

# Multi-modal Stimulus-selective Response Modification: Cross-modal Properties of Sensory LTP-like Synaptic Plasticity

Christoffer Hatlestad



Hovedoppgave ved Psykologisk institutt

UNIVERSITETET I OSLO

Høst 2017



# **Multi-modal Stimulus-selective Response Modification: Cross-modal Properties of Sensory LTP-like Synaptic Plasticity**

*An event-related potentials (ERP) study investigating properties of the long-term potentiation-like (LTP-like) plasticity observed in the stimulus-selective response modification (SRM) paradigm, across auditory and visual modalities.*

© Christoffer Hatlestad

2017

“Multi-modal Stimulus-selective Response Modification: Cross-modal Properties of Sensory LTP-like Synaptic Plasticity”

Christoffer Hatlestad

<http://www.duo.uio.no>



# Abstract

**Background:** Long-term potentiation (LTP) and depression (LTD), innate mechanisms of synaptic plasticity, remain the principal candidate underlying learning and memory in the intact human brain. However, demonstrations of LTP and LTD have been limited to animal models and *in vitro* human brain slices. Recently, the modulation of sensory-evoked potentials following tetanic high frequency sensory stimulation has emerged as a potential non-invasive index of naturally occurring LTP in neocortex. This paradigm has been coined stimulus-selective response modification (SRM), and has been demonstrated using both visual and auditory stimulation. Intriguingly, recent findings from animal models have established that the SRM phenomenon shares important features with LTP. Prior reports have focused on the demonstration of the SRM effect in a single sensory modality, limiting the range of possible inferences to within-modality territory. Building on this, the current study is the first to introduce a multi-modal SRM approach, aiming to probe for cross-modal associations of the SRM phenomenon.

**Methods:** EEG was recorded during a novel dual visual/auditory SRM paradigm and visual and auditory evoked potentials (VEPs/AEPs) were collected from 41 participants. Amplitude values were measured from the peaks of visual components C1, P1, and N1, and auditory components P50, N1, and P2. Responder rates were calculated and compared across a selection of criteria.

**Results:** Significant SRM-driven modulations of component amplitudes were found at visual components C1, P1, and N1, and also in the P1-N1 absolute difference, and at auditory component P2, and in the N1-P2 absolute difference. Responder rates were generally higher for the visual than the auditory data. A nominally significant cross-modality correlation between visual component C1 and auditory component P2 was evident.

**Conclusion:** The current multi-modal SRM approach appears to effectively index LTP-like plasticity in both the visual and the auditory modality. The finding of a nominally significant correlation between SRM-driven amplitude modulations of sensory ERP components in each modality, suggests a common mechanism for sensory-induced LTP-expression in both modalities.

# Thesis details

## Author

Christoffer Hatlestad

## Title

Multi-modal Stimulus-selective Response Modification: Cross-modal Properties of Sensory LTP-like Synaptic Plasticity

## Supervisors

- Stein Andersson, PhD (Department of Psychology, University of Oslo)
- Torgeir Moberget, PhD (NORMENT, Oslo University Hospital)

## Note on thesis data

The thesis data are extracted from an extensive project investigating human LTP-like plasticity as measured within the SRM framework. This project is led by thesis supervisor prof. Stein Andersson. The author, Christoffer Hatlestad, has been part of the project group for the past two years. His contributions include development of the experimental paradigm, extensive piloting, and processing and analyses of ERP data.





# Preface and acknowledgment

I can remember the moment this particular adventure began. I was asked if programming of experimental paradigms was something I would enjoy. And of course, naïve and slightly over-confident, without any prior experience of even the simplest of code, I accepted. I was given a MATLAB script, providing code for running a basic pattern-reversal visual evoked potential paradigm.

Now, two years and countless of hours spent coding later, my scripts have not only made the current thesis possible, but have also contributed to several projects, small and large. Perhaps I am still slightly over-confident.

The pillars on which my scientific interest is built, were raised in the autumn of 2013. Responsible was Torgeir Moberget, who is as much of an inspiration today as he was then. For all the time you have spent tutoring and inspiring me, you will always have my deepest gratitude.

However, a sustainable career is not built on inspiration alone. Since the spring of 2014, Stein Andersson has provided the best framework a young and somewhat headstrong student could hope for. I have always had the feeling of working *with* you, and not *for* you, an important source of fuel for my progression. You are a brilliant supervisor. Thank you.

To Trine Rygvold Waage, for collecting data like the hero you are. We still have much to do.

To friends and family, for your acceptance and understanding during this period of intense work. Whether I need study participants or Red Bulls, you always contribute.

Finally, to Sunniva, my soon-to-be wife, for being accepting and supportive, regardless of how many hours I spend in front of the computer screen, staring tirelessly at tiny voltage fluctuations.

Hopefully, the thesis will contribute to the stimulation of some synapses in the reader!



# Table of contents

<b>1</b>	<b>Introduction .....</b>	<b>1</b>
1.1	<i>Background .....</i>	1
1.1.1	Terminology .....	3
1.2	<i>Synaptic plasticity: Long-term potentiation .....</i>	3
1.2.1	Relevance to memory and learning .....	3
1.2.2	Neurobiological foundation .....	4
1.3	<i>Stimulus-selective response modification .....</i>	5
1.3.1	The SRM paradigm .....	5
1.3.2	SRM and LTP: Shared features .....	6
1.3.3	Modality-specificity .....	7
1.4	<i>Electrophysiology: Event-related potentials (ERP) .....</i>	8
1.4.1	ERP fundamentals .....	8
1.4.2	Application of ERP .....	9
1.4.3	Relevant ERP components .....	11
1.5	<i>The current study .....</i>	13
1.5.1	Multi-modal approach .....	13
1.5.2	Methodological considerations .....	13
1.5.3	Responder rates .....	14
1.5.4	Hypotheses .....	14
<b>2</b>	<b>Methods .....</b>	<b>16</b>
2.1	<i>Participants .....</i>	16
2.2	<i>Procedures .....</i>	16
2.2.1	Visual stimulus-selective response modification (V-SRM) .....	16
2.2.2	Auditory stimulus-selective response modification (A-SRM) .....	17
2.3	<i>EEG/ERP data .....</i>	18
2.3.1	EEG recording .....	18
2.3.2	Processing of EEG/ERP data .....	19
2.3.3	ERP measurements .....	20
2.4	<i>Analyses .....</i>	21
2.4.1	Data selection, extraction, and computation .....	21
2.4.2	Statistical approaches .....	22
<b>3</b>	<b>Results .....</b>	<b>24</b>
3.1	<i>Replication: Amplitude modulation of components .....</i>	24
3.1.1	Descriptive statistics .....	24
3.1.2	Component amplitude modulation .....	27
3.1.3	Statistical power .....	30
3.2	<i>Responder rates .....</i>	30
3.3	<i>Cross-modal effects .....</i>	30
3.3.1	Correlational analysis: Within-subject effect sizes .....	30
3.3.2	Cross-modality responder rates .....	31
<b>4</b>	<b>Discussion .....</b>	<b>33</b>
4.1	<i>SRM-induced LTP-like plasticity .....</i>	33
4.1.1	Modality-specific replication .....	33
4.1.2	Within-subject SRM: Responder rates .....	37
4.1.3	Cross-modality correlation .....	39
4.2	<i>Methodological considerations .....</i>	41
4.3	<i>Limitations .....</i>	42
4.4	<i>Themes for future research .....</i>	42
<b>5</b>	<b>Conclusion .....</b>	<b>43</b>

<b>References .....</b>	<b>44</b>
<b>Tables</b>	
1.1: SRM protocol parameters in a selection of relevant publications .....	14
2.1: V-SRM parameters .....	17
2.2: A-SRM parameters .....	18
2.3: Epoch rejection parameters .....	20
3.1: Descriptive statistics of components of interest .....	24
3.2: Modulation of VEP components .....	28
3.3: Modulation of AEP components .....	28
3.4: Analyses of statistical power .....	30
3.5: Responder rates by criteria .....	30
3.6: Correlation matrix for within-subject effect sizes .....	31
3.7: Cross-modality responder rates by within-subject effect size criteria .....	32
<b>Figures</b>	
1.1: Components of the AEP .....	12
1.2: Components of the VEP .....	12
2.1: V-SRM experimental setup .....	17
2.2: A-SRM experimental setup .....	18
3.1: Box plots of component measures .....	25
3.2: Grand average of all VEPs (including SEM) .....	26
3.3: Scalp amplitude topography for the VEP components .....	26
3.4: Grand average of all AEPs (including SEM) .....	27
3.5: Scalp amplitude topography for the AEP components .....	27
3.6: Box plots of VEP components voltage modulations .....	29
3.7: Box plots of AEP components voltage modulations .....	29
3.8: Visual C1 and auditory P2 relationship .....	31

# 1 Introduction

## 1.1 Background

The processes of memory and learning are imperative to all biological organisms, crucially enabling adaptive behaviour. The declarative (explicit) memory function underpins conscious recollection of knowledge and events in context, whereas its non-declarative (implicit) counterpart comprises changes in skilled behaviour, and changes in the ability to detect or identify familiar stimuli in the environment (Milner, Squire, & Kandel, 1998). At the neurophysiological level, these processes are implemented in structural and functional experience-dependent changes in the central nervous system (CNS). Collectively, such mechanisms are referred to as mechanisms of *neuroplasticity*. A well-characterised form of plasticity in the CNS, implemented as alterations of synaptic efficacy, is known as *long-term potentiation* (LTP) (and its inverse, *long-term depression*; LTD) (Bliss & Lomo, 1973). Importantly, LTP and LTD share critical features with memory, suggesting a fundamental role in the neural basis of memory functions. Furthermore, investigations into psychiatric patient groups, largely depression (Castrén, 2013; Marsden, 2013), schizophrenia (Bhandari, Voineskos, Daskalakis, Rajji, & Blumberger, 2016), and bipolar disorder (Schloesser, Huang, Klein, & Manji, 2007; Soeiro-de-Souza et al., 2012), provide support for the hypothesis that synaptic plasticity may be an underlying cause of the disorders' accompanying behavioural characteristics.

