Teyler et al., 2005; Zaehle et al., 2007).

4.4.6. Conclusion

In conclusion, the results of this study support previous work to demonstrate that visual HFS is sufficient for producing long-term changes in the visual cortex, as assessed by changes in visual evoked potentials. This study is the first to demonstrate developmental differences in the effect of visual HFS on VEPs, with early-adolescents showing different patterns of change compared to late-adolescents and adults. Furthermore, this study also found that adolescents showed significantly greater attenuation of the P2, which may reflect greater LTD processes in adolescence, although further research is needed to confirm this. Notably, this study did not find any significant relationship between sensory responsivity and VEP amplitude (either at baseline, or amount of VEP change following HFS); however, issues with the reliability of certain sensory measures mean that the lack of relationship needs to be taken with caution. Future studies should examine age dependent plasticity differences throughout the adolescent period, in addition to investigating developmental differences in plasticity in other cortical regions.

Chapter 5: Investigating cortical plasticity in the visual cortex of adults with Autism Spectrum Conditions

Abstract

There is increasing evidence implicating NMDA-receptor dysfunction in autism spectrum conditions (ASCs). NMDA receptors play a key role in the molecular processes underlying neuroplasticity, particularly in long-term potentiation (LTP) of cortical synapses. Hence, impaired neuroplasticity may be a primary biomarker of autism. This study investigated this by examining LTP-like changes in adults with ASCs using a paradigm which has been shown to induce LTP non-invasively by presenting individuals with repetitive visual stimulation, resulting in a lasting enhancement of visual evoked potentials (VEPs). Furthermore, autism is often associated with differences in processing sensory stimuli, with a greater incidence of over- or under-responsiveness to sensory stimuli in ASC than in the neurotypical population. Consequently, this study also aimed to examine whether altered visual plasticity in ASC may also be related to the more extreme sensory responsiveness observed in this population. To that end, EEG was recorded for high-functioning adults with autism (n = 16) and age- and gender-matched neurotypical controls (n = 15) whilst they completed the visual cortical plasticity paradigm. Results failed to replicate previous findings demonstrating that exposure to repetitive visual HFS results in long-term changes to visual evoked potentials. No long-term effects of visual HFS were found for either ASC or NT participants, although significant short term changes to VEP components were observed for both groups. Possible explanations for the lack of long-term effects following HFS are discussed. As predicted, sensory responsivity scores were more extreme in individuals with ASCs, compared to neurotypical participants, but there was no significant association between sensory responsivity and VEP amplitude to sensory stimulation during baseline VEP assessments. The results of this study provide a base for larger replication studies to build on, to determine the neural mechanisms underlying sensory processing differences in ASC.

5.1. Introduction

Autism spectrum conditions are characterised by persistent deficits in social communication and interaction (including deficits in social-emotional reciprocity, deficits in non-verbal communication, and deficits in developing, maintaining and understanding relationships), as well as restricted repetitive patterns of behaviour, interests, or activities (APA, 2013). The brain regions and neural mechanisms that underlie the altered social communication and integration of sensory information in ASC are still unknown. Most of our understanding of the mechanisms that might underlie the pathophysiology of ASC has come from research focussing on identifying genetic mutations associated with ASC, and studying their effects in animal models (Bourgeron, 2015). Approximately 1000 genetic variations have been identified as being implicated in ASC (SFARI, 2019). The functions of these target genes are diverse; however, there do appear to be groups of target genes that share commonalities. Of particular interest to this study are the recent findings linking function of the glutamatergic system to ASCs.

The glutamatergic system is the major excitatory neurotransmitter system in the brain, and has been found to be involved in learning and memory (Riedel, Platt, & Micheau, 2003), neuronal development (Spitzer, 2006), and synaptic plasticity (Mahato et al., 2018). There is increasing evidence to suggest that changes in both metabotropic glutamate receptors (mGluRs; Bhakar, Dölen, & Bear, 2012; Zoghbi & Bear, 2012), and ionotropic glutamate receptors (iGluRs), such as NMDA receptors are associated with ASCs (Lee, Choi, & Kim, 2015; Uzunova, Hollander, & Shepherd, 2014). Several clinical studies have identified genetic variants of NMDA receptor sub-unit genes, such as the GRIN2B which encodes for the GluN2B subunit (Kenny et al., 2014; O'Roak et al., 2012; O'Roak et al., 2012; O'Roak et al., 2011; Tarabeux et al., 2011), and the GRIN2A gene which encodes for the GluN2A subunit (Yoo et al., 2012). As discussed in Chapter 1.7, NMDA receptors contain four subunits; therefore, it is likely that ASC-related GRIN2A/GRIN2B variants will change the functional properties of NMDA receptors. Further evidence highlighting the relationship between reduced NMDA receptor function and ASC comes from pharmacological research, showing that NMDA receptor agonists can improve ASC symptoms, such as social withdrawal (Posey et al., 2004) and repetitive behaviour (Urbano et al., 2014). Similarly, several animal models have shown that altering NMDA-receptor function can lead to significant changes in ASC-like phenotypes (such as repetitive stereotyped grooming behaviours; Blundell et al., 2010; Chung et al., 2015; Schmeisser et al., 2012; Won et al., 2012). Collectively, these results provide strong evidence for an association between reduced NMDA-receptor function and ASCs. Consequently, the first aim of this study was to assess the functioning of the glutamatergic system in ASCs, specifically NMDA receptor functioning, by indirectly examining neuroplasticity in autistic adults using a sensory-induced potentiation paradigm.

At the time of writing, there is no published literature examining the effect of visual tetanization on VEPs of adults with autism spectrum conditions, so there is little research available to make directional hypotheses. However, Çavuş et al. (2012) demonstrated reduced LTP-like changes in individuals with schizophrenia compared to neurotypical controls. Like ASC, schizophrenia is also associated with reduced NMDA-receptor function (Tsai & Coyle, 2002); therefore, it is reasonable to predict that individuals with ASCs may also show reduced LTP-like changes compared to neurotypical individuals following visual HFS. Furthermore, Çavuş et al. also demonstrated that greater HFS-driven VSSR power was also associated with greater N1b potentiation for neurotypical participants, but not for schizophrenic participants. However, the results of the previous study (Chapter 4) failed to find any significant relationship between HFS-driven VSSR power and degree of potentiation for healthy adults and adolescents. Consequently, one of the planned analyses was to examine the relationship between HFS-driven VSSR power and degree of VEP change, but no predictions were made regarding directional effects due to inconsitency of findings in previous research.

As well as the observable symptoms of ASC (such as impaired social interaction, language and communication), unusual subjective sensory and perceptual experiences (such as hyper- and hypo-sensitivity to sensory stimuli) are increasingly being recognised as key features of ASCs. Accordingly, there is increasing research interest in sensory abnormalities in ASC, with the hope that assessing sensory experiences in ASCs may offer a second source of information (alongside the current assessment of behaviour) that could optimize the diagnosis of ASCs (Horder et al., 2014). For example, Robertson & Simmons (2013) reported significant linear correlations between GSQ measures and self-reported ASC symptoms (in individuals both with and without a diagnosis of ASC). Building on the work of Robertson and Simmons, Horder and colleagues (2014) replicated findings demonstrating associations between ASC symptoms and GSQ measures, but also with two other sensory measures, the AASP (Dunn, 1999) and the Cardiff Anomalous Perception Scale Crane (Bell, Halligan, & Ellis, 2006) in individuals with and without diagnosis of ASCs. In addition, these associations could not be accounted for by potential confounds such as mental illness, migraines, and family history of ASCs. Goddard, & Pring (2009) used the AASP to assess sensory processing in adults with ASCs, and found that over 90% of participants reported sensory abnormalities on at least one sensory quadrant. Furthermore, there were striking within-group differences, demonstrating that people with ASCs can experience very different, but equally severe, sensory processing difficulties. Given the heterogeneous nature of sensory responsivity differences in ASCs, it is important to first understand the neural underpinnings of basic sensory processing in ASCs.

The second aim of this study was to determine whether possible differences in plasticity between ASC and NT adults may also help to explain why autistic people are more likely to exhibit atypical responses to sensory stimuli in the environment. As was previously outlined in

Chapter 4.1, there is evidence demonstrating how sensory stimulation can alter future perceptions of sensory stimuli. For example, Heynen and Bear (2001) showed that LTP induction in adult rats lead to an enhanced cortical visual response to a full field flash, and that responses to grating stimuli were increased across a range of spatial frequencies. Similarly, in human adults, Clapp et al. (2012) found evidence to suggest that high frequency visual stimulation not only resulted in detectable LTP in the visual cortex but also a parallel improvement in visual detection thresholds. Based on these findings, it seems plausible to suggest that individual differences in sensory responsivity may (in part) be due to previous sensory experiences that have altered neurological thresholds. Consequently, the present study aimed to examine whether heightened sensory responses (as measured by VEP amplitude) are related to self-reported sensory responsivity. Following from this, it was also predicted that participants with higher levels of sensory responsivity would show less change in VEP amplitude following HFS, compared to participants with lower levels of sensory responsivity, because they are closer to ceiling effects due to prior tetanization from sensory experiences.

5.1.1. Aims of the present study

As in the previous chapter, this study will again employ the visual cortical plasticity paradigm, which has been shown to successfully induce LTP-like changes to VEPs with high frequency visual stimulation, in order to examine neuroplasticty in ASCs. Based on the research discussed above, demonstrating impairment in NMDA-R functioning in ASC, it was hypothesized that visual plasticity would be reduced in adults with ASCs compared to neurotypical adults, as reflected by smaller potentiation of the N1 following visual HFS. It was also predicted that autistic adults would have a similar visual steady state response (VSSR) to neurotypical participants in response to the tetanizing HFS, indicating that their reduced potentiation is not due to reduced attention to the tetanus (the visual HFS). The relationship between HFS-driven VSSR power and degree of VEP change will also be examined, although due to conflicting findings in previous research, no predictions about this relationship are made.

This study also aimed to test the hypotheses that 1) sensory responsivity scores would be more extreme in autistic participants, compared to NT participants; 2) participants with higher sensory responsivity scores would exhibit greater VEPs in response to baseline stimuli (in accordance with Dunn's (1999) theory of sensory processing style, and evidence demonstrating tetanization from previous sensory experiences (Clapp, Hamm, Kirk, & Teyler, 2012b; Heynen & Bear, 2001)); and 3) assuming that participants with higher levels of sensory responsivity show a potentiated response to baseline stimuli, it was predicted that they would also show less change in VEP amplitude following HFS compared to those with lower sensory responsivity scores.

5.2. Method

5.2.1. Participants

Participants were recruited through Sheffield Autism Research Lab's participant database, as well as through advertisements on social media and emails to the university's volunteer's lists. Anyone who indicated that they were currently taking anti-depressants, sedatives, or other medications with psychoactive properties was not invited to take part. Participants with ASCs were asked to provide details of the clinic/clinician who gave their ASC diagnosis, and how old there were when they received the diagnosis to ensure that they had received a clinical diagnosis of an ASC from a certified health professional. All participants were paid to compensate them for their time.

In total, 32 participants took part in the study (16 ASC and 16 NT) with both groups matched on age and gender; however, data from one NT participant was removed from analyses as there was evidence to suggest they did not adequately receive the tetanizing stimulation from the visual HFS (this was based on visual inspection of the participants' spectral plot, which showed no peak at the tetanizing frequency, or corresponding harmonics), most likely as a result of not looking at the screen for long enough. Participant demographic information for the 31 participants included in analyses is presented in Table 5.1.

Table 5.1
Demographic Information

Variable		Group	
		ASC	Neurotypical
N		16	15
Gender	Female	5	5
	Male	9	10
	Binary	2	-
Age (years)	*M*	37.88	38.73
	Range	19 – 67	20 – 66
Age at time of diagnosis (years)	*M*	29.93	-
	Range	3 – 61	-

5.2.2. Experimental paradigm

Participants first completed several questionnaire measures (see section 4.2.3 for more details). Following that, the EEG cap and sensors were set up (see section 2.3.1. for more details). Participants then started the Visual Cortical Plasticity paradigm (Figure 5.1). A more detailed description of this paradigm can be found in Chapter 2.4.1.

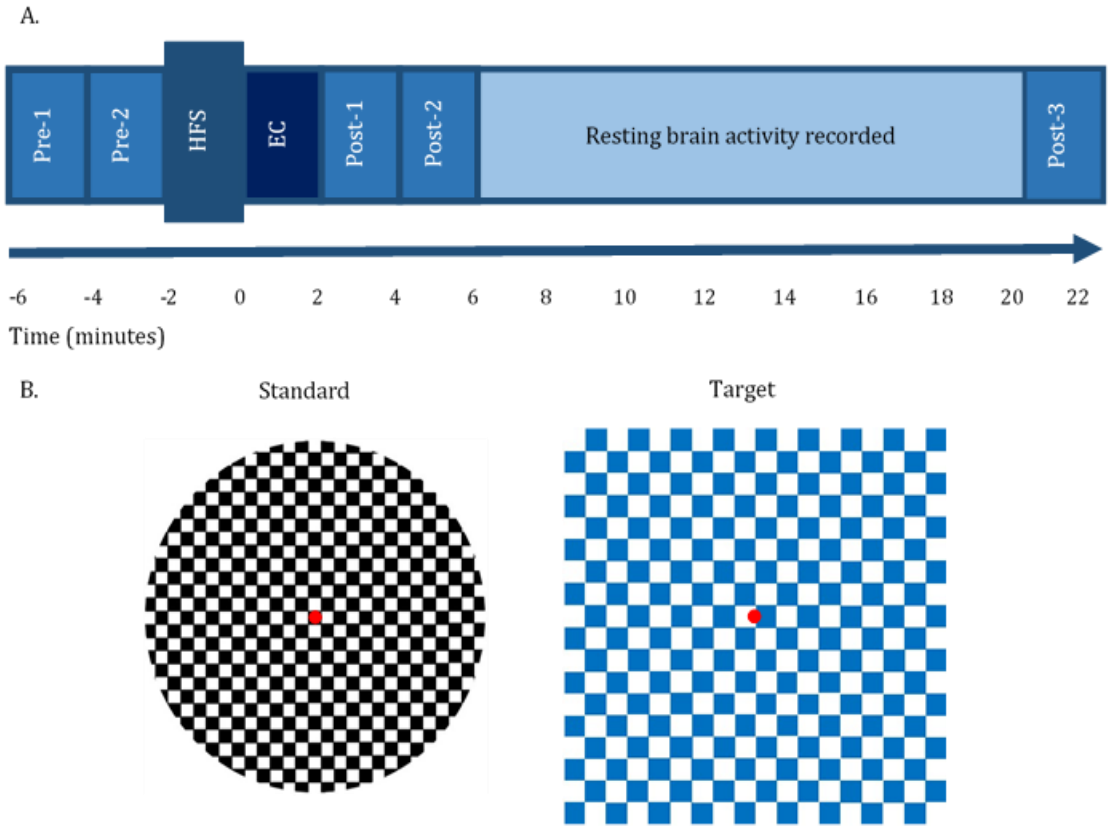


Figure 5.1. Visual Cortical Plasticity Paradigm: timeline and stimuli. During VEP assessment blocks (Pre-1, Pre-2, Post-1, Post-2, and Post-3), participants are asked to maintain focus on a red central fixation dot whilst the frequently presented standard circle (90% of trials; Figure 4.1.B Left) or infrequently presented target square (10% of trials; Figure 4.1.B Right) is shown centrally (~0.83Hz). To monitor attention and provide further focus, participants are asked to press the spacebar every time the target square appears. During the HFS block, designed to induce potentiation, participants are asked to maintain focus on the central fixation dot as the standard circle is repeatedly presented at ~8.87Hz for 2 minutes. Participants closed their eyes for 2 minutes following HFS (EC). Resting data was collected during the interval between Post-2 and Post-3.

5.2.3. EEG Processing and Analysis

5.2.3.1. EEG Processing

See Chapter 2.3.1 for more information about the EEG acquisition and processing.