Traditionally, investigations of LTP in humans have been limited. Although well-documented in animal models, valid non-invasive approaches suited for human research have remained elusive. However, recently, LTP-like plasticity effects have been indexed using the event-related potential (ERP) technique of the electroencephalogram (EEG) during a paradigm of tetanic (high-frequency) sensory stimulation, occasionally referred to as *stimulus-selective response modification* (or *potentiation*) (SRM/SRP) (Clapp, Hamm, Kirk, & Teyler, 2012; Clapp, Kirk, Hamm, Shepherd, & Teyler, 2005; Teyler et al., 2005). The phenomenon is usually referred to as a *LTP-like* plasticity effect, as its precise neural implementation remains unclear. However, the plasticity effect displayed in the SRM paradigm shares several of the defining features of LTP. The growing body of literature on the SRM plasticity effect in humans and animal models is steadily building evidence of an

association between sensory-induced modification of evoked potentials and LTP (Cooke & Bear, 2012).

The current study aims to build upon the recent advances in non-invasive investigations into synaptic neuroplasticity. It targets the stimulus-selective response modification (SRM) paradigm as a potential biomarker, non-invasively indexing capacity for, or integrity of, cortical LTP-expression. Importantly, biomarkers associated with plasticity might be of significant clinical application, considering the possible role of aberrant plasticity processes in several psychiatric disorders, including depression, bipolar disorder, and schizophrenia. Intriguingly, several studies have reported abnormalities in regard to visual SRM-induced plasticity in these patient groups (Cavuş et al., 2012; Elvsåshagen et al., 2012; Jahshan, Wynn, Mathalon, & Green, 2017; Normann, Schmitz, Fürmaier, Döing, & Bach, 2007).

Previous work on the SRM paradigm have focused on a single sensory modality; either visual or auditory. To the extent of available literature, evidence of SRM-plasticity has never been documented in both modalities within the same individuals over the course of one session. By extending the SRM paradigm into the cross-modal domain, the current study provides the means for assessments beyond those of system-specific effects. Importantly, in conceptualising the integrity of plasticity processes as a global property, rather than specific to a sensory system, correlation between SRM measures of different modalities would provide evidence in favour of the generalised LTP hypothesis (Cooke & Bear, 2012). Moreover, system-specific plasticity indices have less explanatory power in regard to clinical disorders than an index reflecting a global capacity. The main aim of the project the current study is part of, is to develop and validate reliable methods and analysis approaches for indexing SRM-induced plasticity across multiple modalities.

The thesis will provide an introduction to relevant aspects of long-term potentiation (LTP), stimulus-selective response modification (SRM), and the event-related potential technique (ERP). Methodological considerations for the current study will be discussed in light of these themes. Thereafter, an account of the current study follows, including a discussion of results in light of existing basic research on the SRM phenomenon.

### 1.1.1 Terminology

Various terminology has been used on the current phenomenon, and no consensus on terms is readily apparent. The reference to *stimulus-selective response modification (SRM)* in this report, echoes that of *stimulus-selective (or stimulus-specific) response potentiation (SRP)* used in a number of publications. *Modulation* and *modification* is used interchangeably. The term *modulation/modification* is chosen to emphasise the ambiguity regarding the polarity of electrophysiological potentials, as discussed by Lahr et al. (2014) in the context of fMRI.

## 1.2 Synaptic plasticity: Long-term potentiation

### 1.2.1 Relevance to memory and learning

Memories and learned skills are the behavioural manifestation of their neural underpinnings. The current principal candidates to facilitate these processes are *long-term potentiation (LTP)* and *depression (LTD)*. However, the idea that structural changes in the synapses of neural networks are at the core of memory function, is not of recent date. This notion was introduced at the beginning of the 20<sup>th</sup> century by Santiago Ramón y Cajal (Bliss & Collingridge, 1993). Later, the Hebbian model of synaptic strength modulation as the cellular mechanism for learning and memory formation, was instated as a refinement of Cajal's early proposal (Hebb, 1949). Hebb postulated that changes in synaptic strength occur as a consequence of coincidental pre- and post-synaptic activations of the same synapse. Such synchronous activity would enhance the specific synapse's probability of being activated again, by lowering its threshold of firing, over a prolonged period of time. The first experimental demonstration of the Hebbian model, was described in an abstract by Norwegian physician Terje Lømo (Lømo, 1966). The term LTP was first coined in a landmark publication some years later (Bliss & Lømo, 1973). In a recent review, influential LTP researcher Roger A. Nicoll states the following about the term-coining publication (2017): "It is impossible to overstate the importance of this paper; it is truly a landmark in the field of neuroscience (...)". As the short-term aspects of LTP (i.e. commonly within the first hour after induction) are both more extensively documented and more relevant to the current report than long-term properties of LTP, the thesis will limit its discussion of LTP to the former aspects.

During the last four decades, the body of literature on LTP has been rapidly growing, mainly targeting cellular and molecular mechanisms through the study of animal models. While a

thorough review of this literature is beyond the scope of the current thesis, three context-relevant characteristics of LTP will need to be considered; longevity, input-specificity, and associativity. These features are closely tied in with the aforementioned Hebbian postulates regarding the strengthening or weakening of synaptic efficacy as the neural fundament for the formation of memories, and have all been substantially documented at the cellular and molecular level (Bliss & Cooke, 2011). Longevity refers to the long-lasting durability of memories, a property that is also evident in LTP; one study demonstrated stable elicitation of LTP in the rat dentate gyrus that lasted months and up to a year (Abraham, Logan, Greenwood, & Dragunow, 2002). At the cellular level, input-specificity translates into the capacity for neighbouring synapses to be independently potentiated or de-potentiated, possibly explaining the important Hebbian principle of specificity in memory function. On the other hand, human learning and memory functions are also inherently associative. LTP is also associative, in the way insufficiently stimulated synapses get potentiated when the weak stimulation co-occurs with LTP-sufficient stimulation at other synapses on the same cell. Consequently, considering the fit between LTP characteristics and the Hebbian learning model, LTP is considered a necessary, albeit not exclusive, plasticity mechanism underlying learning and memory in the brain.

### **1.2.2 Neurobiological foundation**

To date, research on LTP and LTD in humans has been limited due to its inherently invasive nature. No direct demonstration of LTP or LTD at the level of the synapse in the intact, living human brain has been reported (Cooke & Bliss, 2006). Knowledge has primarily evolved from the study of rodent brain slices, and more recently excised slices of human cortical tissue acquired from surgical resection on patients with severe epileptic seizures. Importantly, the properties associated with LTP displayed in human brain slices are highly similar to those evident in animal models (Beck, Goussakov, Lie, Helmstaedter, & Elger, 2000; Chen et al., 1996). The complex cellular and molecular mechanisms enabling the expression of LTP are extensively documented and considered well understood (Feldman, 2009; Lüscher & Frerking, 2001; Lømo, 2012; Malinow, 2003). In short, LTP is induced by increasing the density of AMPA receptors sensitive to glutamate inside the post-synaptic cell membrane. This process is made possible through the release of specific ions in post-synaptic NMDA receptors, leading to activation of the kinases responsible for the increase of the mentioned AMPA receptors. This cascade of micro-processes, which results in a more efficient synapse



by the way of heightened post-synaptic glutamatergic excitation, is initiated when a sufficiently strong depolarisation of the post-synaptic neuron co-occurs with pre-synaptic activity.