5.2.3.2. Selecting Time Windows for EEG analysis

Grand-grand averaged ERPs were calculated by collapsing data across all groups and conditions, and time windows selected based on what best captures each ERP component in the collapsed average. The grand-grand averaged VEPS for posterior electrode sites are presented in Figure 4.3. Based on these collapsed averages, three time windows were selected based around the N1 (90-150ms) and the P2 (150-270ms). This method of selecting time windows for analysis ensures that the ERP component is captured without biasing the selection to the part of

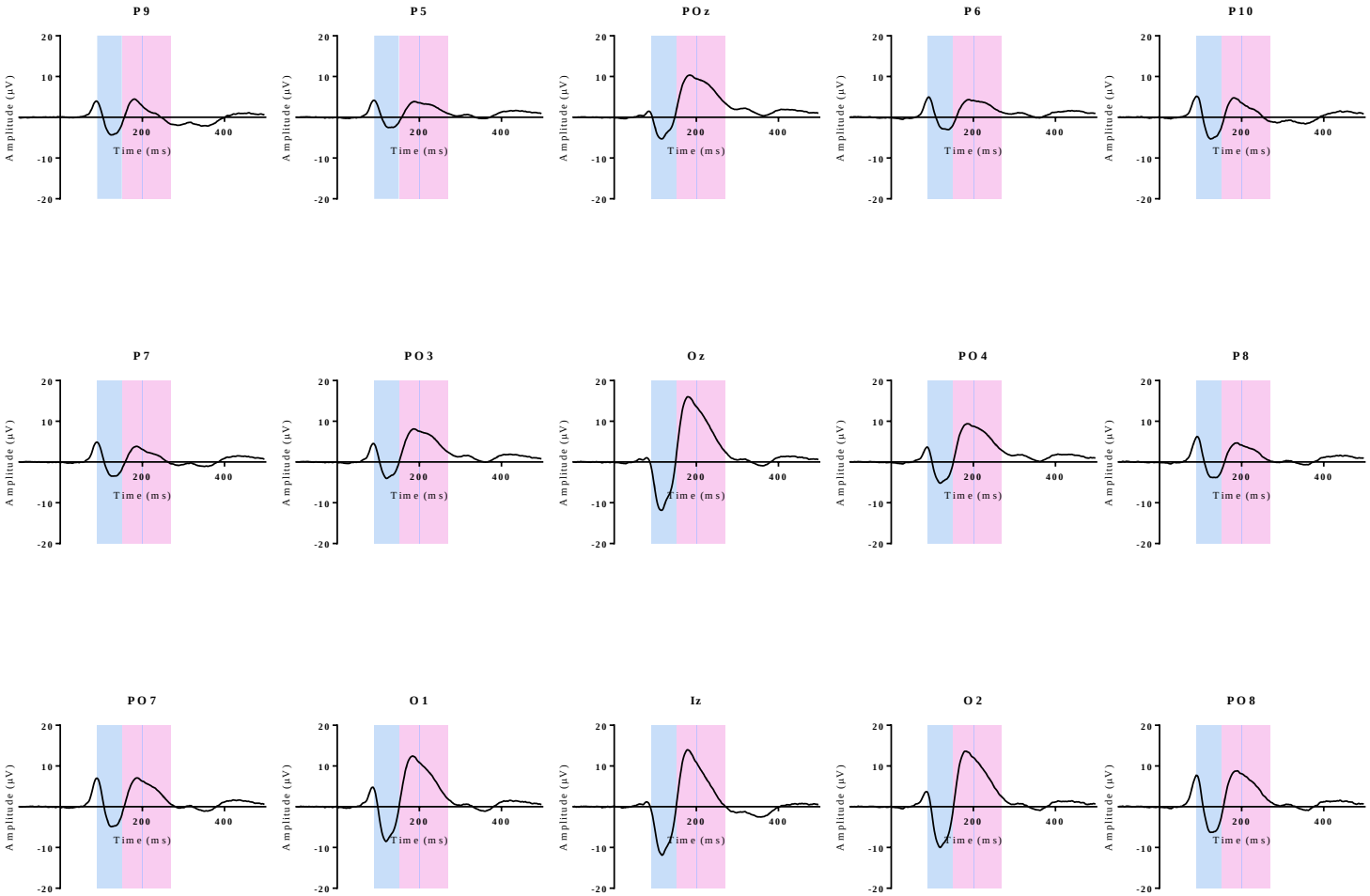


Figure 5.2. Grand-grand averaged visual evoked potentials (VEPs) from posterior electrodes, used to select time windows used in statistical analyses of VEP components. The two different coloured columns represent the time windows selected around the N1 and P2 VEP components for analyses (N1 blue column = 90-150ms; P2 pink column = 150-270ms).

the waveform that shows the biggest difference between groups/conditions (Luck, 2014). Previous research (Chapter 4) showed no effect of visual HFS on the P1, therefore it is not examined in the present study.

5.2.3.3. Selecting Electrodes for EEG Analysis

The grand-averaged waveforms and scalp topographies (Figure 5.4) were visually examined to assess where maximal activity was observed. Both the scalp topographies and grand-averaged ERP waveforms indicated overall maximal activity at occipital sites; therefore, an occipital cluster was selected, averaging data across electrodes Oz, Iz, O1 and O2. This is the same as the cluster of electrodes that were selected for analyses in the previous chapter, again, allowing for easier comparison of results between the two studies.

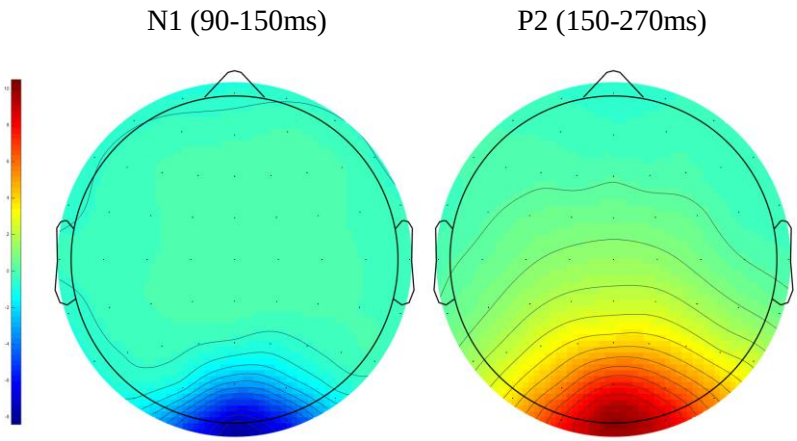


Figure 5.3. Scalp topographies depicting mean amplitude across N1 and P2 time windows for data averaged across all participants (N = 31) and all VEP assessments (Pre-1, Pre-2, Post-1, Post-2, and Post-3).

5.2.4. Questionnaire Measures

5.2.4.1. Adolescent Adult Sensory Profile (AASP)

See Chapter 2.3.2.3 for more information about this questionnaire.

5.2.4.2. Glasgow Sensory Questionnaire (GSQ)

See Chapter 2.3.2.4 for more information about this questionnaire.

5.2.4.3. Depression Anxiety and Stress Scale (short-form version; DASS-21)

See Chapter 2.3.2.5 for more information about this questionnaire.

5.2.4.4. Social Responsiveness Scale (SRS-2)

The Social Responsiveness Scale, Second Edition (SRS-2; Constantino & Gruber, 2012) is a 65-item, Likert-scale, self-report measure of symptoms associated with autism. It covers the various dimensions of interpersonal behaviour, communication, and repetitive/stereotypic behaviour that are characteristic of ASCs. Thirty-five items on the SRS-2 relate to the social impairment criteria for autism, described in the DSM-IV. More specifically, these questions aim to capture the four basic elements of reciprocal social behaviour: (1) the extent to which the individual recognises social cues, (2) the individual's capacity for appropriately interpreting those cues, (3) the individuals' capacity to appropriately respond to those cues, and (4) the individuals' general tendency to engage socially. Examples of questions capturing social behaviour include "I have trouble keeping up with the flow of a normal conversation", "I am regarded by others as weird or odd", and "I avoid eye contact or am told that I have unusual eye contact". Twenty items on the SRS-2 relate to stereotypic behaviours and restricted interests (*e.g.* "I have repetitive behaviours that others consider odd", "I can't get my mind off something once I start thinking about it"). Six items capture communication difficulties (*e.g.* "I take things too literally, and because of that, I misinterpret the intended meanings of parts of a conversation"). Finally, five items aim to capture miscellaneous symptoms frequently associated with autism, but also commonly observed in other psychological or neurodevelopmental disorders *(e.g.* "I am not well coordinated"). Participants respond to items on a 4-point scale, ranging from "Not True" to "Almost Always True".

Five scales can be derived from the SRS-2 questionnaire that assess the social and behavioural aspects of ASC. (1) Social Awareness measures the individual's ability to pick up on social cues and represents the sensory aspects of reciprocal social behaviour (8 items). (2) Social Cognition measures the individual's ability to interpret social cues once they are picked up and represents the cognitive-interpretive aspects of reciprocal social behaviour (12 items). (3) Social Communication includes expressive social communication and captures the "motoric" aspects of reciprocal social behaviour (22 items). (4) Social Motivation measures the extent to which an individual is motivated to engage in social interpersonal behaviour, with elements of social anxiety, inhibition and empathic orientation also included in these items (11 items). Finally, (5) Restricted Interests and Repetitive Behaviour includes stereotypical behaviours or highly restricted interests that are characteristic of autism (12 items). On all scales, higher scores indicate more impairment or deficits in reciprocal social behaviour.

Raw scores for each scale, and the total raw score for all 65 items, can be converted into T-scores that are based on ratings collected in a nationally representative standardization sample. The T-score values are most often used when using the SRS-2 in clinical or school practice settings, when the main aim is to assess the extent of social communication deficit in

the observed individual. However, in research studies, where the main aim is often concerning group characteristics, raw summed scores tend to be used. Consequently, the raw summed scores for the SRS-2 scales were used in this study.

5.2.4.5. Wechsler Abbreviated Scale of Intelligence (2-Subtest Version)

The Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) was developed as a short and reliable measure of intelligence, for use in clinical, psychoeducational, and research settings. For the purposes of this study, only two subtests of the WASI were administered (Vocabulary and Matrix Reasoning) as a means for estimating general cognitive functioning of participants. The WASI Vocabulary subtest is a 42-item task where participants are orally and visually presented with words that the participant orally defines. The participants definition is then scored (up to 2 points per item) based on how accurate their definition is. The Matrix Reasoning subtest is a series of 35 incomplete gridded patterns that the participant completes by selecting one of 5 possible choices presented below, with 1 point collected for each correct answer. The Vocabulary test aims to measure verbal ability, whereas the Matrix Reasoning test aims to measure non-verbal fluid reasoning.

Age-corrected T-scores are then calculated from the summed sub-test raw scores. T-scores are used because they have a wider range of score points and can therefore better differentiate the levels of ability reflected by the subtest raw scores. Combining the Vocabulary and Matrix Reasoning T-scores allows for estimation of the participants IQ score, by referring to a conversion table provided in the WASI manual. Use of the WASI in this study allows for comparison of intellectual ability between ASC and NT participants, to ensure that both groups are equally matched as far as possible.

5.2.5. Statistical Analyses

Detailed descriptions of planned analyses conducted in this chapter, and justifications for why these analyses were conducted, are provided in Chapter 2.4.2.

5.3. Results

Analyses directly relating to hypotheses outlined in the introduction are clearly indicated by their sub-heading. All other analyses, although not directly related to the hypotheses outlined in the introduction, still assess important group differences that may affect interpretation of other analyses. Summary of the key findings are presented at the end of this results section in Tables 5.7 and 5.8.

5.3.1. Visual Evoked Potential Analyses

5.3.1.1. Assessing differences between baseline VEP assessments

A 3-way mixed ANOVA was conducted to determine if there were any differences in mean amplitude between the two pre-HFS VEP assessments (pre-HFS 1 and pre-HFS 2), between the 2 participant groups (ASC and NT) at the occipital electrode cluster location for each VEP component under investigation (N1 and P2). The Shapiro-Wilk tests indicated that the assumption of normality had been met for all cells of the design apart from mean P2 amplitudes measured for NT participants during pre-HFS 1 (p = .026) and pre-HFS 2 (p = .041). However, ANOVAs are robust to violations of normality when sample sizes are roughly equal, so the analysis was run as planned. Two extreme outliers from the NT group were identified, as assessed by inspection of a boxplot, but they were kept in analyses as they did not materially affect the outcome, as assessed by comparison of results with and without the outliers.

The results of the ANOVA showed that there was no significant three-way interaction between pre-HFS VEP assessment, ERP component, and participant group, F (1, 29) = .00, p = .966, η_p^2 = .000. There was also no significant two-way interaction between pre-HFS assessment and participant group, F (1, 29) = .18, p = .678, η_p^2 = .006. There was, however, a significant two-way interaction between pre-HFS assessment and ERP component, F (1, 29) = 36.68, p < .001, η_p^2 = .572. BH-corrected pairwise comparisons revealed that there were no significant differences between mean N1 amplitudes measured during pre-HFS 1 and pre-HFS 2 (pre-HFS 1 M = -5.73, SE = 1.08; pre-HFS 2 M = -6.18, SE = 1.22; p = .154). However, mean P2 amplitude was significantly greater in pre-HFS 2 compared to pre-HFS 1 (pre-HFS 1 M = 7.36, SE = 1.01; pre-HFS 2 M = 8.96, SE = 1.00; p < .001). Consequently, as in Chapter 4, rather than including the mean of both Pre-HFS blocks, all subsequent analyses will compare Post-HFS blocks to mean amplitudes recorded only during Pre-HFS 2 (which will be known as ‘baseline’ from hereon).

5.3.1.2. Grand-averaged ERPs and scalp topographies

Grand average VEPs for pre- and post-HFS assessments in ASC and NT groups are presented in Figure 5.6 and Figure 5.7 respectively. The grand-averaged scalp topographies for mean amplitude across the ERP time windows for ASC and NT participants are presented in Figure 5.8 and Figure 5.9 respectively.

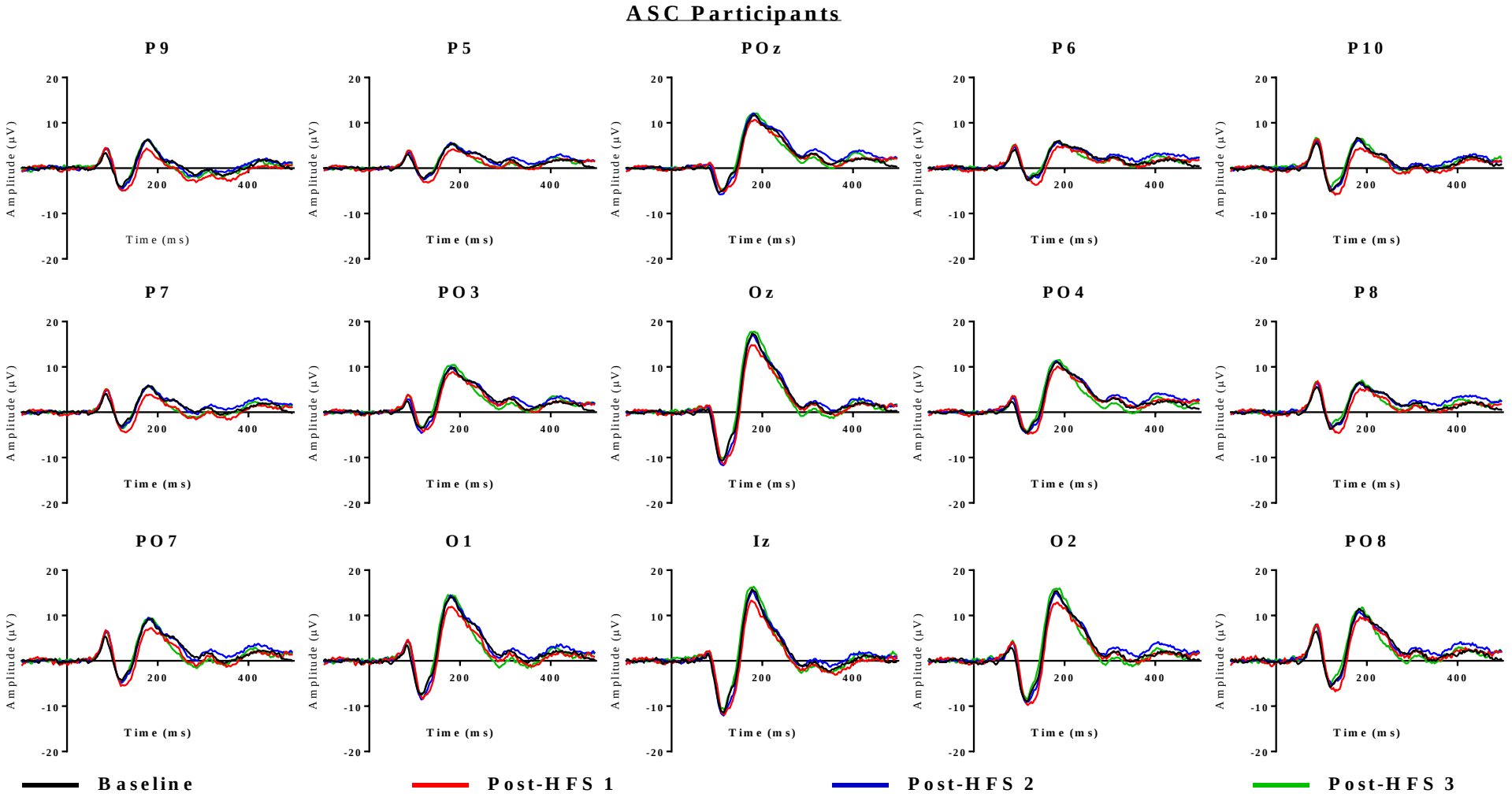


Figure 5.4. Grand-averaged visual evoked potentials (VEPs) elicited by the standard circle for ASC participants (N = 16) across posterior electrode sites and VEP assessments: Baseline (4-2 minutes before HFS; black line), Post-HFS 1 (2-4 minutes post-HFS; red line), Post-HFS 2 (4-6 minutes post-HFS; blue line), and Post-HFS 3 (20-22 minutes post-HFS; green line).

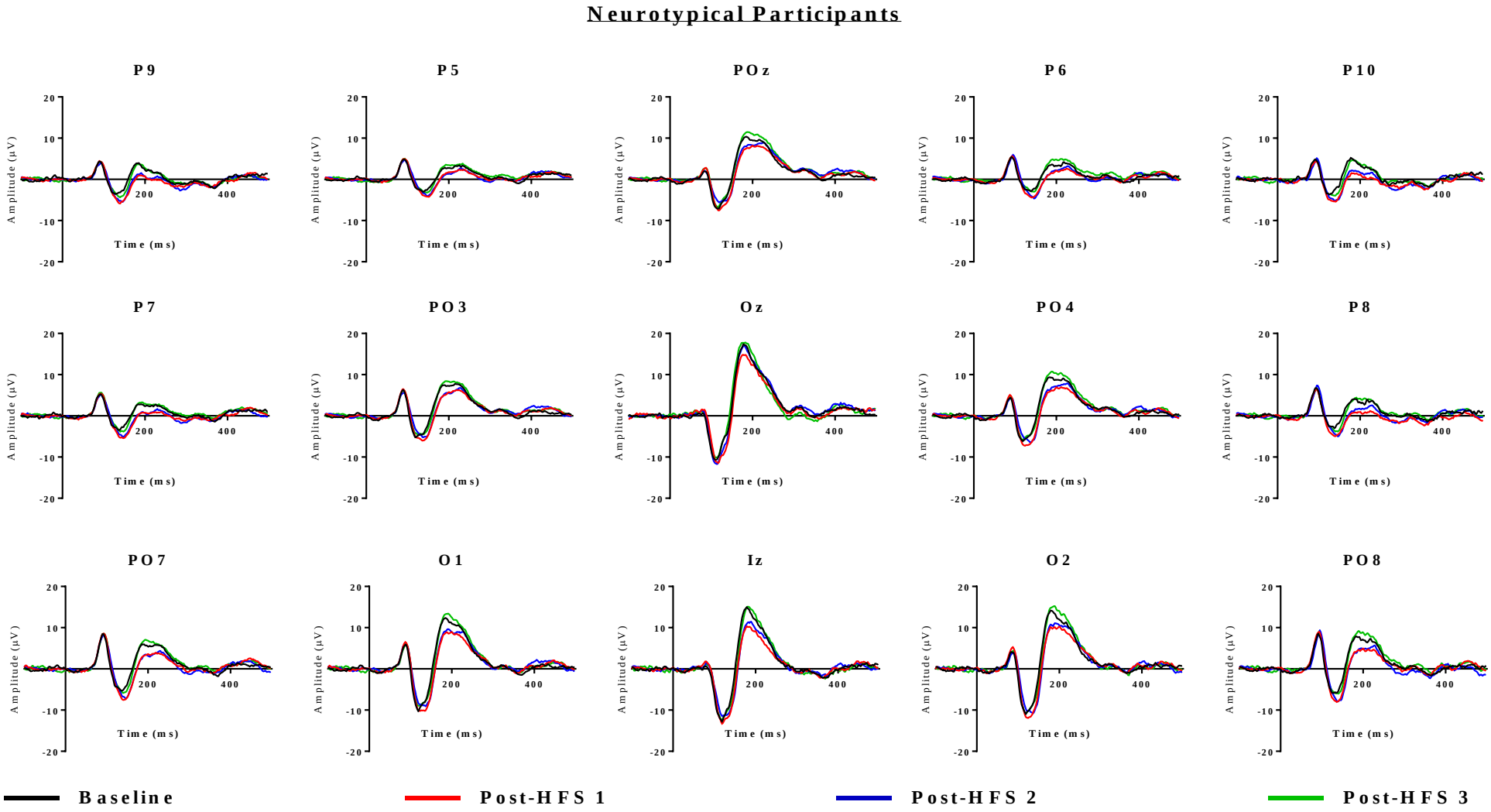


Figure 5.5. Grand-averaged visual evoked potentials (VEPs) elicited by the standard circle for NT participants (N = 15) across posterior electrode sites and VEP assessments: Baseline (4-2 minutes before HFS; black line), Post-HFS 1 (2-4 minutes post-HFS; red line), Post-HFS 2 (4-6 minutes post-HFS; blue line), and Post-HFS 3 (20-22 minutes post-HFS; green line).

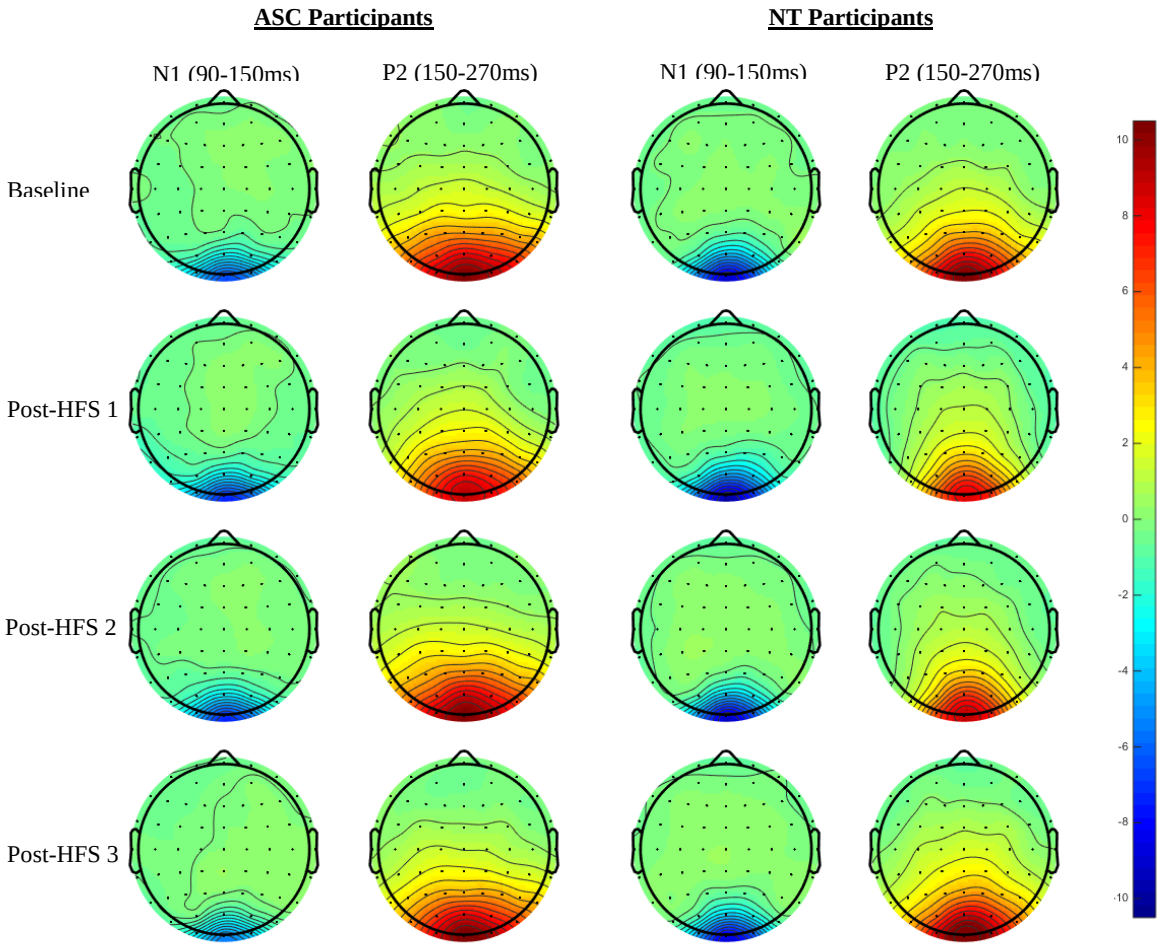


Figure 5.6. Scalp topographies depicting mean N1 and P2 amplitude grand-averaged data in VEP assessments (Baseline, Post-1, Post-2, and Post-3) for participants with autism spectrum conditions (ASC) and neurotypical (NT) participants. Colour scale is standardized across both ASC and NT groups.

5.3.1.3. Assessing the effect of visual-HFS on VEP components in ASCs

A three-way mixed ANOVA was conducted to determine the effect of group (ASC and NT), VEP assessment (baseline, Post-1, Post-2, and Post-3), and ERP component (N1 and P2) on mean amplitude observed over the occipital cluster. Prior to running the ANOVA, exploration of the data revealed that the assumption of normality had been violated for two cells of the design. However, ANOVA's are robust to violations of normality when sample sizes are roughly equal, so the analyses was run as planned. Two extreme outliers from the NT group were identified with mean baseline P2 amplitudes baseline above the group mean (1.92 and 2.34 *SD* above the group mean respectively), as assessed by inspection of a boxplot. Removal of these outliers did not materially affect the outcome the ANOVA, as assessed by analyses with and without the outliers, so they were kept in the analysis.

Results of the ANOVA revealed that there was no statistically significant three-way interaction effect between group, VEP assessment, and ERP component, F (1.84, 13.67) = 2.61, p = .087, η_p^2 = .083. There were also no statistically significant two-way interactions between ERP component and group (F (1, 29) = .08, p = .782, η_p^2 =.003), or between VEP assessment and ERP component (F (1.84, 53.37) = 1.13, p = .327, η_p^2 =.037). There was no significant main effect of group (F (1, 29) = .72, p = .402, η_p^2 =.024).

There was a significant main effect of VEP assessment on overall mean amplitude (F (2.54, 73.56) = 10.16, p < .001, η_p^2 =.259). BH-corrected pairwise comparisons revealed that compared to baseline (M = 1.39, SE = .77), overall mean amplitude (across both the N1 and P2) was significantly reduced during post-HFS 1 (M = .12, SE = .77, p < .001), but there were no significant differences from baseline values during post-HFS 2 (M = .88, SE = .84, p = .116) or post-HFS 3 (M = 1.92, SE = .72, p = .174). When comparing post-HFS measures, mean amplitude was significantly reduced in post-HFS 1 compared to post-HFS 2 (p = .004) and post-HFS 3 (p < .001). Similarly, mean amplitudes measured during post-HFS 2 were significantly reduced compared to those measured in post-HFS 3 (p = .013). Collectively, these results suggest that visual HFS lead to a short-term reduction in mean amplitude of both the N1 and P2 in both groups of participants, but mean amplitudes were not significantly different from baseline from post-HFS 2 onwards.

There was also a significant main effect of ERP component (F (1, 29) = 83.94, p < .001, η_p^2 =.743), whereby mean amplitudes measured over the N1 time window (M = -6.25, SE = 1.14) were significantly negative in polarity compared to mean amplitudes measured over the P2 time window (M = 8.40, SE = 1.04) that were much more positive (p < .001), which is to be expected.

Together, these results suggest that there were no significant differences in VEPs between NT and ASC participants. Furthermore, visual HFS did not lead to any long-term changes in VEP for either group, although there were significant short-term changes to VEPs for both groups. ERPs for both ASC and NT participants are presented in Figure 5.7. Mean N1 and P2 amplitudes for each group are also presented graphically (with 95% confidence intervals) in Figure 5.8.

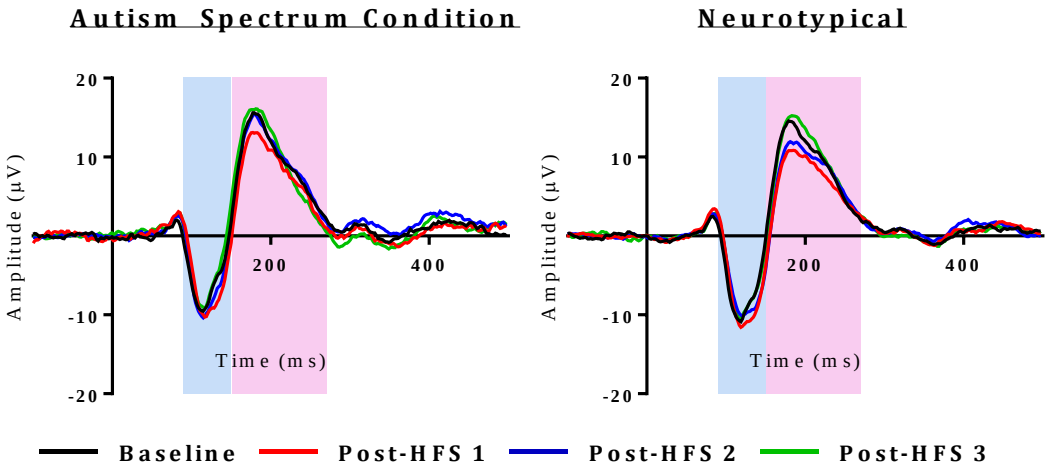


Figure 5.7. Grand-averaged visual evoked potentials (VEPs) elicited by the standard circle for ASC participants (N = 16) and NT participants (N = 15) over the occipital electrodes cluster (Oz, Iz, O1, and O2) for all VEP assessments: Baseline (4-2 minutes before HFS; black line), Post-HFS 1 (2-4 minutes post-HFS; red line), Post-HFS 2 (4-6 minutes post-HFS; blue line), and Post-HFS 3 (20-22 minutes post-HFS; green line).

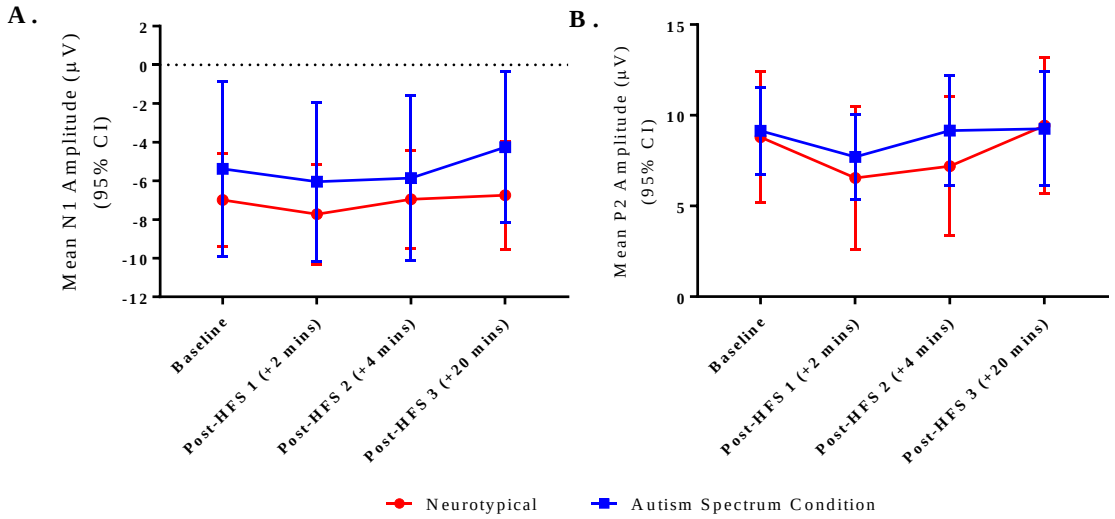


Figure 5.8. **A**: Mean N1 amplitude for each VEP assessment (baseline, post-HFS 1, post-HFS 2, post-HFS 3) and group (neurotypical participants (red); participants with autism spectrum conditions (blue)). **B:** Mean P2 amplitude for each VEP assessment and each group. Error bars show 95% confidence intervals.