## **1.3 Stimulus-selective response modification**

### **1.3.1 The SRM paradigm**

LTP has been most extensively studied in preparations of hippocampal tissue, but has also been demonstrated in slices of neocortex (e.g. rat, Kirkwood and Bear (1994)). Neuronal systems of neocortical origin are generally more available to non-invasive approaches, suitable for research in humans. Specifically, sensory-induced cortical activity has been identified as an accessible index of the integrity of LTP. This approach utilises training-independent sensory learning (TISL; Dinse & Tegenthoff, 2015), sensory-based learning, employing sensory stimulation protocols translated from the protocols used to induce LTP on the cellular level. Essentially, such protocols adhere to the principles of LTP-induction following high-frequency stimulation, and LTD-induction following low-frequency stimulation. Basic auditory and visual TISL stimulation (pure tone beeps and checkerboard textures, respectively) elicits cortical local field potentials, which may be reliably measured using electroencephalography (EEG) and its derivative, the event-related potential technique (ERP). A brief introduction to this method of assessment is given in a later section. In the SRM paradigm, local field potentials originating from the sensory system and sensory cortices of the modality in question, are measured before and after the presentation of a high-frequency tetanic sensory stimulation (i.e. a TISL protocol). Interestingly, the voltage amplitudes of the sensory-evoked potentials are altered after the tetanic stimulation compared to pre-stimulation levels. The phenomenon has been demonstrated in both visual (e.g. Teyler et al., 2005) and auditory modality (e.g. Clapp, Kirk, et al., 2005), separately, employing the ERP technique, and also using functional magnetic resonance imaging (fMRI) (Clapp, Zaehle, et al., 2005; Zaehle, Clapp, Hamm, Meyer, & Kirk, 2007). Importantly, as will be discussed in the following section, the SRM-induced alterations of sensory-evoked potential amplitudes share several defining properties with the LTP model. The event-related potential complexes in focus, are the visual evoked potential (VEP) and the auditory evoked potential (AEP), in visual and auditory research respectively. The VEP and AEP will be briefly considered in a later section.

The original publication reporting the SRM effect demonstrated the selective potentiation of the voltage amplitude of the N1b component of the human VEP (Teyler et al., 2005). The procedure consisted of repeated presentations of briefly flashing black and white checkerboards, followed by a high frequency (tetanic) stimulation phase, where the same stimuli were presented at a significantly higher rate, before returning to the original presentation frequency. Importantly, the observed amplitude alteration was only evident after the tetanic stimulation, and remained potentiated up to an hour after the induction. Shortly after, the same group applied similar principles to an auditory equivalent of the paradigm, reporting selective potentiation of the N1 component of the AEP following a tetanic stimulation of a specific pure tone (Clapp, Kirk, et al., 2005). Subsequent studies have focused on elucidating the association between the sensory-induced LTP-like synaptic plasticity demonstrated in the SRM paradigm, and LTP as a basic phenomenon. Recently, attention has turned toward exploring this phenomenon in relation to various factors known to be associated with plasticity in humans, like physical activity (Smallwood et al., 2015) and ageing (Spriggs, Cadwallader, Hamm, Tippett, & Kirk, 2017).

### **1.3.2 SRM and LTP: Shared features**

To further the understanding of LTP/LTD-dependent neuroplasticity in humans, non-invasive assessment techniques have been sought after. In this regard, the SRM paradigm is considered one of the most promising approaches. This notion is supported by research indicating that the SRM phenomenon shares many of its features with LTP. In essence, the altered evoked potential amplitude in the post-stimulation assessment compared to pre-stimulation, is considered to represent, at the neuronal level, a modulation of synaptic communication in the stimulated sensory system. Following this line of thought, the tetanic stimulation in the SRM paradigm is designed as a sensory equivalent to the high frequency electrical stimulation applied in LTP studies in animal models and in excised human brain tissue. Consequently, the SRM effect might have potential as a non-invasive biomarker of the integrity of LTP-expression in living humans (Cooke & Bear, 2010). The majority of research on the SRM paradigm has sought to establish whether the measured electrophysiological alterations comply with the same principles as those of LTP. There is promising evidence indicating that several of the fundamental hallmarks of LTP, which was briefly discussed in relation to memory function earlier, are closely related to the expression of the SRM effect as well. In humans, the issues of input specificity (McNair et al., 2006),

stimulus orientation specificity (Ross et al., 2008), long-lasting in terms of duration, low-frequency de-potentialization (e.g. Teyler et al., 2005), and N-methyl-D-aspartate (NMDA) receptor dependency (Forsyth, Bachman, Mathalon, Roach, & Asarnow, 2015) have all been addressed. Moreover, the role of brain-derived neurotrophic factor (BDNF), and the genes involved in its expression, in LTP (Pearson-Fuhrhop, Kleim, & Cramer, 2009) is similarly evident in the SRM phenomenon (Lamb et al., 2015). Also, a convincing line of evidence comes from equivalent experiments in mice (Cooke & Bear, 2010, 2014) and rats (Eckert, Guévremont, Williams, & Abraham, 2013).

### **1.3.3 Modality-specificity**

LTP-like plasticity effects, as discussed from the perspective of SRM, have been demonstrated in other neuronal systems in humans, including motor cortex, demonstrated as modulation of motor-evoked potentials (MEP) in the paired-associate stimulation (PAS) paradigm (Müller-Dahlhaus, Orekhov, Liu, & Ziemann, 2008; Player, Taylor, Alonzo, & Loo, 2012). Also in cognitive learning tasks using motor skill learning, LTP-like effects have been demonstrated (Cantarero, Lloyd, & Celnik, 2013; Reis et al., 2009; Xu et al., 2009). However, it remains unclear if the levels of modulation are associated between the different systems within the individual (Klöppel et al., 2015). One study identified a significant correlation between LTP-like plasticity induced through the PAS protocol, and motor skill learning, as indexed by the rotary pursuit task (Frantseva et al., 2008). Two other studies, however, failed to reach the same conclusion (Klöppel et al., 2015; López-Alonso, Cheeran, Río-Rodríguez, & Fernández-del-Olmo, 2014). Similarly, List et al. (2013) found no association between LTP-like PAS effect and scores on neurocognitive assessments (executive functions, verbal fluency, verbal memory, visuospatial skills, and verbal and spatial working memory). The contrasting conclusions may be due to high inter-individual variability of LTP-like effects (Klöppel et al., 2015), which in turn might be influenced by factors such as age (Müller-Dahlhaus et al., 2008), time of day (Sale, Ridding, & Nordstrom, 2007), and attention (Stefan, Wycislo, & Classen, 2004).

To the extent of the author's knowledge, only one published study has targeted the potential association between the plasticity effects induced by the TISL protocol (SRM) and by the PAS protocol (Klöppel et al., 2015). The study also included both a motor and a verbal learning task. In comparing effect sizes and responder rates from the different LTP-like

plasticity-inducing approaches, they found evidence of correlation between potentiation of VEP and MEP components, suggesting a common pathway of LTP-like plasticity across the motor and visual systems. However, no correlation between PAS-induced potentiation and motor skill learning was found. The authors suggest that the role of higher cognitive functioning, and its influencing factors, might be implicated as a moderator in these findings. As motor skill learning relies more heavily on higher cognitive functioning than the PAS and SRM protocols do, a correlation between the two latter might be more prominent. The same line of reasoning would also apply to the association between SRM-induced effects across visual and auditory modalities.

## **1.4 Electrophysiology: Event-related potentials (ERP)**

### **1.4.1 ERP fundamentals**

In the current study, electrophysiological data were acquired using scalp-recorded electroencephalography (scalp EEG). Electrophysiological signals recorded from the scalp are advantageous in several ways, most prominently as a non-invasive way of exploring temporal (and to some degree, spatial) dynamics of various brain processes. In this regard, in order to isolate specific processes, the event-related potential (ERP) technique is commonly applied. At the core of ERP lies the time-locking of electrophysiological signals to given stimuli. This allows detailed investigation of temporal properties of the brain's processing of the stimulus in question. Importantly, and in contrast to other brain imaging methods, electric potentials may be recorded without delay, resulting in accurate measures of voltage in the time domain. The electrical potentials of interest are elicited by neurons involved in the processing of the given stimulus within the brain, primarily reflecting post-synaptic potentials from relatively homogenous populations of neurons. Upon depolarisation, the voltage distribution of the neuron and its immediate extracellular space is redistributed into that of a dipole. As any single post-synaptic potential is too small to be detected by electrodes at the scalp, rather large groups of spatially aligned neurons constitute the main source of electrophysiological potentials observable at the scalp. If spatially aligned and depolarised at approximately the same time, the sum of the neurons' resulting electromagnetic fields might achieve sufficient strength to stand out from spontaneous neural activity. The vector sum of the individual dipoles is relatively accurately represented as a single *equivalent current dipole*. Usually, the term *dipole* in ERP context refers to these aggregated representations. Moreover, the simultaneous firing of a relatively dense population of equivalently oriented

neurons generally signals execution of some specialised task, such as the initial processing of an external stimulus or a given stage in a task-dependent cognitive process.

As briefly mentioned, spontaneous electrophysiological activity is present at all times, and for event-related potentials to be meaningful, they need to stand out from the background “noise”. An important principle in ERP-based research, is to register the occurrence of the phenomenon in question over a large number of trials. Most ERP components of interest are made up of small but consistent voltage deflections, where any single recording is almost certainly obscured by larger, spontaneous potentials. However, if a large enough number of trials are averaged, random spontaneous voltage fluctuations not related to the stimulus will be cancelled out, leaving only the potentials of interest. Importantly, only potentials independent from the time-locking stimulus are suppressed in this manner. The remaining waveform is usually referred to as an event-related potential waveform (ERP waveform). More often than not, the ERP waveform still contains a considerable proportion of noise, due to various sources of confounding potentials, including, but not limited to, ocular or muscle activity, and alternating current circuits (line noise). Several approaches have been developed to maximise the signal-to-noise ratio in ERP waveforms, such as the application of frequency-based filters.

### **1.4.2 Application of ERP**

Several aspects of ERP waveforms may be subject for investigation. Traditionally, voltage amplitudes and latencies have been the most prominent recipients of scientific attention. The term *ERP component* is commonly used to describe a specific amplitude deflection at a specific latency elicited by a specific class of stimuli or tasks. Consequently, components are in this sense represented in the ERP waveform by voltage deflection peaks, of either positive or negative polarity. The peak polarity depends directly on the direction of the electromagnetic field the potential represents. However, despite the defining appearance of components in the ERP waveform, most components actually reflect the sum of multiple neural generators, active at approximately the same time. Thus, the traditional use of the term *component* in the context of ERP does not entail descriptions of true, well-isolated potentials directly associated with a given neural process. This is known as *the superposition problem*, because various potentials from different sources are superimposed onto the same waveform (Luck, 2014). Regardless, the functional definition of ERP components as context-specific

voltage deflections has been an important cornerstone in the field for five decades. Numerous components have been coined, associated with a wide range of sensory and cognitive processes. In spite of their limitations in precisely capturing isolated neural processes, ERP components serve as easily recorded indices of context-specific electrophysiological activity in the brain. Importantly, most ERP components are consistently observed in all healthy humans, paving the way into investigations of the abnormal.

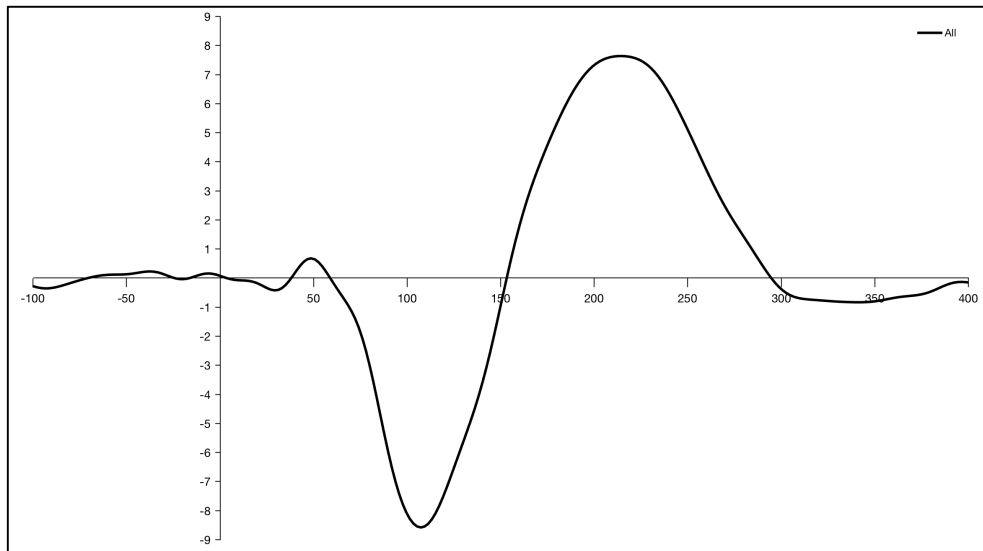
The application of ERP components as potential biomarkers holds great clinical promise. Inexpensive and relatively easy to administrate, even for large samples, ERP waveforms are directly related to neurotransmission, and may easily be investigated in animal models (Luck, 2014). Recent advances in methods and technology have promoted this application further, recruiting various approaches in order to manage the inherent impediments of ERP. Two important issues in this regard, are the noted superposition problem of ERP, and the localisation of the neural generators underlying the observed potentials. The spatial resolution of ERP is limited to calculating the distribution of voltage across the scalp at any given time or interval. Consequently, an increase of electrode density will improve the spatial resolution. However, regardless of the number of electrodes, the available voltage distribution pattern will remain at the level of the scalp, unable to address the actual origins of the signal within the brain. Several approaches aim to localise such deep sources, building on the well-documented assumption that an ERP waveform arises from the sum of potentials from distinctive populations of neurons, i.e. equivalent current dipoles. As the observable waveform is a mix of signals from all dipoles, the challenge lies in identifying each source and its contribution to the observed signal. Consequently, a waveform recorded at any given scalp electrode is a weighted sum of all source waveforms. The weighting is based on the electrode's relative position, orientation, and conductivity properties. Similarly, for each source (dipole), there is a weight for each electrode. All weights for a single source taken together, these weights constitute the scalp distribution of the source. In order to take advantage of these features, independent component analysis (ICA) is often employed (Delorme, Palmer, Onton, Oostenveld, & Makeig, 2012; Makeig & Onton, 2012). However, a thorough account of ICA is not of significant relevance to the current study, and is thus not provided.

### 1.4.3 Relevant ERP components

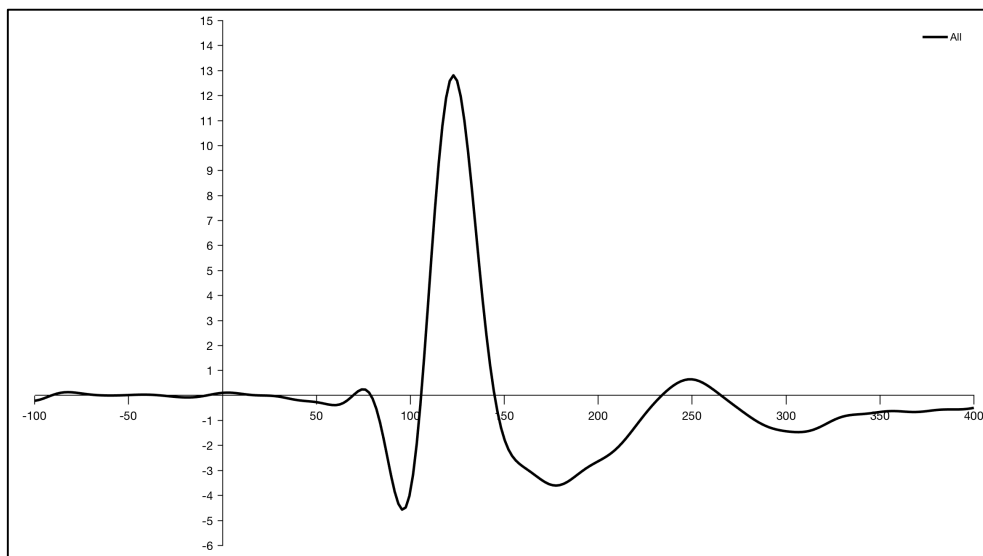
Traditionally, ERP components, when defined as characteristic task-dependent voltage deflections, have been separated into three main categories. These are sensory components, cognitive components, and motor components (Luck, 2014). Sensory components, often referred to as *exogenous* components, are grouped on the basis of their mandatory elicitation to the presence of an external stimulus. These potentials occur early in the ERP waveform, with onset latencies up to approximately 200 ms (Pratt, 2012), and are largely bottom-up driven, although certain components are to some degree susceptible to top-down modulation, such as attention (Hillyard & Anllo-Vento, 1998). In contrast, *endogenous* cognitive components are exclusively task-dependent, and are elicited by the neural substrates of task-related cognitive processes. In general, the cognitive components are evident from approximately 200 ms post-stimulus, and beyond. Motor components on the other hand, are summed potentials directly related to the preparation and execution of a given motor response. The categorisation of ERP components is a functional one, and the outlined category boundaries are not always clear-cut. The summed nature of observable ERP components, as discussed above, contributes to the blotting out of category boundaries, as any observed component might reflect combined potentials belonging to different categories. Relevant to the current study, sensory components associated with tone beeps and checkerboard textures will be considered briefly.

Modality-specific sensory evoked potentials, namely the auditory evoked potential (AEP) and the visual evoked potential (VEP), are extensively studied and well-documented phenomena. Both consist of early latency sensory components and, in tasks involving at least some cognitive effort, are followed by some potentials reflecting cognitive processing. The early sensory potentials arise from external stimuli traversing its corresponding sensory system, and ultimately arriving the relevant primary sensory cortex through a thalamic route. When present, late latency cognitive components represents task-relevant processing in various cortical areas, including secondary and tertiary sensory cortices. The scope of the current study encompasses primarily the sensory components of the sensory evoked potential complexes. The typical sensory components of the AEP include the P50, N1, and P2 (figure 1.1). VEP sensory components, on the other hand, are represented by the C1, P1, and N2 (figure 1.2). However, it must be noted that these components are all found to be somewhat susceptible to modulation by top-down processes, such as attention (Karns & Knight, 2009;

Proverbio, Zotto, & Zani, 2010; Woldorff & Hillyard, 1991). As will be discussed in the following section, the early components of the sensory evoked potentials from elemental auditory and visual stimulation, are potentially well suited as biomarkers associated with synaptic plasticity.