5.3.2. Hypothesis: There will be no group differences in HFS-driven VSSR power.

To examine whether there were differences between ASC and NT participants in the tetanizing effect of the visual HFS, and power spectra of EEG recorded during HFS were calculated (see Chapter 2.3.1.3 for more information). A summary VSSR power measure was derived by averaging parieto-occipital channels where the VSSR response was largest (Oz, Iz, O1, O2, POz, PO7, PO8, PO3, PO4). The power spectra for this averaged cluster is presented in Figure 5.9, and demonstrates that HFS-driven VSSR was observed, as evident in the peak power value at 9Hz (the frequency bin closest to the HFS frequency of ~8.87Hz).

The 9Hz VSSR power values (μV^2/Hz) were positively skewed, therefore a non-parametric Mann-Whitney U test was run to determine if there were any group differences in HFS-driven VSSR power. Three extreme outliers were identified, through inspection of boxplots, but they were kept in analyses as they didn't materially affect the results, as assessed by comparison of results with and without the outliers. Results found that HFS-driven VSSR power was not significantly different between ASC participants (median = 18.57) and NT participants (median = 17.82), U= 135, z = .59, p = .572. Therefore, there were no group differences in the tetanizing effect of visual HFS for ASC and NT participants.

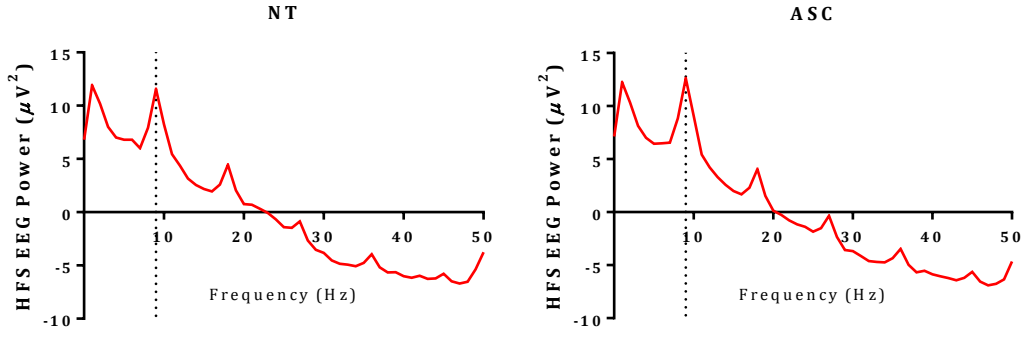


Figure 5.9. Power spectra of EEG recorded during HFS. These spectra represent data averaged across posterior electrode sites (Oz, Iz, O1, O2, POz, PO7, PO8, PO3, PO4), where VSSR response was largest. The VSSR is evident in these spectra as a peak power value at 9Hz. NT = Neurotypical group; ASC = Autism spectrum conditions group.

5.3.2.1. Hypothesis: HFS-driven VSSR power predicts degree of VEP change

Given that previous analyses (section 5.3.1.3) had shown that neither ASC or NT participants showed any significant long-term effects changes to VEP amplitude following visual HFS, it was no longer appropriate to test the relationship between HFS-driven VSSR power and VEP change in this study.

5.3.3. Assessing group differences in number of trials and EEG channels removed during processing of EEG data

5.3.3.1. Number of trials removed during EEG processing

A two-way mixed methods ANOVA was conducted between group and VEP assessment on total number of standard circle trials included after EEG processing. One significant outlier was detected (an ASC participant who had 69 trials included in the baseline VEP assessment, which is 1.63 SD below group mean), as assessed by inspection of a boxplot. The interaction effect and main effect of group were unaffected by inclusion or exclusion of the outlier, however the main effect of VEP assessment was significant when the outlier was included (F (1.74, 50.54) = 3.54, p = .042, η_p^2= .109) but was not significant after they were removed (F (2.24, 62.60) = 2.80, p = .063, η_p^2= .091); consequently, the more conservative approach was to continue with the analyses after removing the outlier.

There was no statistically significant interaction between group and VEP assessment on total number of standard circle trials remaining after pre-processing of EEG data (F (2.24, 62.60) = .88, p = .432, η_p^2= .030). There was also no significant main effect of group (F (1, 28) = .01, p = .906, η_p^2= .001). Together, these results show that number of trials removed due to noise during the pre-processing of EEG data was comparable across groups and blocks. Descriptive statistics for number of standard circle trials included in each block are included in Table 5.2.

Table 5.2.

Mean number of standard circle trials in each block for each group (*SD*)

Block	ASC	NT
Baseline	84.80 (3.84)	83.73 (6.09)
Post-HFS 1	85.20 (3.65)	86.53 (3.23)
Post-HFS 2	86.53 (2.95)	86.40 (3.20)
Post-HFS 3	85.60 (4.00)	84.93 (4.54)

Note. Maximum of 90 standard circle trials per block. ASC n = 15. NT n = 15.

5.3.3.2. No significant differences in number of channels removed between groups

Results of a Mann-Whitney U test concluded that there were no significant differences between ASC and NT groups in the number of channels removed during pre-processing of EEG data, U = 158.00, z = 1.51, p = .140. On average, 6 channels were removed per participant during pre-processing (min = 0, max = 13).

5.3.4. Task performance

5.3.4.1. Response Accuracy to Oddball Targets

To assess if group differences in VEP amplitude could be due to group differences in attention (as measured by task performance), Mann-Whitney U analyses were run to compare response accuracy at each block between ASC and NT participants. Results revealed that there were no statistically significant differences between the two groups across any of the blocks (all *p*'s > .05). To assess whether there was an effect of block on response accuracy, a related-samples Friedman's ANOVA by Ranks was conducted. The results showed that there was no statistically significant effect of block on response accuracy to oddball targets, χ^2 (3) = 1.35, *p* = .719. Descriptive statistics for response accuracy data is presented in Table 5.7.

5.3.4.2. Reaction Times to Oddball Targets

A two-way ANOVA was run to determine if there were any differences in reaction time across the blocks, and between ASC and NT groups. Descriptive statistics for reaction time data is presented in Table 5.7.

The results of the ANOVA found that there was no significant interaction between group and block, *F* (3, 87) = .82, *p* = .488, η_p^2= .027. There was also no significant main effect of group, *F* (1, 29) = .08, *p* = .784, η_p^2= .003, indicating that ASC and NT participants had similar reaction times when responding to the target square. However, a significant main effect of block was found, *F* (3, 87) = 10.15, *p* < .001, η_p^2= .259. BH-corrected pairwise comparisons showed that reaction times were significantly quicker during baseline, compared to reaction times measured at Post-1 (*p* = .003), Post-2 (*p* < .001) and Post-3 (*p* < .001). No significant differences were found between reaction times measured in Post-HFS blocks (*p* > .10). In summary, both ASC and NT participants' reaction times to the target square were quickest at baseline and were slower following HFS.

Table 5.3.
Descriptive statistics for reaction times (s) and response accuracy to target square stimulus

Block	Mean RT	SE	Accuracy (%)	SD
Baseline (-2 mins)	.338	.008	99.03	.40
Post-HFS 1 (+2 mins)	.352	.009	99.03	.40
Post-HFS 2 (+4 mins)	.356	.009	99.68	.18
Post-HFS 3 (+20 mins)	.359	.010	99.36	.25

5.3.5. Questionnaire analyses

Descriptive statistics for all questionnaire scales are presented in Table 5.4.

Table 5.4.
Descriptive statistics and Cronbach's alpha for the AASP, DASS-21, GSQ, and SRS-2 questionnaire scales

Group	Questionnaire	Scale	Mean	SD	Min	Max	α
ASC (*n* = 16)	AASP	Low Registration	39.56	7.16	25	53	.73
		Sensation Seeking	41.25	5.47	32	54	.42
		Sensory Sensitivity	46.38	8.05	35	66	.71
		Sensation Avoiding	49.25	10.58	30	64	.87
	DASS-21	Depression	5.50	4.18	0	14	.86
		Anxiety	4.50	3.20	0	11	.76
		Stress	9.56	3.92	3	18	.75
	GSQ	Hyper-responsivity to visual stimuli	36.31	13.18	16	65	.90
		Hypo-responsivity to visual stimuli	29.13	7.66	14	42	.68
		Total GSQ Score	65.44	19.31	30	95	.90
	SRS-2	Social Awareness	11.06	2.74	7	16	.25
		Social Cognition	16.81	6.09	5	25	.83
		Social Communication	30.75	10.04	13	48	.86
		Social Motivation	19.38	6.53	3	28	.87
		Restricted Interests and Repetitive Behaviour	17.75	6.33	7	30	.83
		Total SRS Score	95.75	25.34	49	135	.94
NT (*n* = 15)	AASP	Low Registration	31.47	6.86	19	45	.76
		Sensation Seeking	48.07	5.59	41	58	.59
		Sensory Sensitivity	36.00	7.92	25	51	.81
		Sensation Avoiding	35.33	6.83	22	47	.75
	DASS-21	Depression	3.60	3.79	0	13	.89
		Anxiety	2.13	2.20	0	7	.64
		Stress	4.80	4.48	0	16	.93
	GSQ	Hyper-responsivity to visual stimuli	19.53	6.94	7	31	.71
		Hypo-responsivity to visual stimuli	18.40	6.00	6	27	.61
		Total GSQ Score	37.93	11.94	16	58	.82
	SRS-2	Social Awareness	4.87	2.53	0	9	.54
		Social Cognition	6.60	3.96	0	16	.77
		Social Communication	11.80	6.87	2	26	.82
		Social Motivation	9.47	5.64	3	23	.90
		Restricted Interest and Repetitive Behaviour	5.67	3.54	1	13	.79
		Total SRS Score	38.40	18.83	8	70	.94

Note: *SD* = standard deviation; Min = minimum observed score; Max = maximum observed score; α = Cronbach's alpha value; AASP = Adolescent-Adult Sensory Profile; DASS-21 = Depression Anxiety Stress Scale (short form version); GSQ = Glasgow Sensory Questionnaire; SRS-2 = Social Responsiveness Scale (Second Edition).

5.3.5.1. Internal Reliability of Questionnaires

Before addressing whether cortical plasticity is associated with sensory responsivity, it was first important to examine how reliable the questionnaires used to assess sensory responsivity (and other associated variables) in our sample were. Cronbach's alpha values for each scale are presented in Table 5.4. Notably, the Social Awareness scale from the SRS-2, and the Sensation Seeking scale from the AASP had low Cronbach's alpha values for both ASC and NT groups, suggesting poor internal reliability for these scales. However, overall, most scales had acceptable Cronbach's alpha values in both groups.

5.3.5.2. Group differences in questionnaire measures

5.3.5.2.1. Hypothesis: Sensory responsivity will be more extreme in individuals with ASC

Independent measures t-tests were run for GSQ scales assessing responsivity to visual stimuli, as well as general hyper-and hypo-sensitivity to sensory stimuli, and total GSQ score. ASC participants scored significantly higher than NT participants on all GSQ measures: responsivity to visual stimuli [t (24.58) = 3.73, p = .001], hyper-sensitivity to sensory stimuli in general [t (23.02) = 4.47, p < .001], hypo-sensitivity to sensory stimuli in general [t (29) = 4.32, p < .001], and total GSQ score [t (25.23) = 4.80, p < .001] (see Figure 5.10). Together, these results demonstrate that ASC participants have more extreme responses to visual stimuli, and sensory stimuli in general, compared to NT participants.

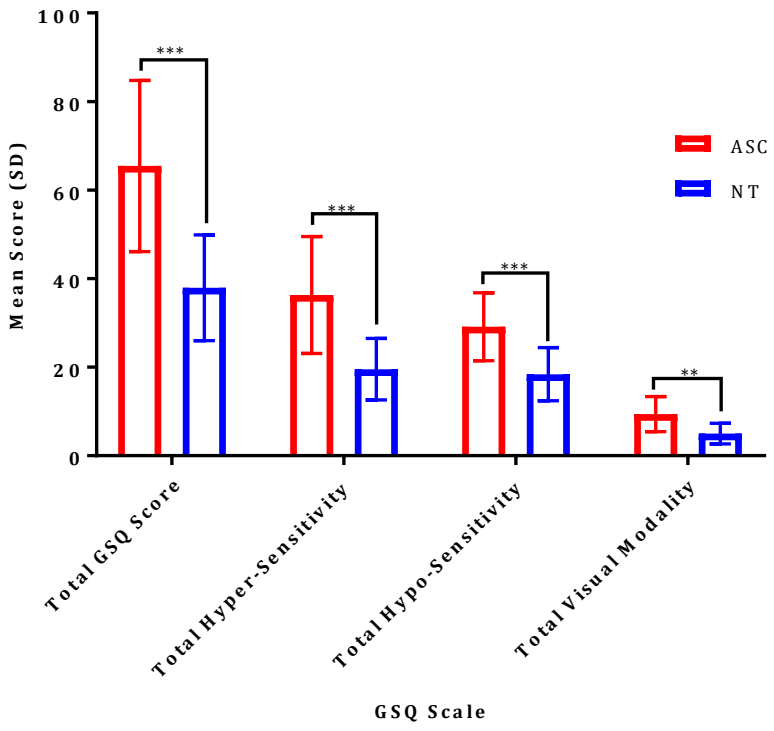


Figure 5.10. Mean Glasgow Sensory Questionnaire (GSQ) scores for ASC and NT Groups. *** p <.001. ** p < .010. Error bars represent standard deviation.

Independent measures t-tests were also run for all AASP scales. Results found that ASC participants had significantly higher scores than NT participants on the Low Registration scale [t (29) = 3.21, p = .003], the Sensory Sensitivity scale [t (29) = 3.62, p = .001], and the Sensation Avoiding scale [t (29) = 4.32, p < .001]. In contrast, ASC participants had significantly lower scores than NT participants on the Sensation Seeking scale [t (29) = 3.43, p = .002]. Overall, these results suggest that ASC individuals are more likely to avoid sensory stimuli, are more sensitive (and likely to be bothered by) to sensory stimuli, are more likely to miss or take longer to respond to sensory stimuli, and less likely to seek out sensory stimulation compared to NT individuals (see Figure 5.11).

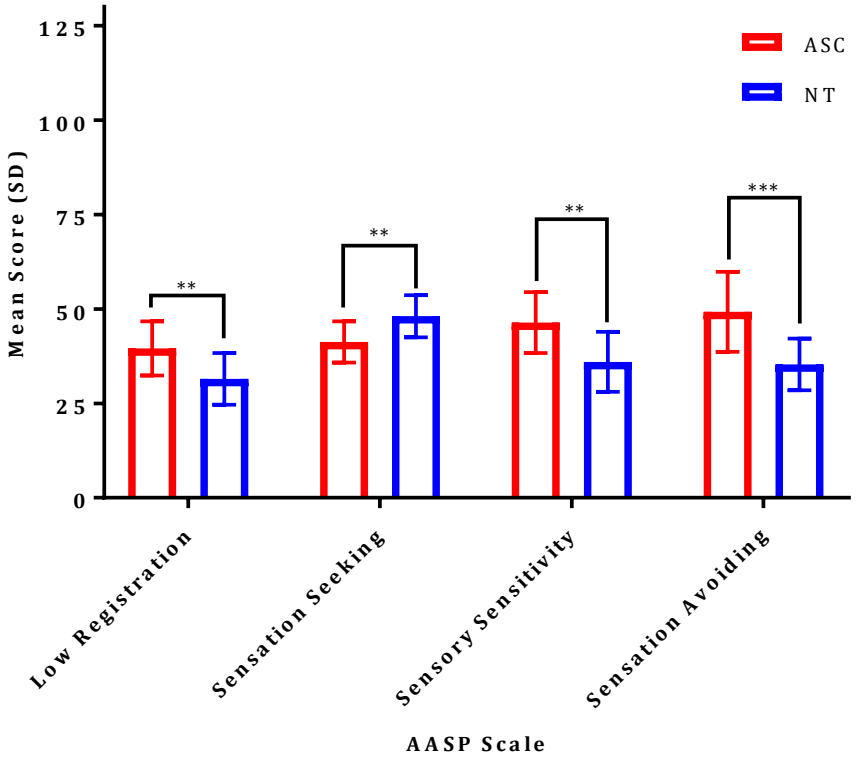


Figure 5.11. Mean Adolescent and Adult Sensory Profile (AASP) scores for ASC and NT Groups. *** p <.001. ** p < .010. Error bars represent standard deviation.

5.3.5.2.2. Group differences in DASS-21 scores

DASS-21 scores were positively skewed on all measures for NT participants' only; therefore, non-parametric Mann-Whitney U tests were run to assess differences between ASC and NT groups in self-reported levels of depression, anxiety and stress. It was found that ASC participants experienced higher levels of anxiety (median = 4.00) compared to NT participants (median = 1.00; [U = 175.00, z = 2.20, p = .030]), and higher levels of stress (median = 9.50) compared to NT participants (median = 4.00; [U = 197.00, z = 3.05, p = .002]). However, there were no statistically significant differences in levels of depression between ASC and NT groups, U = 152.5, z = 1.29, p = .202.

5.3.5.2.3. Group differences in SRS-2 scores

An independent measures t-test confirmed that there were significant differences between ASC and NT participants total SRS scores, t (29) = 7.11, p < .001, with ASC participants scoring significantly higher than NT participants (see Figure 5.12). Further exploration of SRS subscales revealed that ASC participants scored significantly higher on all SRS subscales compared to NT participants; Social Awareness [t (29) = 6.52, p < .001], Social Cognition [t (29) = 5.49, p < .001], Social Communication [t (29) = 6.09, p < .001], Social Motivation [t (29) = 4.51, p < .001], and Restricted Interest and Repetitive Behaviours [t (23.83) = 6.61, p < .001] (see Figure 5.2). These results confirm that NT participant's scores were within normal limits for the general population, whereas the ASC participant's scores indicated moderate deficiencies in reciprocal social behaviours (according to banding of scores provided in the SRS-2), which may lead to disturbances in everyday social interactions (Constantino & Gruber, 2012).

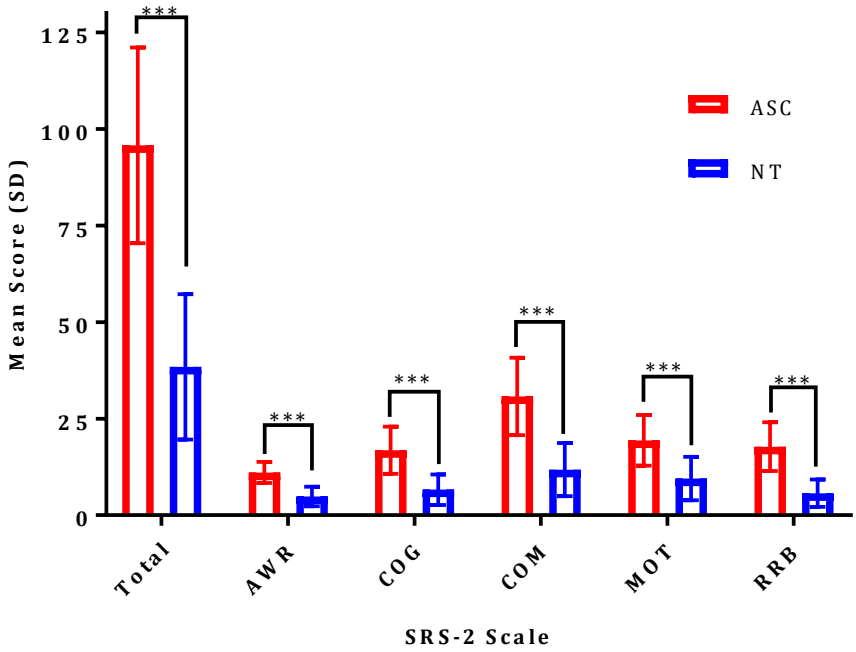


Figure 5.12. Mean Social Responsiveness Scale (SRS-2) scores for ASC and NT Groups. *** = p <.001; Total = Total SRS Score. AWR = Social Awareness score; COG = Social Cognition score; COM = Social Communication Score; MOT = Social Motivation score; RRB = Restricted Interests and Repetitive Behaviours score.

5.3.5.2.4. Group differences in WASI scores

An independent measures t-test confirmed that there were no significant differences in IQ scores between ASC and NT participants, t (29) = .29, p = .773 (descriptive statistics of IQ score are presented in Table 5.5). Comparisons between both groups in terms of performance on each individual test was also assessed. Again, the results revealed that there were no significant differences between ASC and NT participants performance on the vocabulary subtest, t (29) =

.12, p = .908. Before assessing group differences in performance on the matrix reasoning sub-test, one extreme outlier was identified, but was kept in analyses as their inclusion made no material differences to the results as assessed by comparison of analyses with and without the outlier. No significant differences were found between ASC and NT participants performance on the matrix reasoning sub-test, t (29) = .54, p = .591. Together, these results confirm that the autistic and neurotypical samples in this study were matched in their levels of intelligence.

Table 5.5

IQ Scores for Autism Spectrum Condition and Neurotypical Groups

	Group					
	ASC			NT		
IQ Measure	Mean	SD	Min-Max	Mean	SD	Min-Max
Vocabulary sub-test (T-scores)	61.25	7.49	46-72	61.53	5.83	50-71
Matrix Reasoning sub-test (T-scores)	61.50	6.32	47-70	60.07	8.29	35-69
Total IQ Score	122.75	11.53	94-134	121.60	10.36	100-133

Note. Min-Max = minimum and maximum observed scores.

5.3.6. The Relationship between Sensory Sensitivity and Visual Evoked Potentials

5.3.6.1. Hypothesis: Participants with higher sensory responsivity scores will show larger visual evoked potentials at baseline.

Previous analyses (section 5.3.5.2.1) showed that ASC participants had significantly higher scores on all measures of sensory perception, as well as experiencing significantly higher anxiety and stress levels compared to NT participants (section 5.3.5.2.2). Partial Pearson's product-moment correlations were run to assess the relationship between sensory measures and mean VEP amplitude at baseline, after controlling for anxiety and stress, for ASC and NT participants. There were two outliers, but they were kept in analyses as they didn't materially affect the results, as assessed by comparison of analyses with and without the outliers.

Results of the correlation analyses are presented in Table 5.6. Bivariate Pearson's correlations established that there were no statistically significant relationships between mean VEP amplitude at baseline and sensory measures for NT or ASC participants. Similarly, Pearson's partial correlations showed that there were still no significant relationships between mean VEP amplitude at baseline and sensory measures after controlling for anxiety and stress scores. These results suggest that there is no relationship between sensory sensitivity and mean VEP amplitude at baseline for NT or ASC participants. However, it is also worth noting that this is relatively small sample; therefore, any small effect sizes may not be detected due to under-powered analyses.

Table 5.6.
Bivariate and partial Pearson correlation coefficients for the relationship between mean VEP amplitude at baseline and sensory responsivity measures

			Sensory Measure			
			Sensory Sensitivity (AASP)		Total GSQ Score	
Group	Analysis	VEP component	*r*	*p*	*r*	*p*
ASC	Bivariate Pearson's correlation	N1	.06	.816	.13	.637
		P2	-.13	627	-.31	.236
	Partial Pearson's correlation (controlling for anxiety and stress scores)	N1	-.39	.173	-.13	.665
		P2	-.06	.828	-.27	.360
NT	Bivariate Pearson's correlation	N1	-.10	.719	.03	.920
		P2	-.13	.653	.01	.974
	Partial Pearson's correlation (controlling for anxiety and stress scores)	N1	-.27	.367	-.21	.502
		P2	-.16	.596	-.07	.813

5.3.6.2. Hypothesis: Participants with higher sensory responsivity scores will show a smaller degree of change in VEP amplitude following high-frequency stimulation

Given that previous analyses (section 5.3.1.3) had shown that neither ASC or NT participants showed any significant long-term effects changes to VEP amplitude following visual HFS, it was no longer appropriate to test the relationship between sensory responsivity and VEP change in this study.

5.3.7. Summary of Results

A summary of the key findings related to hypotheses outlined in the introduction are presented in Table 5.7. In addition, Table 5.8 summarises findings of all other analyses testing for differences between ASC and NT participants that are not directly related to the hypotheses outlined in the introduction but may affect interpretation of these key findings.

Table 5.7.

Summary of key findings

Hypothesis	Finding	Summary
1. Visual plasticity is reduced in ASC	✗	Neither ASC nor NT participants showed significant long-term changes to VEPs following visual HFS (although both groups did show a significant short term potentiation of the N1 and attenuation of the P2 after HFS).
2. There will be no group differences in HFS-driven VSSR power	✓	No significant group differences in HFS-driven VSSR power were observed, suggesting that group differences in plasticity are not due to differing levels of tetanization.
4. Sensory responsivity will be more extreme in ASC participants	✓	ASC participants scored significantly higher on all measures of sensory responsivity (AASP and GSQ) compared to NT participants, apart from on the sensation seeking measure where ASC participants scored significantly lower than NT participants
5. Participants with higher sensory responsivity scores will have larger VEPs at baseline	✗	No significant relationship was found between sensory responsivity measures and VEP amplitude at baseline for ASC or NT participants

Table 5.8.

Summary of all other analyses testing differences between ASC and NT participants

Area of Analysis	Were there significant group differences in …?	Result
Data quality	…the number of epochs used to generate grand-averaged VEPs?	×
	…the number of channels removed during processing of EEG data?	×
Questionnaire measures	… IQ scores (including scores on vocabulary and matrix reasoning tests)?	×
	…scores on the Social Responsiveness Scale (SRS-2)?	✓[a]
	…scores on the Depression Anxiety & Stress Scale (DASS-21)?	✓[b]
Task performance	…response accuracy to oddball target squares?	×
	…reaction times when responding to oddball target squares?	×

Note. [a] NT participant's scores were within normal limits for the general population, whereas ASC participant's scores indicated moderate deficiencies in reciprocal social behaviours which may lead to disturbances in everyday social interactions. [b] ASC participants had significantly higher anxiety and stress scores compared to NT participants, with no significant group differences in depression scores.

5.4. Discussion

The results of this study failed to replicate previous findings shown by others (Çavuş et al., 2012; Clapp et al., 2012; Teyler et al., 2005) and our own work (Chapter 4) demonstrating that exposure to repetitive visual HFS results in long-term changes to visual evoked potentials. No long-term effects of visual HFS were found for either ASC or NT participants, however both groups did show significant short-term changes to VEP amplitude. Both groups had comparable levels of entrainment to the visual HFS, as assessed by HFS-driven VSSR power, and performance across other task-related measures was also equal across the two groups. As predicted, sensory responsivity scores were more extreme in individuals with ASCs, compared to neurotypical participants, but there was no significant association between sensory responsivity and VEP amplitude to sensory stimulation during baseline VEP assessments. The following sections will discuss these results in more detail, and try to understand why the findings of this study are different from what was predicted.

5.4.1. No long-term effect of visual HFS on VEPs

Prior to testing, it was hypothesized that visual plasticity would be significantly reduced in individuals with ASC compared to NT individuals. However, the results of this study found that neither ASC nor NT participants showed any long-term changes to VEPs following visual HFS. Interestingly, there were significant short term changes (up to 4 minutes post-HFS) to both VEP components (indicating potentiation of the N1 and attenuation of the P2); this effect was not significantly different between the two groups. This is inconsistent with out prediction that potentiation would be reduced in individuals with ASC compared to NT participants. Rather, this would suggest that either there are no differences in glutamatergic function in ASC, or that glutamatergic differences do not affect short-term changes in plasticity, although more research is needed to answer this. Overall, these findings are in contrast with other studies that have used similar paradigms and have successfully demonstrated LTP-like changes in NT adults (such as Çavuş et al., 2012; Clapp et al., 2012; Sanders, Thompson, Corballis, Maslin, & Searchfield, 2018; Spriggs et al., 2017; Teyler et al., 2005) and the findings we report in Chapter 4.

Several lines of evidence indicate that the lack of LTP-like changes to the VEP following visual HFS were not due to poorer task performance. Firstly, ASC and NT groups had comparable HFS-driven VSSR power, suggesting that participants attended to the tetanizing stimulus equally well and exhibited comparable neuro-oscillatory entrainment to the HFS. Notably, HFS-driven VSSR power for NT adults in this study was even higher than that reported for adults in the previous study, suggesting that the absence of LTP-like changes to the VEPs in this study is not due to poorer entrainment to the visual HFS. Secondly, both ASC and NT groups showed comparably high hit rates (> 95 %) and similar reaction times in response to oddball target squares. In addition, both groups had similar signal-to-noise ratios, as similar

numbers of channels, and trials per block, were removed during pre-processing of EEG data. Therefore, it is at present unclear why this study was unable to demonstrate long-term effects of visual HFS on VEPs.

One possible explanation may be due to the study's relatively small sample size. It is recommended in correlation analyses that sample sizes larger than 30 are required for most research questions (although samples as small as 10 participants per group may be appropriate if there are tight experimental controls, such as matched pairs). In multivariate analyses it is recommended that the sample size should be several times as large as the number of variables (Sekaran & Bougie, 2013). However, the sample used in this study was not much smaller than that used in the previous chapter where significant long-term effects of visual HFS were detected (NT adults in Chapter 4, $n = 18$; NT adults in Chapter 5, $n = 15$). Hence, it is possible that a small sample size might be less of an issue in this case, and that the paradigm is potentially less reliable than the literature would suggest.

Ideally, the sample size would have been larger and whilst there was a lot of interest from people with ASCs, many potential participants were excluded from taking part. Firstly, the flickering image used as the HFS was off-putting for many people with ASCs, particularly those prone to migraines, so they were advised not to take part. Secondly, given that this study was assessing NMDA receptor function, participants who were taking medications containing psychoactive substances (such as antidepressants) were excluded from taking part, to limit any possible confounding variables. Rates of depression and anxiety are more prevalent in adults with autism than in the general population, especially in individuals without intellectual disability, with one study finding that 35% of individuals with ASCs questioned were taking antidepressants (Buck et al., 2014). Consequently, many people with ASCs who expressed an interest in the study were prevented from taking part for these reasons, which resulted in a smaller sample than was desired.

Another difference between the NT adult samples tested in this chapter and the previous chapter is that the adults tested in the present chapter were on average older (mean age = 38.7 years) than the adults tested in the previous chapter (mean age = 25.8 years). At present, only one study has looked at the effect of aging in adulthood on visual plasticity, demonstrating that only younger adults show long-term potentiation of the N1, but that younger and older adults both show long-term potentiation of the P2a, suggesting that the threshold for LTP, but not LTD, changes with age (Spriggs et al., 2017). Critically, the younger adult group in Spriggs' study had a mean age of 24.27 years (range 18-35 years, SD = 4.56), which is more similar to the adult sample tested in Chapter 4 (albeit with a wider range of ages). However, the older adult group in Spriggs' study was considerably older (mean age 77.32 years, range = 68-91 years, $SD = 5.94$) than any of the samples used in this doctoral work. Interestingly, the healthy

control sample used in Çavuş' (2012) study of visual plasticity in schizophrenia was very similar in age (mean age = 37.8 years) to the NT sample in the present study, suggesting that age of the participants may not have been a factor for not observing longer-term change in VEPs following HFS. Consequently, more research is needed to establish why the significant short-term effects of visual HFS observed in this study were not maintained for a longer period of time, as has been observed in the previous literature.

5.4.2. Sensory Responsivity and Visual Plasticity

This study also aimed to explore the relationship between sensory responsivity and visual cortical plasticity. The prediction that ASC participants would have more extreme sensory responsivity scores than NT participants was confirmed. More specifically, the results showed that individuals with ASCs had significantly higher scores on AASP measures of Low Registration, Sensory Sensitivity and Sensation Avoiding compared to NT individuals, but significantly lower scores on the Sensation Seeking scale. Similarly, individuals with ASC also reported significantly higher scores on relevant GSQ scales (including on measures of the visual modality, and total hyper- and hypo-responsivity), as well as significantly higher total GSQ scores which indicates more extreme responses to sensory stimuli. This is consistent with previous research showing that autism traits were significantly correlated with AASP and GSQ scores, even after controlling for trait anxiety scores and other potential confounds (Horder et al., 2014). Interestingly, individuals with ASC also reported significantly higher levels of anxiety and stress compared to NT individuals, which reflects the association between sensory responsivity and negative affect found in Chapter 3.