**Figure 1.1.** Components of the AEP. The plot represents the FCz channel (referenced to average of P9/P10) grand average of both baseline and post-stimulation measures across all subjects included in the current study. The three components of interest, are represented by the peaks at approximately 50 ms (P50), 100 ms (N1), and 220 ms (P2). Time points are not corrected in regard to equipment signal transfer latency.



**Figure 1.2.** Components of the VEP. The plot represents the Oz channel (referenced to average of AFz) grand average of both baseline and post-stimulation measures across all subjects included in the current study. The three components of interest, are represented by the peaks at approximately 100 ms (C1), 125 ms (P1), and 175 ms (N1). Time points are not corrected in regard to equipment signal transfer latency.



## **1.5 The current study**

### **1.5.1 Multi-modal approach**

The current study is the first to investigate the SRM phenomenon in both auditory and visual modalities within the same experimental session (repeated measures design). As discussed, previous work has indicated an association between LTP-like plasticity induced by the PAS protocol and by the visual SRM paradigm (Klöppel et al., 2015), suggesting a global, in contrast to system-specific, index of plasticity integrity or capacity. Building on this line of evidence, the current design aims to address possible cross-modal effects within the SRM protocol, implemented as exposure-based visual and auditory learning. Previous work has targeted either visual or auditory evoked potentials in absence of the other, principally seeking to solidify the link between the SRM protocol and LTP as studied in animal models. As discussed, the integrity of LTP mechanisms is not assumed to be system-specific, but global, encompassing a multitude of systems in the brain. Evidence that the SRM plasticity effect is independent of the sensory system in which it is evoked, will strengthen the potential application of the SRM effect as an index of global LTP integrity in humans.

### **1.5.2 Methodological considerations**

Although key elements are consistent across independent demonstrations of the SRM phenomenon, certain protocol parameters vary. Key elements include the presence of a simple, non-complex visual or auditory stimulus, a sensory stimulation block, either of high presentation frequency or prolonged duration, and probes to assess sensory-evoked potentials pre- and post-stimulation. In visual paradigms, parameters that have seen variation extend to stimulus design (checkerboard, sine grating), stimulus display technique (flash, reversal/inverting), tetanus frequency (2 Hz, ~8.6 Hz, 19 Hz), and tetanus duration (2 minutes, 10 minutes). In regard to the auditory experiments, which are relatively fewer, the protocols have been more uniform. See table 1.1 for a summary of parameters in a selection of relevant publications.

Parameters of the current study reflect a combination of parameters proven effective in several previous studies, and are ultimately the results of extensive pilot testing. Importantly, developing efficient methods and analysis approaches for indexing SRM-induced LTP-like plasticity, is an overarching focus of the extensive project as a whole.

**Table 1.1.** SRM protocol parameters in a selection of relevant publications. \* = control and experimental group; \*\* = two distinct experiments.

<i>Visual</i>	<b>Stimulus</b>	<b>Tetanus</b>	<b>Study <i>n</i></b>
<i>Teyler et al., 2005</i>	Checkerboards	Flash, 33 ms duration; 9 Hz; 2 min.	6
<i>McNair et al., 2006</i>	Sine gratings	Flash, 33 ms duration; 8.6 Hz, 2 min.	8
<i>Normann et al., 2007</i>	Checkerboards	Reversals; 2 / 19 Hz; 2 / 10 min.	74/40 *
<i>Ross et al., 2008</i>	Sine gratings	Flash, 33 ms duration; 8.6 Hz; 2 min.	18
<i>Çavus et al., 2012</i>	Checkerboards	Flash, 33 ms duration; 8.87 Hz; 2 min.	22/19 *
<i>Elvsåshagen et al., 2012</i>	Checkerboards	Reversals; 2 Hz; 10 min.	40/26 *
<i>Klöppel et al., 2015</i>	Checkerboards	Reversals; 2 Hz; 10 min.	37
<i>Smallwood et al., 2015</i>	Sine gratings	Flash, 33 ms duration; 8.6 Hz, 2 min.	21
<i>de G. Porto et al., 2015</i>	Checkerboards	Flash; 33 ms duration; 9 Hz, 2 min.	17
<i>Jahshan et al., 2017</i>	Checkerboards	Flash; 33 ms duration; 8.87 Hz; 2 min.	64
<i>Spriggs et al., 2017</i>	Sine gratings	Flash; 33 ms duration; 8.6 Hz; 2 min.	30/19 *

<i>Auditory</i>	<b>Stimulus</b>	<b>Tetanus</b>	
<i>Clapp et al., 2005</i>	1 kHz pure tone	~13 Hz, 2 min.	12/10 **
<i>Mears &amp; Spencer, 2012</i>	1 kHz pure tone	11 Hz, 2.4 min.	17/15 *
<i>Teo et al., 2014</i>	1 kHz pure tone	13 Hz, 2 min.	64
<i>Lei et al., 2017</i>	Various	~13.3 Hz, 4 min.	10

### 1.5.3 Responder rates

Another issue to consider in regard to the SRM paradigm, is the definition of *individual response*, i.e. the criterion for categorising *responders* and *non-responders*. This issue has significant implications for the ratio of responders to non-responders. Importantly, LTP is conceptualised as a normally occurring physiological phenomenon, and consequently, the rate of responders should be high, provided the effectiveness of the SRM paradigm and the current parameters. Defining VEP responders as individuals displaying an increase of mean amplitude of the visual P1 component from baseline to post-stimulation, Klöppel et al. (2015) reported a visual SRM responder rate of ~75 % (25 of 33 subjects); however, the responder issue has only rarely been addressed previously.

### 1.5.4 Hypotheses

The primary objective of the current study is to investigate a potential association across modalities of the LTP-like plasticity phenomenon implemented by the SRM paradigm. This is the first application of a dual auditory/visual SRM protocol, as previous work has exclusively focused on either one. In line with results from Klöppel et al. (2015), we expect a positive correlation between effect sizes of the two SRM protocols. Similarly, we expect that

individual response in one paradigm (i.e. being a responder) predicts response in the other. Responders and non-responders are operationally defined as individuals displaying a modulation above a set criterion, in the expected direction, of a component in question.

Subsidiary aims are to replicate previous demonstrations of the SRM effect. Importantly, the current replications will be considered in the larger context of a multi-modal approach, being demonstrated sequentially in a single experimental session. In regard to the visual paradigm, the selective amplitude increase (i.e. more negative) of the N1 component amplitude is expected (McNair et al., 2006; Ross et al., 2008; Smallwood et al., 2015; Spriggs et al., 2017; Teyler et al., 2005). In addition, an increase (i.e. more positive) of the P1 component amplitude, and reduction (i.e. more positive) of the C1 component amplitude have also been documented (Elvsåshagen et al., 2012; Klöppel et al., 2015; Normann et al., 2007). Contrary to the visual SRM paradigm, robust findings in the auditory paradigm are less frequent. The current study aims to replicate the findings of Clapp, Kirk, et al. (2005), who identified a selective modulation of the N1 component of the auditory evoked potential. Similarly, Teo et al. (2014) found an increase of the absolute difference between auditory N1 and P2. However, this effect was only evident 25 minutes post-stimulation, and not immediately after the tetanic stimulation. Pilot data for the current study indicated a potential early-phase role of the auditory P2 component as well.

## 2 Methods

### 2.1 Participants

41 healthy subjects (28 females, 13 males; mean age 31.9 years, SD 11.0 years) participated in the study after providing informed consent. However, due to variability in data quality, the sub-paradigms utilise slightly different samples. five participants were excluded from the visual SRM paradigm ( $n = 36$ ), whereas three were excluded from the auditory SRM paradigm ( $n = 38$ ). For the cross-modal analyses, requiring intact data from both the visual and the auditory paradigms, a total of 34 participants were included. Normal or corrected-to-normal visual acuity was required, along with absence of any psychiatric or neurological condition. All participants were screened using a basic audiometry sequence for deficiency of hearing. Participants were recruited through advertisement at the Department of Psychology, University of Oslo, and social media platforms, such as Facebook. All procedures were approved by the regional ethics committee (REK).

### 2.2 Procedures

The employed experimental EEG/ERP paradigm consisted of the two modality-selective sub-paradigms run sequentially; the visual stimulus-selective response modification paradigm (V-SRM), followed by the auditory stimulus-selective response modification paradigm (A-SRM). In addition, a non-stimulus block for recording resting-state EEG and a loudness-dependent auditory evoked potential paradigm (LDAEP), were included. However, only the V-SRM and the A-SRM data are considered in the current report. For the whole session, participants were seated 0.7 m from the LCD screen on which visual stimuli were presented. For all visual stimuli, the full screen was utilised. Auditory stimuli were delivered through Etymotic ER-1 insert earphones (Etymotic Research, Inc.).