Compared to the sample studied in Chapter 4, there was greater variance in sensory responsivity scores in the present study, with more participants reporting more extreme sensory processing styles. It was expected that this increased variance in sensory responsivity scores would be beneficial for the analyses exploring the relationship between sensory responsivity measures and VEP amplitude. However, correlation analyses revealed no significant relationships between sensory responsivity measures and baseline VEP amplitude. This may in part be due to the small sample size (n = 31), meaning that it is unlikely any small effect sizes would be detected. Furthermore, given that there was no long-term effect of visual HFS on VEP amplitude, it was no longer appropriate to test the relationship between sensory responsivity and change in VEP amplitude. Consequently, this study was unable to fully test the relationship between sensory responsivity and sensory-induced plasticity.

5.4.5. Conclusion

The present study failed to replicate previous findings demonstrating that exposure to repetitive visual HFS results in long-term changes to visual evoked potentials. Instead, both groups of ASC and NT individuals showed equivalent levels of short-term changes to VEP

amplitude following HFS, suggesting that short-term plasticity is not reduced in ASC compared to matched neurotypical controls. Notably, in this study, no long-term changes in VEP amplitude were found following visual HFS. This is despite both groups showing similar levels of neural entrainment to the tetanizing stimulation to participants in the previous study, where LTP-like changes to VEPs were observed. Consequently, it is unclear why previous findings were not replicated in the present study, and future work needs to explore the reliability of the paradigm used in this study to induce changes in visual cortical plasticity.

Chapter 6: General Discussion

6.1. Key findings and general discussion

As outlined in the first chapter of this doctoral thesis, the overall aim of this work was to investigate the role of sensory processing and cortical plasticity in typical and atypical development. The three empirical studies reported in Chapter's 3, 4, and 5 all aimed to tackle different aspects of this overall aim. Specifically, this doctoral work aimed to examine the relationship between sensory processing, negative affect, and risk-taking in the transition from early adolescence to adulthood (Chapter 3), and to see whether changes in cortical plasticity might help to explain individual differences in sensory responsivity in typically developing individuals (Chapter 4) and in individuals with a neurodevelopmental condition (Chapter 5). This section will recap the main research questions of these studies and summarise their key findings, evaluating their importance based on the strengths and limitations of the studies, and how they relate to the existing literature.

6.1.1. Sensory processing is significantly related to psychological and behavioural outcomes in the transition from adolescence to adulthood in typically developing individuals

Sensory processing difficulties are associated with many neurodevelopmental disorders and mental health conditions, such as Fragile X Syndrome (Sinclair, Oranje, Razak, Siegel, & Schmid, 2017), ADHD (Ghanizadeh, 2011; Parush, Sohmer, Steinberg, & Kaitz, 2007; Reynolds & Lane, 2009), schizophrenia (Javitt, 2009; Javitt & Freedman, 2015), obsessive compulsive disorder (Dar, Kahn, & Carmeli, 2012), and post-traumatic stress disorder (Engel-Yeger, Palgy-Levin, & Lev-Wiesel, 2013). Consequently, the majority of sensory processing research has aimed to identify patterns of sensory processing difficulties that are unique to specific mental health conditions (Royeen & Lane, 1991). However, it is important to have a good understanding of the role that sensory processing plays in neurotypical individuals, in order to have the foundations to then assess how sensory processing abilities deviate in various mental health conditions. There have been some attempts to examine sensory responsivity in neurotypical adults (Ben-Avi et al., 2012; Chung, 2006; Engel-Yeger & Dunn, 2011b, 2011a; Engel-Yeger & Shochat, 2012; Hebert, 2015; Jerome & Liss, 2005; Johnson & Irving, 2008; Pohl et al., 2003) and in neurotypical children (although primarily as control groups in studies looking at neurodevelopmental disorders or sensory processing difficulties; Davies et al., 2009; Davies & Gavin, 2007; Lane et al., 2012; Tomchek & Dunn, 2007), but very few studies have examined sensory processing in typically developing adolescents.

The study reported in Chapter 3 aimed to address this gap in the literature by investigating the role of sensory processing in the transition from adolescence to adulthood in typically developing individuals. The study sought to examine previously unexplored relationships between sensory processing and difficulties characteristic of the adolescent period; namely increased mental health issues and risk-taking behaviours by administering self-report

sensory processing (AASP), negative affect (DASS-21), and risk-taking (RT-18) measures to 418 typically developing adolescents and adults (aged 11-30 years).

The first important finding from this cross-sectional study was that there were no age-related changes in measures of Sensory Sensitivity, Sensation Seeking or Sensation Avoiding during the transition from early-adolescence to adulthood which is consistent with previous research showing no age-related changes in auditory, visual, oral and touch processing (also measured by the Sensory Profile) in neurotypical individuals aged 3-56 years (Kern et al., 2006). However, adults had significantly lower Low Registration scores compared to the three younger age groups, suggesting that adults are less likely to miss salient sensory stimuli compared to adolescents or young adults, possibly due to more mature neural networks in adulthood (Arain et al., 2013). The second important finding from this study was that sensory processing styles were significantly related to negative affect and risk-taking behaviours in the transition from adolescence to adulthood.

The second important finding from this study was that sensory processing is significantly related to psychological and behavioural outcomes in adolescents and adults free of any psychological conditions. More specifically, greater levels of anxiety, depression, and stress were reported by adolescents and adults who are more likely to be hyper-sensitive to sensory stimuli, and more likely to avoid strong sensory stimuli. A greater tendency to miss salient sensory stimuli was also related to increased anxiety and stress in all age groups, but was only related to increased depression in early- and late-adolescents. These findings are particularly important, given the sparsity of research investigating sensory processing in typically developing adolescents. Furthermore, they are consistent with findings from typically developing children and adults, that also demonstrate that extreme sensory processing styles are associated with greater levels of negative affect (Batya Engel-Yeger & Dunn, 2011a; Goldsmith et al., 2006; Moya Kinnealey & Fuiek, 1999; Zickgraf & Elkins, 2018).

These studies are correlational in nature; therefore, it is not possible to establish any causal relationship between sensory processing and negative affect, although it is hypothesized that anxiety contributes to sensory sensitivity by increasing arousal and vigilance to sensory stimuli, making individuals more likely to notice and react to aversive sensory stimuli (Green & Ben-Sasson, 2010). Others have suggested that the relationship between sensory sensitivity and depression is thought to stem from exposure to repeated aversive experiences, and the tendency to become unpleasantly over-aroused by the environment, leading to social withdrawal (Aron & Aron, 1997; Liss et al., 2008). Given that adolescence is associated with the onset of many mental health conditions (de Girolamo, Dagani, Purcell, Cocchi, & McGorry, 2012; Kessler et al., 2005), it is important to understand the risk factors and protective factors for mental health during this developmental stage. The results of this doctoral thesis suggest that extreme

responses to sensory stimuli during adolescence may predict or contribute to poorer mental health outcomes in typically developing adolescents.

The results of this study are the first to demonstrate relationships between sensory processing styles and risk-taking in typically developing adolescents and adults. Sensation seeking and risk-taking behaviours were positively related, which is consistent with previous literature demonstrating increased risk-taking in adolescents and adults who are more prone to sensation seeking (Greene et al., 2000; Malmberg et al., 2010; Rollison & Scherman, 2002; Scholes-Balog, Francke, & Hemphill, 2016; Zhang, Zhang, & Shang, 2016). This is also consistent with Dunn's model of sensory processing (Brown et al., 2001; Dunn, 1997), which suggests that risk-taking behaviours are a result of high neurological thresholds and active self-regulation strategies. Dunn posits that individuals who score highly on sensation seeking (which correlates strongly with risk-taking behaviours) will experience pleasure from exciting sensory environments and behaviours, will often show risk-taking behaviours that are expressed by a lack of physical boundaries, and may be seen by others as irresponsible, impatient, and lacking in respect (Brown, Tollefson, Dunn, Cromwell, & Filion, 2001; Dunn, 1997). Furthermore, this study is also the first to show reduced risk assessment was associated with increased sensation seeking and a greater tendency to miss salient sensory stimuli. Collectively, these results demonstrate strong associations between sensory responsivity, negative affect, and risk-taking during the transition from early-adolescence to adulthood, and provides a foundation for future studies examining sensory responsivity in adolescence.

One suggestion I would make for future research would be to investigate potential gender differences in the relationships between sensory responsivity, negative affect, and risk-taking. One of the limitations of the study reported in Chapter 3 was that the sample was majoritively female (approximately 72% of the total sample). Given that it is widely acknowledged that gender differences in risk-taking, anxiety, and depression exist in adolescence, it is unfortunate that this could not be examined in relation to sensory responsivity; however, there were great difficulties with recruiting male participants across all age groups, which is not uncommon in research (Patel, Doku, & Tennakoon, 2003). In terms of gender differences in sensory responsivity, the literature is fairly limited but appears to suggest there are no significant gender differences in children (Bar-Shalita, Goldstand, Hahn-Markowitz, & Parush, 2005; A. Ben-Sasson et al., 2009; Lewin, Wu, Murphy, & Storch, 2015), but that adult females may have greater sensory sensitivity than adult males (Engel-Yeger et al., 2011). As there is very little research examining sensory responsivity in typically developing adolescence, it is unclear whether there are gender differences in sensory processing styles during adolescence. If gender differences in sensory responsivity are found, then it may also help to explain gender differences in risk-taking and negative affect.

During my review of the literature, and searches of the internet, I was concerned with the number of articles depicting adolescence as a period of development to be feared by parents and caregivers. Adolescence is regularly referred to as a period of "storm and stress", although there is an increasing movement to challenge this perspective (Hollenstein & Lougheed, 2013). Whilst adolescence isn't always easy to navigate, the majority of individuals will transition from adolescence to adulthood successfully, gaining employment, having good social relationships, and adapting to and dealing with increased responsibilities. Yet the stereotype that adolescents are moody, selfish, and lacking in respect still persists. I feel that this stereotype of adolescence is problematic for two reasons. Firstly, adolescents who do not fit the stereotype may feel that there is something "wrong" with them – indeed, my own parents questioned why I wasn't taking more risks and breaking more rules as a teenager! This may push some adolescents towards more risky activities, in order to fit in with what they believe is expected of them. Secondly, adolescents who are experiencing significant difficulties with managing their emotions and behaviours may not receive the help they need if these behaviours are considered "normal" in adolescence, which may mean these difficulties continue into adulthood. By establishing that extreme sensory processing styles are associated with increased risk-taking and increased negative affect, the findings from this doctoral thesis suggest there is a possibility of identifying at-risk teens based on their sensory responsivity and offering them targeted interventions before they begin to experience significant difficulties. Furthermore, by demonstrating the functional significance of sensory responsivity during this developmental stage, this body of work testifies to the importance of furthering our understanding of sensory responsivity during adolescence. It solidifies the notion that adolescence is a critical period of development, associated with challenging behaviours and emotions that may still not be fully understood.

6.1.2. Visual tetanic stimulation is a safe and non-invasive method of examining LTP-like changes in the visual cortex, but more research is needed to establish the influence of low-frequency stimulus presentation in VEP assessments on VEP changes

The majority of research investigating long-term potentiation (LTP) has been carried out on animal subjects or brain slice preparations, due to the need to insert an electrode into desired afferent fibres in order to administer tetanisation and induce LTP. However, an alternative non-invasive method of inducing LTP-like changes was developed (Çavuş et al., 2012; Clapp et al., 2012; Teyler et al., 2005), whereby high-frequency visual stimulation induces LTP-like changes in the visual cortex, as measured by visual evoked potentials (VEPs), with many of the hallmarks that are characteristic of LTP (input specific, long-lasting, and frequency dependent). This paradigm thereby offers the opportunity to non-invasively measure LTP-like changes in populations that may have altered cortical plasticity. Although there are many forms of cortical plasticity, perhaps the most well understood molecular mechanism of

synaptic plasticity is NMDA receptor dependent LTP/LTD. The functioning of NMDA receptors is thought to have a significant effect on how plastic neural networks are, and consequently how adaptive brains responses to sensory stimuli are.

6.1.2.1. Visual tetanic stimulation produces developmentally regulated changes to VEPs in typically developing adolescents and adults

The study presented in Chapter 4 examined possible developmental differences in cortical plasticity in the transition from adolescence to adulthood in typically developing individuals. It has been shown in rodents that during adolescence, NMDA receptors are more efficient and allow more calcium ions into the post-synaptic cell, signalling the molecular cascade that controls synaptic strength (Schramm et al., 2002), making the adolescent brain more plastic than in adulthood. Prior to this doctoral thesis, developmental differences (in adolescence) in plasticity had only been studied in animal models (Izumi & Zorumski, 1995; Kirkwood, Lee, & Bear, 1995; Liao & Malinow, 1996; Schramm et al., 2002). Therefore, using the same paradigm as Çavuş et al (2012), I examined whether it was possible to replicate findings from the rodent literature in humans, using visual tetanic stimulation to induce LTP-like changes in the visual cortex.

To that end, early-adolescents (aged 13-14 years; n = 18), late-adolescents (18-19 years; n = 19) and adults (aged 25-26 years; n = 20) completed the Visual Cortical Plasticity Paradigm, alongside questionnaire measures of sensory processing (AASP and GSQ), and negative affect (DASS-21). Results found that visual HFS led to relatively long-term changes (+20 minutes) in VEPs in both adolescents and adults; however, the latency and persistence of these differences was dependent on participants' age. Early-adolescents only showed short term potentiation of the N1 (up to 6 minutes post-HFS), whereas late-adolescents and adults both showed significant long-term potentiation of the N1 (up to 22 minutes post-HFS). Furthermore, analyses exploring the degree of change in VEP amplitude revealed that all age groups had a similar degree of N1 potentiation in the earliest VEP assessments (post-1 and post-2), and whilst this degree of potentiation was maintained by late-adolescents and adults for 20 minutes following HFS, early-adolescents showed a quick return to baseline N1 amplitudes. For the visual P2 component, the reverse pattern was observed, with early-adolescents showing significant long-term attenuation of the P2, but late-adolescents and adults only showing short-term attenuation of the P2. Interestingly, early-adolescents showed a significantly greater degree of attenuation of the P2 compared to the two older age groups, suggesting that plasticity may indeed be greater during adolescence than in adulthood. All age groups had comparable HFS-driven VSSR power, suggesting that participants attended to the tetanizing stimulus equally well, regardless of age, and exhibited comparable neuro-oscillatory entrainment to the HFS. However, unlike in

previous studies (Çavuş et al., 2012), no significant correlation was found between HFS-driven VSSR power and degree of change in VEP amplitude, following HFS.

There is reasonable consistency amongst published studies showing that visual tetanic stimulation leads to potentiation of the visual N1 (in neurotypical adults at least; Çavuş et al., 2012; Clapp et al., 2012; McNair et al., 2006). However, as discussed in Chapter 4.4, only one study has also examined changes to the visual P2 following visual HFS. Spriggs and colleagues (2017) examined LTP-like VEP changes in young (18-35 years) and older (68-91 years) participants, and found that whilst only younger adults showed potentiation of the N1, both groups showed significant potentiation of the P2a (the first part of the P2 component) in response to tetanized and non-tetanized stimuli. The authors suggested that because the P2 was also attenuated for non-tetanized stimuli, these changes indicate an active depotentiation (or LTD) of the VEP, resulting from repeated presentations of stimuli at a low frequency (~ 1Hz). Consequently, alterations to the P2 component may be more reflective of LTD-like changes induced by low-frequency presentation of stimuli in VEP assessments, rather than due to changes induced by high-frequency visual stimuli. Whilst there are some methodological differences between the study reported in Chapter 4, and that of Spriggs and colleagues (such as type of stimuli presented, and density of electrode arrays), their results do raise some important questions about sensory tetanisation paradigms.

The issue of inducing LTD-like changes by repeated slow-frequency presentations in VEP assessment blocks was considered early on in the development of sensory tetanisation paradigms. For example, Teyler et al. (2005) initially measured post-HFS changes in VEPs by presenting visual stimuli at ~1Hz for four 7-minute blocks (2-9, 15-21, 30-37, and 45-52 minutes after the end of tetanic stimulation). However, they soon recognised that presenting stimuli at a low frequency for extended periods of time was actually inducing LTD-like changes in the VEP (which were mitigated by removing two of the post-HFS assessment blocks). In a later study run by the same group (McNair et al., 2006), post-HFS blocks were considerably shorter in length, ranging from 206 seconds to 306 seconds per block, and fewer in number (only two post-HFS blocks were used, compared to four in the previous study). From then on, researchers (including myself) appeared to assume that these shorter, less-frequent blocks were not powerful enough to induced LTD-like changes. However, Spriggs' (2017) study suggests that the case may not be fully closed, and I would suggest that future research using sensory tetanic stimulation uses a similar paradigm to that of Spriggs and colleagues, whereby VEPs are measured in response to both tetanized and non-tetanized stimuli so that LTP- and LTD-like changes can be assessed separately. Unfortunately, this study was published after testing was completed for the Chapter 4 study, and was well under way for the Chapter 5 study so it was not possible to use this paradigm in this doctoral work.

6.1.2.2. More research is needed to establish whether visual tetanic stimulation produces altered LTP-like changes in individuals with ASCs, compared to neurotypical individuals

In individuals with ASCs, NMDA receptor function is thought to be reduced due to genetic variants of NMDA receptor sub-unit genes, associated with ASCs, which alter the functional properties of NMDA receptors. In support of this, pharmacological research has shown that NMDA receptor agonists can improve autistic symptoms, such as social withdrawal (Posey et al., 2004) and repetitive behaviour (Urbano et al., 2014). Furthermore, several animal models have shown that altering NMDA-receptor function can lead to significant changes in ASC-like phenotypes (such as repetitive stereotyped grooming behaviours; Blundell et al., 2010; Chung et al., 2015; Schmeisser et al., 2012; Won et al., 2012). Altered cortical plasticity in ASCs has also been demonstrated in studies using repetitive TMS (Jung et al., 2012; Oberman et al., 2010, 2012); however, cortical plasticity in ASC had not yet been examined using visual tetanic stimulation prior to this doctoral work. Therefore, having successfully used the Visual Cortical Plasticity Paradigm to assess developmental changes in cortical plasticity in typically developing individuals, the study reported in Chapter 5 aimed to examine cortical plasticity in individuals with a neurodevelopmental condition (namely, autism) compared to neurotypical controls. To that end, participants with ASCs (n = 16) and age- and gender-matched neurotypical controls (n = 15) completed the Visual Cortical Plasticity Paradigm, as well as questionnaire measures of sensory processing (AASP and GSQ), negative affect (DASS-21), and social responsiveness (SRS-2).

The results of this study failed to replicate previous findings, including the results in Chapter 4, demonstrating that exposure to repetitive visual HFS results in long-term changes to visual evoked potentials. No long-term effects of visual HFS were found for either ASC or NT participants; however, both groups did show significant short term changes to the VEP (reflected by potentiation of the N1 and attenuation of the P2). This was unexpected, as it was predicted that potentiation would be significantly reduced in individuals with ASCs compared to NT controls. Instead, the findings suggest that there are no differences in glutamatergic function in ASC, or that glutamatergic differences do not affect short-term changes in plasticity; although more research is needed to establish which of these is most plausible. Both groups had comparable levels of entrainment to the visual HFS, as assessed by HFS-driven VSSR power, and performance across other task-related measures was also equal across the two groups. Therefore, it is at present unclear why this study was unable to demonstrate long-term effects of visual HFS on VEPs. One possible explanation may be due to the study's relatively small sample size. As discussed in Chapter 5.4.2, there were many individuals with ASC who were interested in taking part in the study, but were prevented for one reason or another. As a result, the sample was smaller than desired.

Despite the fact this study did not necessarily achieve what it set out to, I do still believe it offers a valuable contribution to the literature by demonstrating that this type of paradigm can be used with individuals with ASC (although it may not be suitable for all individuals with ASC, such as those with extreme sensory over-responsivity, epilepsy, or migraines). Furthermore, the main 3-way interaction was approaching significance, which suggests that further investigation with a larger sample size is definitely warranted. If a larger study does indeed show that cortical plasticity is altered in individuals with ASCs, then sensory tetanization paradigms may also become a useful tool for aiding clinical assessment of ASCs. Given that current methods of diagnosing ASC are largely based on subjective observations by a trained clinician, having an objective diagnostic criterion that may reflect a core dysfunction in glutamatergic function and synaptic plasticity in ASCs could result in much earlier diagnosis, and prevent misdiagnosis and inappropriate intervention for individuals with ASCs.

6.1.3. No relationships were observed between sensory responsivity measures and visual cortical plasticity

One of the aims of this doctoral thesis was to examine possible neural mechanisms underlying individual differences in sensory responsivity. Specifically, this doctoral thesis aimed to determine if individual differences in neuroplasticity are related to self-reported levels of sensory responsivity. As discussed above, neuroplasticity was assessed by examining changes in VEPs following high-frequency visual stimulation, that are thought to reflect LTP-like changes in the visual cortex. It was hypothesized that individuals with high levels of sensory sensitivity would have greater VEP amplitudes at baseline assuming that their previous sensory experiences have induced potentiation of synapses in sensory cortices, in accordance with Dunn's (1999) theory of sensory processing, and evidence demonstrating potentiated neural responses resulting from previous sensory experiences (Clapp, Hamm, Kirk, & Teyler, 2012; Heynen & Bear, 2001). Furthermore, assuming that participants with higher levels of sensory responsivity show a potentiated response to baseline stimuli, it was also predicted that participants with higher levels of sensory responsivity would show less change in VEP amplitude following HFS, compared to participants with lower levels of sensory responsivity, because they are closer to ceiling effects due to prior tetanization from sensory experiences.

As has already been mentioned, the study reported in Chapter 5 failed to show any significant long-terms effects of visual HFS on VEPs. Therefore, assessing the relationship between sensory responsivity and degree of VEP change was no longer possible, but analyses were still run to assess the relationship between sensory responsivity scores and baseline VEP amplitudes. The results showed that neither of the EEG studies in this doctoral thesis found any significant relationships between sensory responsivity and VEP amplitudes at baseline, or degree of VEP change following visual HFS (in Chapter 4). There are several possible reasons

these studies failed to find any evidence in support of a relationship between sensory responsivity and cortical plasticity, as assessed by VEPs.

The first possibility is that the null hypothesis is true, and there is no relationship between sensory responsivity and visual cortical plasticity. However, as discussed in Chapter 4.4.4, evidence from sensory gating paradigms suggests that there are differences in adaptive responses to sensory stimuli between individuals with and without sensory processing difficulties. For example, children with sensory processing difficulties show impaired sensory gating compared to typically developing children in P50 suppression (Davies & Gavin, 2007); a finding that has also been observed in adults with schizophrenia (for review and meta-analysis see Patterson et al., 2008; Freedman et al., 1987). Furthermore, sensory gating performance on pre-pulse inhibition tasks has been shown to be affected by blockade of NMDA-receptors, in animal models of schizophrenia (for a review see Geyer, Krebs-Thomson, Braff, & Swerdlow, 2001). Collectively, these findings suggest that a relationship between sensory responsivity and cortical plasticity is very plausible, and that it is unlikely that the null hypothesis is true.

A second possible explanation may be that the self-reported measures of sensory processing were not valid and/or reliable. Cronbach's alpha values were calculated for all questionnaire scales used in this doctoral thesis, and whilst most scales had Cronbach's alpha values indicated adequate levels of internal consistency for the majority of scales, there were several instances where scales had Cronbach's alpha values that were below an adequate level, particularly in Chapter 4. More generally, sensory responsivity questionnaires may not be the best method for assessing an individual's threshold for sensory stimulation, as they assume that an observable reaction accurately captures the complexity of processing sensory input (Schauder & Bennetto, 2016). However, for practical reasons, measuring sensory responsivity with questionnaires, rather than behavioural measures, was most appropriate for this body of work as it allowed data to be collected quickly (which is important particularly with developmental and atypical samples), and ensured that participants weren't too fatigued before starting the EEG experiments.

Considering the validity of each questionnaire measure, the AASP has been criticised for measuring affective responses and perceptual processes, and not basic sensory function (Tavassoli, Hoekstra, & Baron-Cohen, 2014). For example, there are items that assess visual attention (e.g. "I miss the street, building, or room signs when trying to go somewhere new"), and affective reactions towards sensory stimuli (e.g. "I dislike having my back rubbed" or "I become frustrated when trying to find something in a crowded drawer"). Therefore, the AASP may not be fine-grained enough to dissect sensory processes with the precision required to assess the relationship between sensory responsivity and cortical plasticity. The GSQ appears to have better face validity than the AASP in that respect; however, it was specifically designed for

studying sensory processing in individuals with ASCs, and may therefore be less suited to studying sensory processing in neurotypical individuals. Consequently, self-report measures of sensory processing may be useful for clinicians who are concerned with behavioural responses to sensory stimuli, but may not be measuring aspects of sensory processing that are more related to cortical plasticity (such as neurological threshold perhaps). Future studies examining the relationship between sensory responsivity and neuroplasticity may benefit from measuring sensory sensitivity using more physiological measures (such as a sensory gating paradigm).

In a broader sense, there are limitations to using self-report measures, which may be amplified in developmental studies where the age or condition of the participant can affect their level of understanding of items and propensity to be biased when answering questions. Steps were taken to reduce bias in self-report measures as much as possible; participants were informed that all responses would be confidential and remain anonymous, participants were left to complete questionnaires on their own but had opportunity to ask questions if they didn't understand a particular item.

6.1.4. Using a variety of methodological techniques is the best approach for examining sensory processing and cortical plasticity in typical and atypical development

A key strength of this doctoral work was the inclusion of experimental studies and multiple forms of measurement, including self-report, behavioural, and physiological measures, to examine sensory responsivity and cortical plasticity in typically and atypically developing individuals. Whilst each of these methodological approaches have their respective advantages and disadvantages, using them together allows the project to capitalise on the advantages of each approach, whilst mitigating some of the draw-backs. For example, self-report measures are quick and easy to administer, but are prone to bias. In contrast, behavioural measures, such as reaction time, and physiological measures, such as EEG, are more objective but may also be considered more reductionist. By using all of these various methods in this body of work, a more complete assessment of sensory responsivity and cortical plasticity in typically and atypically developing populations is achieved.

6.2. Recommendations for future research

This field of research is still relatively new, and therefore there are a lot of questions for future research to address. This section recommends some directions for future research based on findings that have emerged from this doctoral work.

6.2.1. Replication and extension

Due to the paucity of research examining sensory responsivity in typically developing adolescents, and the relatively small sample sizes used in this doctoral thesis, the primary focus of future work in this field should be on replication and extension of the present findings.

6.2.1.1. Sensory Responsivity in Typically Developing Adolescents

Given earlier discussions regarding gender differences in risk-taking behaviours and levels of anxiety and depression (see Chapter 6.1.1), extensions of this work should recruit an equal balance of male and female participants and consider the potential impact of pubertal stage as well as chronological age. In addition, several risk-factors are known to increase the likelihood of adolescents engaging in risky activities (e.g. peer presence; Chein et al., 2011; Gardner & Steinberg, 2005), or of developing mental health conditions (e.g. poor social support; Van Droogenbroeck et al., 2018). Future studies of sensory responsivity in typically developing adolescents should also look to examine how these risk-factors interact with levels of sensory responsivity, risk-taking, and negative affect.

Future research should also seek to study the potential impact of pubertal development on sensory responsivity in adolescence. Although the terms puberty and adolescence are often used interchangeably, they do refer to different things. Puberty refers to the activation of the hypothalamic-pituitary-gonadal axis resulting in gonadal maturation, whereas adolescence refers to the maturation of social and cognitive behaviours (Blakemore et al., 2010; Blakemore & Mills, 2014; Forbes & Dahl, 2010). Males and females often begin and end puberty at different times, with girls showing outward signs of puberty before boys (Patton & Viner, 2007). The effect of puberty on sensory responsivity has, to the best of my knowledge, not yet been examined, although there is some research assessing changes in the sexual salience of sensory stimuli. For example, the smell of an adult female is likely to be perceived differently by a juvenile male (caregiver/mother) compared to an adult male (potential mate; Sisk & Foster, 2004). Furthermore, pubertal stage has been shown to be more strongly linked to risk-taking behaviours than chronological age (Martin et al., 2002; Spear, 2000). However, it is worth noting that puberty and chronological age are difficult to dissociate given that the two are highly correlated. Whilst it is easy to measure an individual's age precisely, pubertal stage can only be roughly estimated with measures that are difficult to validate (Blakemore et al., 2010). Consequently, this doctoral thesis focussed on age-dependent differences in sensory responsivity, with a view to extending this research in the future to study differences in sensory responsivity based on pubertal development.

6.2.1.2. The Visual Cortical Plasticity Paradigm

As discussed earlier in this chapter, the Visual Cortical Plasticity Paradigm has been a useful tool for safely and non-invasively examining LTP- and LTD-like changes in various human populations. However, the paradigm still requires further testing to fully understand the neural mechanisms it is measuring, and the functional significance of these changes. Therefore, the following sections discuss recommendations for future researchers looking to develop sensory tetanization paradigms.

6.2.1.2.1. Combining alternative methods of neuroimaging to assess neural changes following sensory tetanization

Whilst EEG is generally considered to be superior in terms of temporal resolution, it has relatively poor spatial resolution, meaning it is difficult to establish sources of activity in the visual cortex, and therefore how visually evoked components might relate to visual processing. In contrast, fMRI has relatively poor temporal resolution, but superior spatial resolution compared to EEG, meaning that combining results from EEG and fMRI studies would provide a much clearer picture on which regions visual HFS is affecting, and how this relates to VEPs. Currently, only one study has examined changes in hemodynamic responses following visual HFS using fMRI, demonstrating that hemodynamic responses were significantly increased to checkerboards presented at a low frequency after the administration of the photic tetanus (Clapp et al., 2005). To further validate the findings of Chapters 4, it would be useful to examine changes in blood oxygenation level-dependent (BOLD) signals following visual HFS in typically developing adolescents, in order to determine where changes occur and whether there are network changes in response to HFS.

6.2.1.2.2. Assessing neural changes after sensory tetanization at longer time intervals

Another avenue for future research would be to explore changes in cortical plasticity for much longer following HFS in the Visual Cortical Plasticity Paradigm. For practical reasons, in Chapters 4 and 5 VEPs were only assessed up to 22 minutes after visual HFS. Previous studies have examined changes to VEPs for up to 52 minutes following HFS in humans (Teyler et al., 2005), showing that they conformed to the synaptic LTP rules described in rat-based studies of visual HFS, including persistence, input specificity, frequency dependency, and NMDA-dependency (Clapp et al., 2006). Whilst changes observed 20 minutes following HFS are relatively long-term, and changes to make AMPA receptors more conductive are observed within 10-20 minutes of tetanus (Plant et al., 2006), it is likely that more long-term changes (including synthesis of new proteins) are not complete in this timeframe. Consequently, examination of VEPs at later time points after visual HFS (ideally for several hours following HFS, 24 hours post-HFS, and 3-7 days post-HFS) would provide a clearer picture of the time course of changes to cortical plasticity.

6.2.1.2.3. Using sensory tetanization paradigms to assess changes in cortical plasticity across the life span

Key findings from Chapter 4 generally showed significant differences between early-adolescents and the two older age groups (late-adolescents and adults) in terms of cortical plasticity, but relatively few significant differences between late-adolescents and adults. Consequently, future studies examining developmental changes in cortical plasticity would benefit from looking at adolescents aged 15-17 years, to establish when cortical plasticity

becomes adult-like, and how this relates to other psychological and behavioural outcomes. Furthermore, given that sensory tetanization paradigms have been shown to induce LTP-like changes even through passive viewing (for a review, see Sanders et al., 2018), it may also be possible to use these paradigms to assess LTP-like changes in very small infants and children. One study has already investigated differences in cortical plasticity between younger and elderly adults (Spriggs et al., 2017), but it would be useful to establish the pattern of cortical plasticity across the lifespan using this paradigm, and then assess how it relates to other psychological and behavioural measures (particularly in relation to learning and memory).

6.2.1.2.4. Using sensory tetanization paradigms to investigate other factors thought to affect neuroplasticity

There is a wealth of animal literature examining factors that affect LTP and LTD processes, and whilst animal research is important for studying such processes, they can't give us the full picture about how these processes are affected in humans. However, the development of sensory tetanization paradigms means that we can start to investigate some of the factors that animal models have shown to affect neuroplasticity in humans.