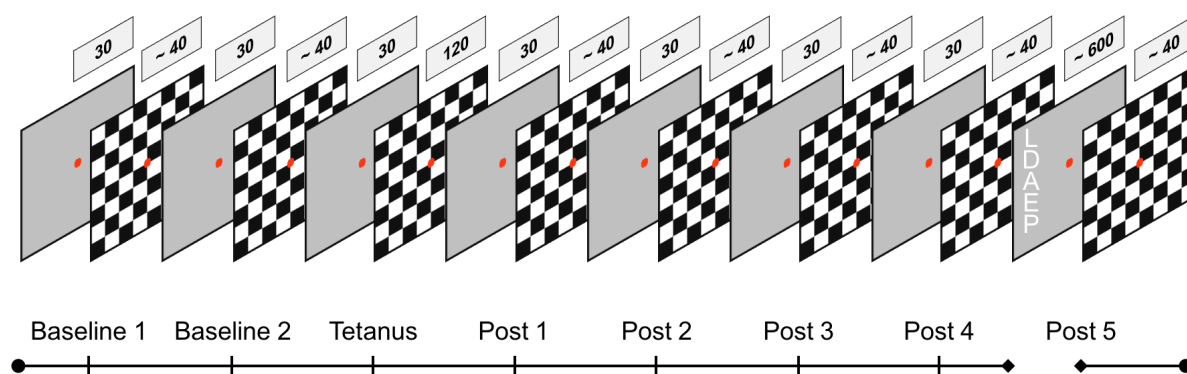
Paradigms were programmed and run using the Psychtoolbox-3 environment (Kleiner et al., 2007) in MATLAB, version 2015a (MathWorks, Natick, Massachusetts).

#### 2.2.1 Visual stimulus-selective response modification (V-SRM)

The V-SRM protocol consisted of two baseline blocks, one tetanic stimulation block, and five post-tetanus blocks. It was run in a single sequence with the LDAEP paradigm making up the prolonged break between the fourth and the fifth post-tetanus blocks. See figure 2.1.

The baseline and post-tetanus blocks each contained 40 checkerboard reversals, with stimulus onset asynchrony (SOA) randomly chosen in the range 500-1500 milliseconds for each reversal (average 1 Hz reversal rate). Participants were instructed to fixate on a red circular dot in the middle of the screen, and to respond with a button press whenever the dot's colour changed to green. Five such response cues were pseudo-randomly interspersed with the trials in each of the baseline and post-tetanus blocks. Response cues were displayed in order to keep the participants focused on the stimulus and fixated on the central dot. All stimulus blocks were separated by a 30 second grey screen.

In the 120 seconds tetanus block, SOA was locked at  $\sim 8.55$  Hz (adjusted to fit screen refresh rate at 60 Hz). No response cues were presented during the tetanus block.



**Figure 2.1.** V-SRM experimental setup. Block durations in seconds.

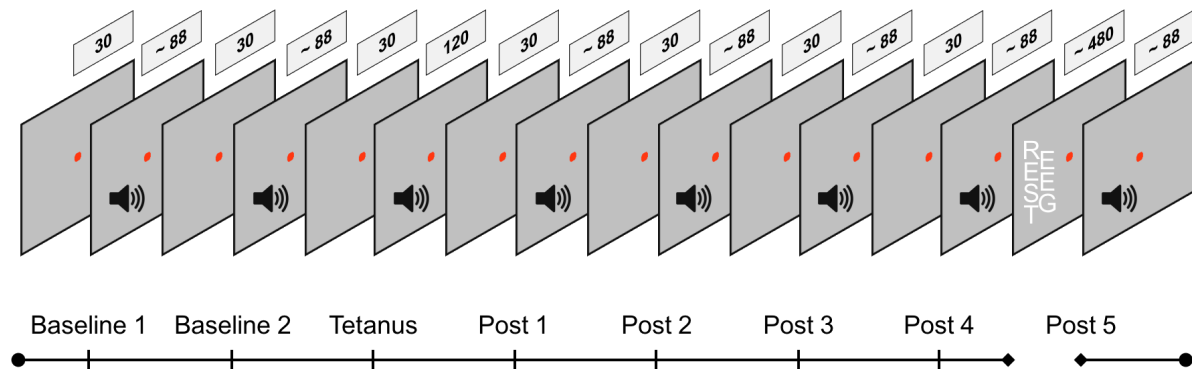
**Table 2.1.** V-SRM parameters.

<i>Stimulus type</i>	White/black checkerboard reversals
<i>Stimulus-onset-asynchrony (SOA)</i>	500 - 1500 ms (random in range)
<i>Tetanus presentation frequency</i>	$\sim 8.55$ Hz

### 2.2.2 Auditory stimulus-selective response modification (A-SRM)

In the A-SRM protocol, parameters were selected to closely resemble those of the design in Clapp, Kirk, et al. (2005); the original account of the auditory SRM paradigm. Pure tones (see table 2.2 for parameters) were delivered binaurally in two baseline blocks, one tetanic stimulation block, and five post-tetanus blocks. In baseline and post-tetanus blocks, SOA varied randomly in the range 1800-2600 milliseconds (average presentation frequency 0.45 Hz). Response cues were given in the same manner as in the visual procedure.

The tetanus block lasted for 120 seconds, with the stimulus presentation frequency locked to ~13.3 Hz (50 ms tones, separated by 25 ms inter-tone silence).



**Figure 2.2.** A-SRM experimental setup. Block durations in seconds.

**Table 2.2.** A-SRM parameters.

<i>Tone frequency</i>	1000 Hz
<i>Duration</i>	50 ms
<i>Intensity (volume)</i>	70 dB SPL
<i>Sampling rate</i>	48 000 samples per second
<i>Stimulus-onset-asynchrony (SOA)</i>	1800 – 2600 ms (random in range)
<i>Tetanus presentation frequency</i>	~ 13.33 Hz
<i>Start/end trim</i>	5 ms ramp

## 2.3 EEG/ERP data

### 2.3.1 EEG recording

The electroencephalographic signals were recorded with a 64-channel BioSemi ActiveTwo system (BioSemi B.V., Amsterdam), using Ag-AgCl electrodes. Four electrodes were placed in near proximity of the eyes; above and below the right eye, and directly lateral to both eyes. Two additional electrodes were fastened to the earlobes, for offline referencing alternatives. The BioSemi system records with a zero-reference principle, making it necessary to re-reference the EEG signals offline for pre-processing and analysis. The raw EEG data were recorded with a sampling frequency of 1024 Hz, with a high-pass filter in accordance with the Nyquist theorem (Luck, 2014). There was no other online filtering of the raw data.

All the experimental paradigms – auditory and visual SRM, LDAEP, and resting state EEG – were recorded in one session, with two roughly equally spaced breaks. The EEG recording was suspended during the breaks.

### 2.3.2 Processing of EEG/ERP data

The raw EEG data were loaded into the EEGLAB environment for offline pre-processing (Delorme & Makeig, 2004). After extracting metadata, adding channel location information, and down-sampling to 512 Hz (a generally acceptable sampling rate for use in ERP studies; see Luck (2014)), the data were high-pass filtered, using a zero-phase Kaiser filter ( $\beta$ : 5.65) with a half amplitude cut-off (-6 dB) at 0.1 Hz, a filter considered acceptable for ERP research (Luck, 2014). Filter properties used in this study are in line with updated best practice guidelines (Widmann, Schröger, & Maess, 2015). Data were then subjected to the CleanLine algorithm (Bigdely-Shamlo, Mullen, Kothe, Su, & Robbins, 2015) for robust suppression of AC power line noise. Next, the PREP pipeline algorithm (Bigdely-Shamlo et al., 2015) were used in order to extract a robust common average to which all signals were re-referenced, without actually removing the channels labelled noisy. A robust common average reference is characterized by an initial removal/interpolation of signals that differ statistically from the other signals (and is therefore deemed “noisy”), before the actual re-referencing. Extremely noisy channels were removed using a modified function from the TrimOutlier-toolbox plugin for EEGLAB. The same methodology was applied in order to remove EEG segments of considerable noise, before independent component analysis (ICA; Delorme et al., 2012) was conducted. The number of independent components returned by the ICA was adjusted in accordance with the EEG data rank. In order to subtract ocular activity resulting from blinks from the EEG data in an unbiased manner, SASICA (Chaumon, Bishop, & Busch, 2015) was implemented, removing independent components correlating highly with the activations of the VEOG channels in the time domain. All subtracted independent components subtracted by SASICA were manually reviewed and validated post-processing. All remaining independent components were manually reviewed, and components reflecting muscle artefacts were subtracted from the data. Due to the limited purpose of the current ICA decomposition (i.e. to subtract blink-related and muscle activity), the recommendation regarding high-pass filtering data at 1-2 Hz half-amplitude cut-off before ICA (Winkler, Debener, Muller, & Tangermann, 2015), was not complied with. Subsequently the data were low-pass filtered, using properties equivalent to the high-filter, albeit with a half-amplitude cut-off at 30 Hz.

The band-pass filtered and cleaned data were then segmented into epochs, time-locked to event markers in the data set. Importantly, the data were split into paradigm-specific units

following epoch segmentation, providing the means for the use of paradigm-specific parameters in subsequent processing. Essentially, such an approach allows the tailoring of processing to each paradigm, an important feature due to the inherent discrepancies between the characteristics of visual and auditory evoked potentials. In order to improve the overall signal-to-noise ratio without rejecting epochs unnecessarily, all signals were assessed within individual epochs, interpolating specific statistically deviating channels within the individual epoch only. This procedure minimizes the chances of an epoch being rejected due to a single noisy channel. A modified version of a function from the FASTER toolbox (Nolan, Whelan, & Reilly, 2010) was employed in this process. Two separate epoch rejection procedures were then applied. Only channels relevant to analyses within each paradigm, including channels of interest in regard to later offline re-referencing, and those in close proximity of these, were taken into consideration. All epochs were first scanned for abnormal within-epoch trends, removing all epochs with trend slopes above a threshold of 60  $\mu\text{V}$ . Subsequently, an adaptive absolute threshold algorithm was utilised to identify epochs with abnormal voltage deflections. However, rather than the traditional stationary voltage threshold, an adaptive approach to this procedure was used. Aiming for  $\sim 7.5$  percent total rejection rate, the algorithm was re-run with adjusted voltage thresholds repeatedly until the mark was hit (or minimum/maximum threshold was reached). See table 2.3 for algorithm parameters. This approach is designed to take into account the inherent individual variations in electroencephalographic voltage amplitudes, conforming to each subject's unique amplitude range. The final voltage rejection threshold was logged for each subject, and manually reviewed for extreme values.

**Table 2.3.** Epoch rejection parameters

<b><i>Trend analysis</i></b>	
<i>Threshold</i>	60 $\mu\text{V}$
<b><i>Voltage threshold</i></b>	
<i>Initial threshold</i>	-125 / 125 $\mu\text{V}$
<i>Minimum threshold</i>	-50 / 50 $\mu\text{V}$
<i>Target rejection percentage</i>	7.5 ( $\pm 0.5$ )

### 2.3.3 ERP measurements

ERP measures were extracted using a customized function built on the measurement tool from EEGLAB plugin ERPLAB (Lopez-Calderon & Luck, 2014). Single-trial data from each



subject were extracted from the data structure provided by EEGLAB using a custom function.

## 2.4 Analyses

### 2.4.1 Data selection, extraction, and computation

The current thesis aims to investigate the main effect of each modality-specific SRM protocol, and whether response in one modality can predict response in the other, by correlating effect sizes and comparing responder rates across modalities. To maintain a minimalistic approach, narrowing the attention to solely encompass these issues, data from baseline blocks and post-stimulation blocks have been reduced to two entities, by averaging the two baseline blocks and the two first post-stimulation blocks, of each modality. Across the two modalities, no significant difference between the first and second baseline blocks, or between the first and second post-stimulation blocks, were found. As such, data will henceforth be referred to as *baseline* (BL) and *post-stimulation* (PS) blocks, a structure employed in all relevant analyses. This approach allows pure statistical assessment of short-term amplitude modulations as an effect of the high-frequency tetanic stimulation. In line with previous research, amplitudes are measured from component peaks; VEP components C1, P1, and N1, including the absolute difference between P1 and N1, and AEP components P50, N1, and P2, including the absolute difference between N1 and P2. Prior to measuring, data were baseline corrected, using the interval from -100 ms to stimulus onset as baseline.

From individual subject VEPs and AEPs, absolute amplitude values ( $\mu\text{V}$ ) and peak latencies were measured using an automated measuring tool implemented in the ERPLAB toolbox. However, all measurements were plotted and confirmed through visual inspection, ensuring the validity of all measures. In order to assess individual responder rates, single-trial data from each participant were considered. Single-trial amplitude values were extracted from the time points provided by the averaged peak latencies. Using these single-trial amplitude values, within-subject effect sizes were computed for all visual and auditory components for each subject. This was done using the following formulae for computing Cohen's  $d$  (Field, 2013):

$$d = \frac{\bar{x}_{PS} - \bar{x}_{BL}}{SD_{BL}} = \frac{\bar{x}_{PS} - \bar{x}_{BL}}{SE_{BL} * \sqrt{n_{BL}}}$$

The single-trial peak-to-peak values were extracted using a custom measurement function built on the EEGLAB structure.

A definite operational definition of a *responder* in regard to the SRM protocol remains unclear. Of available reports, Klöppel et al. (2015) defined VEP responders as subjects who displayed a mean increase of the P1 amplitude post-stimulation compared to baseline. In the current study, this criterion is contrasted to a selection of cut-off limits based on effect sizes.

Component modulations are represented as *amplitude changes* (i.e. not absolute voltage changes), unless otherwise stated, such that an *increase of amplitude* refers to both negative components becoming more negative, and positive components becoming more positive. The opposite applies to *decrease of amplitude*. For ease of understanding, these principles govern the direction of difference testing statistics as well, such that positive values represent an amplitude increase, and negative values a decrease.

#### **2.4.2 Statistical approaches**

Preliminary statistical analyses were performed using both the *conventional approach* and the *jackknife approach* (Luck, 2014; Miller, Patterson, & Ulrich, 1998). In the conventional approach, measurements are taken from single-subject waveforms, which in most cases results in samples with considerable variance. The substantial variance will in some cases impede the statistical power of ERP studies. The aim of the jackknife approach is to reduce sample variance by measuring values from grand averaged data. According to Luck (2014), the essence of the jackknife approach to statistical analysis of ERP data, lies in changing the order of which the mathematical operations are administered. However, as no considerable difference between the two approaches was evident, the jackknifed data were dropped from the final analyses and the current report.

Parametric tests were used, as no violations of the assumption of normality were evident in any variables. Importantly, in repeated measures designs, normality of the difference scores between conditions must be assessed, in place of the condition measures (Field, 2013). All statistical analyses were conducted using IBM SPSS (version 24; IBM, Armonk, New York) and MATLAB (version 2016b; MathWorks, Natick, Massachusetts).

Paired samples *t*-tests were used to compare the voltage levels of each component in baseline and post-stimulation blocks. To assess cross-modal within-subject SRM effects, a bivariate correlation matrix, including all components of interest, was computed. Within-subject effect sizes were subjected to this analysis. In addition, rates of *cross-modal responders* were considered. For the purpose of this computation, all measures of effect size *d* were transformed, such that a positive *d* reflects an amplitude modulation in the hypothesised direction. Unless otherwise stated, all values of *p* reflect a two-tailed test of significance. Where relevant, Bonferroni multiple comparisons correction has been applied.

Statistical power was computed from the effect sizes of the current data, based on a critical one-tailed  $\alpha$  value of 0.05. Moreover, sample sizes required to achieve 80 % power with a critical one-tailed  $\alpha$  criterion of .05 were computed. On the account that the current hypotheses state a directionality of each effect, a one-tailed  $\alpha$  criterion was selected. The power analyses were conducted with G\*Power software (Faul, Erdfelder, Buchner, & Lang, 2009; Faul, Erdfelder, Lang, & Buchner, 2007).

# 3 Results

The principal aim for this study was to investigate the potential relation between modulation of the auditory evoked potentials in the A-SRM paradigm and the modulation of the visual evoked potentials in the V-SRM paradigm. To this end, separate modulation of evoked potential components should be present in both modalities. Consequently, the subsidiary hypotheses of replication of previous results in either paradigm, will be considered first, before attention is directed toward the cross-modal features. Responder rates will be considered for each modality. No significant effects were observed in regard to latency measures, and consequently, latency measures have not been considered in current report.