6.2.1.2.4.1. Stress

Non-human animal studies have found that stress (defined here as a perceived internal or external disturbance of homeostasis) can have differing effects on neuroplasticity depending on the type of stress (for a review, see Joels & Krugers, 2007). When an organism is stressed, information about the stressful situation will be sent to parts of the limbic system, as well as sensory processing areas, with activation of these areas leading to increases in adrenaline and corticosterone (cortisol) levels. Levels of corticosterone have been shown to affect LTP processes, with optimal LTP induction observed with low to moderate amounts of corticosterone, and impaired LTP induction observed in the absence of or very high levels of corticosterone, suggesting and inverted U-shaped dose dependency (Diamond, Bennett, Fleshner, & Rose, 1992). These findings suggest that mild to moderate amounts of acute stress may improve LTP processes, but high levels of acute or chronic stress may impair LTP processes. It would be interesting to see if manipulation of stress levels in humans lead to measurable differences in cortical plasticity, assessed with the Visual Cortical Plasticity Paradigm. One proposal would be to experimentally manipulate stress levels using the Cold Pressor Test (Lovallo, 1975), whereby individuals immerse their non-dominant hand into cold water (0-4°C) to above the wrist, for as long as possible (up to three minutes), and compare changes to VEPs following visual HFS in individuals who had and hadn't completed the Cold Pressor Test beforehand. Alternatively, a quasi-experimental design could investigate alterations in cortical plasticity in individuals experiencing chronic stress (e.g. shift workers, emergency service workers).

6.2.1.2.4.2. Brain derived neurotrophic factor

Increasingly, research is examining the role of brain derived neurotrophic factor (BDNF) in neuroplasticity. BDNF is one of four neurotrophins found in the mammalian CNS that are responsible for the regulation of neuronal growth, maintenance, and survival, as well as being an important molecular mediator of synaptic plasticity in the mature brain (Park & Poo, 2013; Tyler, Alonso, Bramham, & Pozzo-Miller, 2002). Approximately 25-50% of the population carry a single nucleotide polymorphism known as Val66Met which is associated with reduced secretion of BDNF and has previously been implicated in the efficacy of NMDAR-dependent neuroplasticity (Chen et al., 2004; Egan et al., 2003; Hariri et al., 2003; Lamb et al., 2015). Previous studies using the sensory-induced LTP paradigm have demonstrated reduced N1b potentiation in BDNF Met carriers (Thompson et al., *in prep*). Furthermore, Spriggs and colleagues found that LTP magnitude decreased with the increasing number of Met alleles an individual carried (Spriggs et al., 2019). Met carriers also showed a greater increase in P2 enhancement following HFS compared to Val homozygotes (Spriggs et al., 2017). Collectively, these results demonstrate that genetic factors relating to BDNF are strongly implicated in neuroplasticity processes, and research is still continuing to further elucidate the mechanisms by which genetic variants lead to physiological and behavioural differences.

Unfortunately, genetic testing of participants was not an available option for the studies in this doctoral thesis, so it is unclear how much (if any) of an effect genetic variation in BDNF concentration might have had on findings. Regarding developmental changes in BDNF, the human literature is fairly limited, but suggests that the concentration of BDNF increases during the first years of life (0-9 years) then remains relatively consistent from thereon (Katoh-Semba et al., 2007). This suggests that developmental changes in BDNF might not be too much of an issue in Chapter 4, where the youngest participants were 13 years of age. Considerably more research has examined the relationship between BDNF and autism, however the results have been inconsistent. Some researchers have suggested that BDNF is involved in the pathogenesis of autism, due to its effect on the serotonergic system (Nishimura et al., 2007), and have shown that BDNF levels are significantly higher in autistic individuals compared to controls (Correia et al., 2010; Miyazaki et al., 2004; Nelson et al., 2001; Nishimura et al., 2007). However, others have demonstrated reduced BDNF in ASC (Al-Ayadhi, 2012; Nelson et al., 2006; Ramsey et al., 2013) or no differences at all (Connolly et al., 2006; Mansour, Mohamed, Azam, & Henedy, 2010). Therefore, future studies should seek to examine the association between BDNF levels and cortical plasticity, and associated factors, using sensory tetanization paradigms

6.2.2. Longitudinal studies

The present research, and most of the wider literature, uses a cross-sectional approach to investigate sensory responsivity and related constructs in typically and atypically developing populations. Longitudinal studies of sensory responsivity in typically and atypically developing adolescents would overcome a number of limitations associated with cross-sectional studies. For example, as previously mentioned, the results of Chapter 4 indicated several significant differences between early-adolescents and late-adolescents, but few significant differences between late-adolescents and adults. Given that there was approximately a 4-year age gap between early- and late-adolescents, it is unclear when cortical plasticity first appears to be more adult-like. Furthermore, cross-sectional studies may struggle to capture certain behaviours that show a non-linear developmental trajectory from childhood, to adolescence, to adulthood (Casey, 2015). Conversely, longitudinal studies, that take repeated observations of the same cohort of individuals over multiple time points, address many of the issues associated with cross-sectional studies by reducing the error variance associated with comparing different individuals from different age groups. That's not to say longitudinal studies are without their drawbacks; they are more costly in terms of money and time and can suffer if there are high levels of attrition. Despite these limitations, longitudinal studies would allow for examination of changes in individuals sensory responsivity and associated behavioural and psychological constructs as they move through different stages of adolescence into adulthood.

6.2.3. Interventions

Findings from Chapter 3 indicated that individuals with high sensation seeking scores, and low sensory sensitivity scores (i.e. individuals with high neurological thresholds) were more likely to engage in risk-taking behaviours. This may provide an alternative target for intervention programs aimed at reducing risk-taking behaviours in adolescents. Traditionally, intervention programs that are based on educating adolescents about the potential negative consequences of risk-taking activities have been mostly unsuccessful in reducing risk-taking behaviours (Steinberg, 2008), with studies showing that adolescents are as aware as adults of the potential outcomes of risk-taking behaviours (Beyth-Marom et al., 1993). In facts, adolescents may actually believe they are more vulnerable to these negative consequences than adults (Millstein & Halpern-Felsher, 2003). Despite adolescents being aware of, and believing they are vulnerable to the negative consequences of risky activities, they continue to engage in risky-activities anyway (particularly when in the presence of peers; Gardner & Steinberg, 2005). An alternative intervention that works on reducing neurological thresholds in adolescents prone-to risk-taking behaviours to a more typical neurological threshold level might help to reduce their need for strong sensory stimulation, and in turn reduce their desire to engage in risk-taking activities. Sensory Integration Therapy (based on Jean Ayres Sensory Integration Theory;

Ayres, 1972) aims to help individuals with sensory processing issues by exposing them to sensory stimulation in a structured, repetitive way with the hope that over time, neural responses will adapt and process sensory information more efficiently. Consequently, interventions based on Sensory Integration Therapy could be targeted at adolescents who are prone-to risk-taking behaviours, with the aim of reducing their neurological thresholds and their desire for strong sensory stimulation.

6.6.4. Alternative self-report measures of sensory responsivity

This doctoral thesis aimed to explore the relationship between sensory responsivity and cortical plasticity in typically developing adolescents, and adults with ASCs. No relationship between sensory responsivity and cortical plasticity was established in this body of work, although this may be due to limitations with the measures of sensory responsivity utilised in this project. However, other measures of sensory responsivity may still demonstrate a relationship with cortical plasticity. Whilst the AASP is perhaps the most commonly used measure of sensory processing in the literature, there are several other questionnaire measures of sensory processing, including the Sensory Experiences Questionnaire (SEQ; Baranek, David, Poe, Stone, & Watson, 2006), the Sensory Processing Measure (SPM; Parham, Ecker, Kuhaneck, Henry, & Glennon, 2006), the Sensory Perception Quotient (SPQ; Tavassoli, Hoekstra, et al., 2014), and the Sensory Questionnaire (Liss, Saulnier, Fein, & Kinsbourne, 2006). I believe that review of these sensory processing questionnaires is needed to establish what aspects of sensory processing each questionnaire measures, establishing shared and unique variance accounted for by different questionnaires and scales, so that researchers are better able to select the questionnaire most suited to the needs of their study.

6.7. Final conclusions

This doctoral work aimed to advance our current understanding of sensory responsivity and cortical plasticity in typically and atypically developing populations. To achieve this aim, I first examined the relationships between sensory responsivity, risk-taking behaviours, and negative affect in typically developing adolescents as they transition into adulthood. Second, I examined developmental differences in cortical plasticity, again in typically developing adolescents and adults, as a possible neural mechanism underlying individual differences in sensory responsivity. Third, I examined differences in cortical plasticity again, this time in autistic adults and neurotypical matched controls. The results of this body of work argue that sensory responsivity is significantly related to behavioural and psychological outcomes in typically developing adolescents, and that cortical plasticity is developmentally regulated; however more work is needed to understand the neural mechanisms underlying altered sensory processing in ASCs. All of the studies reported in this thesis need to be replicated and extended in the future. Collectively, and significantly, this doctoral work provides the first step in finding

innovative ways to investigate sensory responsivity and cortical plasticity in typically and atypically developing populations.

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Appendix

Appendix 1 – The Life Span Risk-Taking Inventory

Instructions: You will be asked about different emotions and experiences you might have had at different points in your life. A lot of the questions will be about risk-taking.

By risk-taking, we mean engaging in activities or behaviours that could potentially be bad for you.

What you might have thought was risky as a child, you might not consider to be as risky now. So when we ask you about risk-taking in your childhood, and adolescence, please try to answer based on **how you felt at that age**.

Please use the scale below when answering the following questions:

1 = Never

2 = Rarely

3 = Sometimes

4 = Often

5 = Always

Questionnaire

How often did you take **risks** at different points in your life?

	1	2	3	4	5
Childhood	❍	❍	❍	❍	❍
Adolescence	❍	❍	❍	❍	❍
Adulthood	❍	❍	❍	❍	❍

In your **childhood,** did you feel…?

	1	2	3	4	5
Afraid	❍	❍	❍	❍	❍
Happy	❍	❍	❍	❍	❍
Anxious	❍	❍	❍	❍	❍
Confident	❍	❍	❍	❍	❍

Depressed	❍	❍	❍	❍	❍
Safe	❍	❍	❍	❍	❍

In your **adolescence**, did you feel…?

	1	2	3	4	5
Afraid	❍	❍	❍	❍	❍
Happy	❍	❍	❍	❍	❍
Anxious	❍	❍	❍	❍	❍
Confident	❍	❍	❍	❍	❍
Depressed	❍	❍	❍	❍	❍
Safe	❍	❍	❍	❍	❍

In your **adulthood,** do you feel…?

	1	2	3	4	5
Afraid	❍	❍	❍	❍	❍
Happy	❍	❍	❍	❍	❍
Anxious	❍	❍	❍	❍	❍
Confident	❍	❍	❍	❍	❍
Depressed	❍	❍	❍	❍	❍
Safe	❍	❍	❍	❍	❍

In your **childhood** …?

	1	2	3	4	5
Did your friends take risks?	❍	❍	❍	❍	❍
Did you take risks with your friends?	❍	❍	❍	❍	❍
Did you take more risks than your friends?	❍	❍	❍	❍	❍
Did you take more risks than the average child?	❍	❍	❍	❍	❍

In your adolescence …?

	1	2	3	4	5
Did your friends take risks?	❍	❍	❍	❍	❍
Did you take risks with your friends?	❍	❍	❍	❍	❍
Did you take more risks than your friends?	❍	❍	❍	❍	❍
Did you take more risks than the average adolescent?	❍	❍	❍	❍	❍

In your **adulthood** …?

	1	2	3	4	5
Do your friends take risks?	❍	❍	❍	❍	❍
Do you take risks with your friends?	❍	❍	❍	❍	❍
Do you take more risks than your friends?	❍	❍	❍	❍	❍
Do you take more risks than the average adult?	❍	❍	❍	❍	❍

Appendix 2 – Supplementary analyses for Chapter 4

Analyses conducted in Chapter 4.3.1.3 indicated that there was a significant interaction between age group and VEP amplitude. As discussed in that section, inspection of the grand-averaged VEPs (Figure's 4.5 to 4.7) show that there are developmental differences in VEP pattern, whereby early-adolescent VEPs are generally more positive in polarity (as if they are hanging above the x axis) compared to VEPs from older age groups. This is consistent with what we know about changes in neural structure during adolescence associated with changes in VEPs (see Chapter 1.6.4), and also consistent with previous findings from our lab (Levita et al., 2015) which are not related to experimental manipulation. Therefore, pairwise comparisons comparing differences between the age groups for VEP component amplitudes are presented here for transparency. Descriptive statistics are presented in Table A2.1.

Benjamini-Hochberg corrected pairwise comparisons revealed that mean N1 amplitudes for early-adolescents were significantly different to those of late-adolescents and adults during all VEP assessments (all p's <.001). These results demonstrate that whilst early-adolescents mean N1 amplitudes were positive in polarity for each VEP assessment, late-adolescents and adults both had mean N1 amplitudes that were below zero. There were no significant differences between late-adolescents and adults in mean N1 amplitude values during any VEP assessments (all *p*'s > .137). Pairwise comparisons revealed that there were no significant differences between any of the age groups in mean P2 amplitudes, for any of the VEP assessments (all *p*'s > .159).

Table A2.1
Means and Standard Deviations of mean amplitude across VEP time windows measured during baseline and Post-HFS assessments for each age group.

		Age Group					
		Early-Adolescent		Late-Adolescent		Adult	
VEP Assessment	ERP Component	*M*	*SD*	*M*	*SD*	*M*	*SD*
Baseline	N1	6.91	7.43	-3.23	8.69	-6.77	5.61
	P2	15.45	7.99	12.72	6.52	11.91	8.26
Post-HFS 1	N1	4.36	8.54	-5.64	9.63	-9.22	5.67
	P2	8.15	8.30	8.59	6.81	8.48	8.04
Post-HFS 2	N1	4.26	6.70	-4.80	9.34	-8.29	5.95
	P2	9.93	8.64	10.36	7.36	10.07	8.18
Post-HFS 2	N1	7.59	8.91	-4.38	9.01	-7.79	6.02
	P2	12.68	9.07	13.31	6.92	13.28	8.69

Appendix 3 – Supplementary analyses for Chapter 4

A three-way mixed ANOVA was run to examine the effect of VEP assessment (baseline, Post-1, Post-2, and Post-3), hemisphere (left, right), and age group (early-adolescent, late-adolescent, and adult) on mean N1 amplitude measured over two parieto-occipital clusters (left hemisphere = P7 and PO7; right hemisphere = P8 and PO8). Results revealed no significant three way interaction, F (5.60, 151.14) = 1.68, p = .136, η_p^2 = .058. Furthermore, there were no significant two-way interactions between VEP assessment and hemisphere (F (2.80, 151.14) = 1.05, p = .371, η_p^2 = .019), hemisphere and age group (F (2, 54) = 1.06, p = .354, η_p^2 = .038), or between block and age group (F (5.64, 152.40) = 2.02, p = .070, η_p^2 = .070).

There was a significant main effect of block, F (2.82, 152.40) = 7.18, p < .001, η_p^2 = .117. BH-corrected pairwise comparisons revealed that compared to baseline (M = 2.85), mean N1 amplitude over the parieto-occipital clusters was significantly reduced in Post-1 (M = 1.88; p < .001) and Post-2 (M = 1.96; p = .001), but not in Post-3 (M = 2.70; p = .494). There were no significant differences between mean amplitudes measured at Post-1 and Post-2 (p = .787), although amplitudes measured during both of these blocks were significantly smaller than those measured during Post-3 (Post-1 p = .002; Post-2 p = .011). Collectively, these results suggest that visual HFS leads to a short-term reduction in mean N1 amplitude over the parieto-occipital clusters, which returns to baseline values 20 minutes after HFS.

There was also a significant main effect of hemisphere, F (1, 54) = 12.48, p = .001, η_p^2 = .188, whereby activity was significantly more positive over the right hemisphere cluster (M = 3.37) compared to the left hemisphere cluster (M = 1.33, p = .001).

Finally, there was also a significant main effect of age group, F (2, 54) = 18.99, p < .001, η_p^2 = .413. BH-corrected pairwise comparisons revealed that mean N1 amplitude for early-adolescents (M = 8.15) was significantly more positive in polarity compared to late-adolescents (M = 1.18, p < .001) and adults (M = -2.28, p < .001). In addition, mean amplitude for late-adolescents was also significantly greater than for adults (p = .046). These results suggests that mean N1 amplitude over the parieto-occipital cortex was positive in polarity for both adolescent groups, with early-adolescents exhibiting a more positive mean amplitude, but negative in polarity for adults.

Collectively, these results demonstrate that following HFS, there were short-term reductions in mean N1 amplitude over the parieto-occipital cortex, but they had returned to baseline values after 20 minutes. Furthermore, activity was significantly more positive over the right hemisphere cluster, compared to the left, and was significantly more positive in early-adolescent participants, compared to late-adolescents and adults.