## 3.1 Replication: Amplitude modulation of components

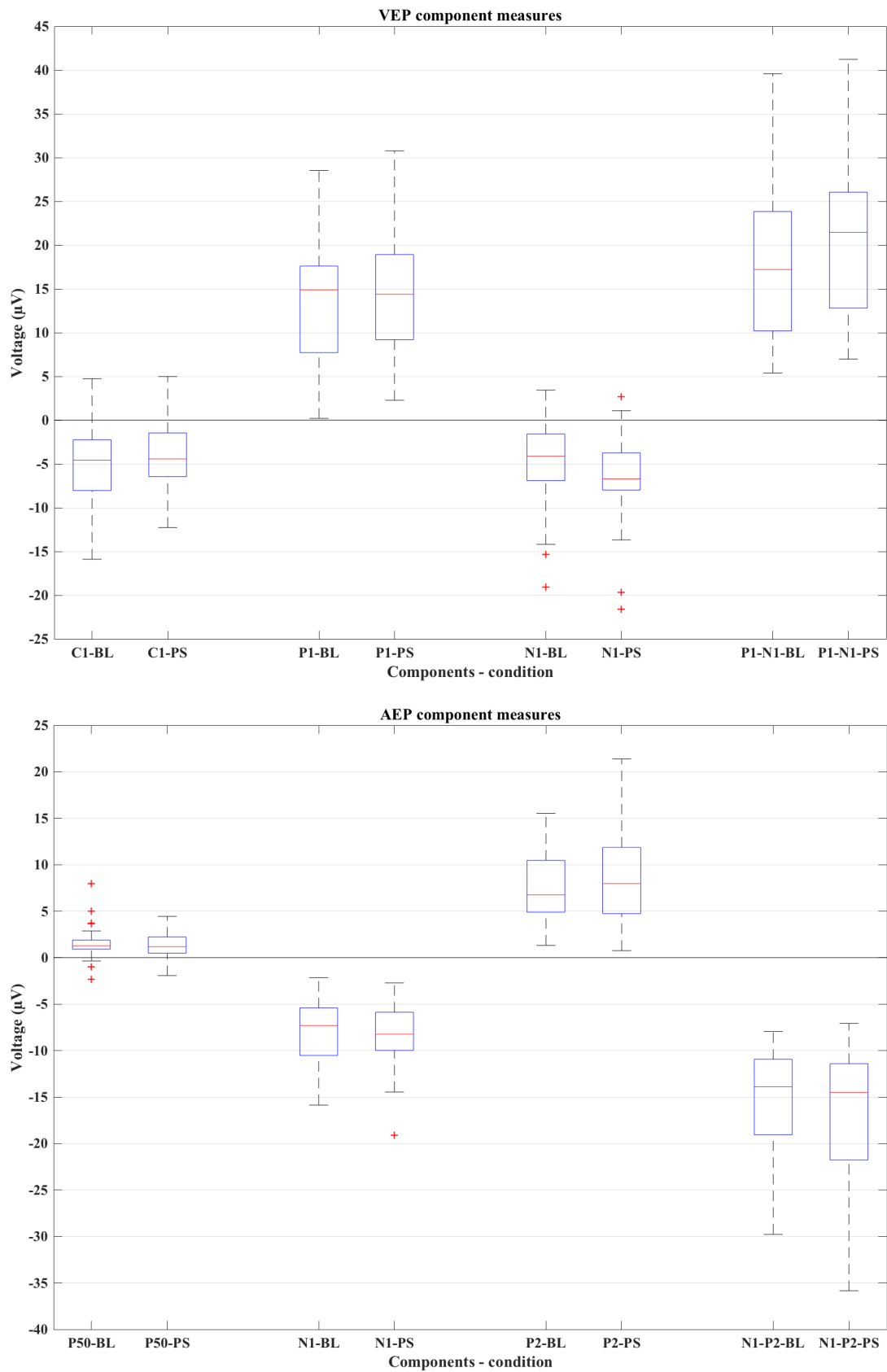
### 3.1.1 Descriptive statistics

A total of 36 subjects were included in the V-SRM data (27 females; mean age 31.1 years, SD 11.1 years, range 18-65 years), while the A-SRM data comprised 38 subjects (26 females; mean age 32.2 years, SD 11.3 years, range 18-65). Data consisted of peak voltage values of visual C1, P1, and N1, and auditory P50, N1, and P2. In addition, the absolute difference between visual P1 and N1, and between auditory N1 and P2, were included as variables.

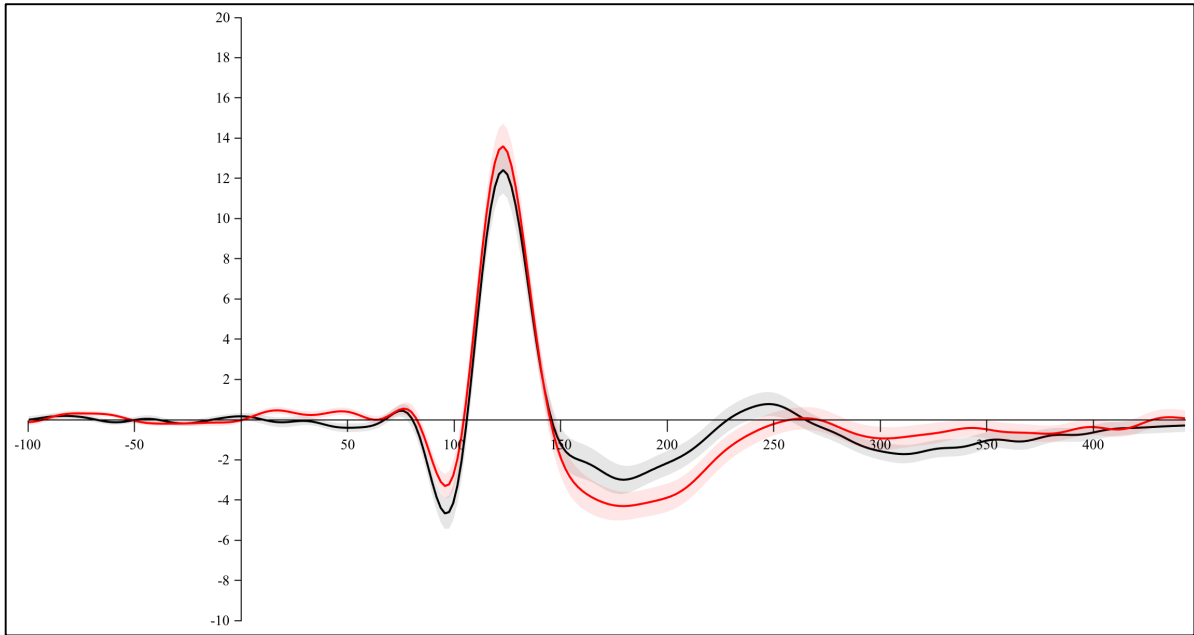
Table 3.1 and figure 3.1 summarises descriptive statistics of all selected measures.

**Table 3.1.** Descriptive statistics of components of interest. Standard error based on results from 1000 bootstrap samples. Values in  $\mu\text{V}$ . BL = Baseline; PS = Post-stimulation.

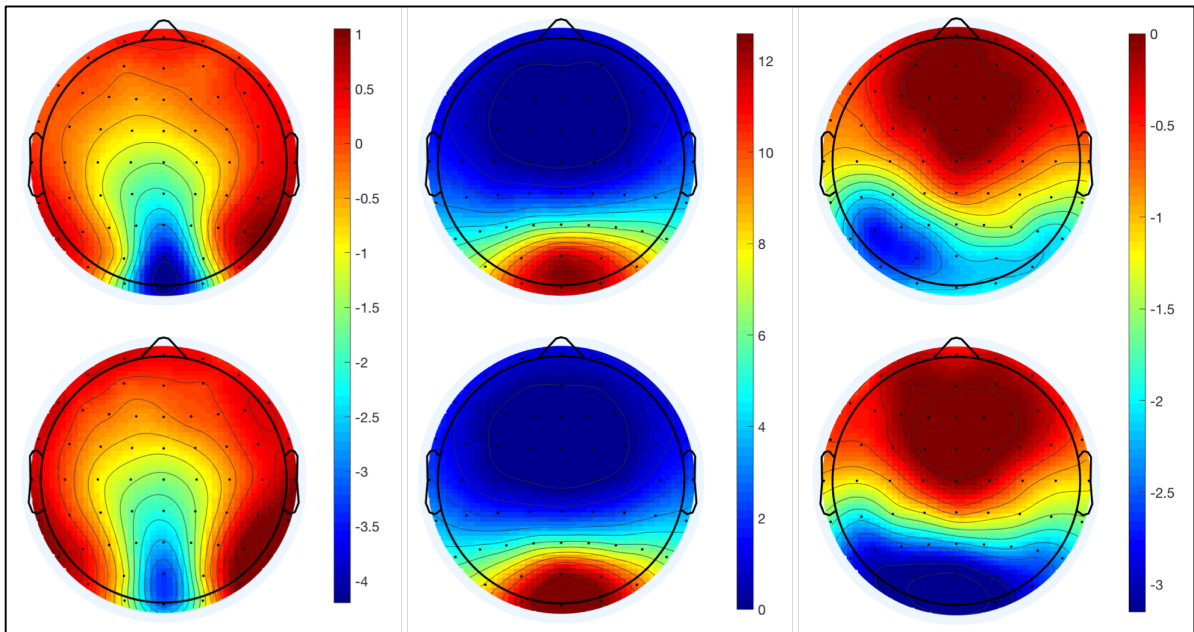
V-SRM		Mean	SD	SE	A-SRM		Mean	SD	SE
C1	BL	-5.47	4.78	0.80	P50	BL	1.55	1.64	0.27
	PS	-4.89	4.34	0.72		PS	1.31	1.34	0.22
P1	BL	13.34	6.84	1.14	N1	BL	-7.98	3.51	0.57
	PS	14.15	6.94	1.16		PS	-8.44	3.49	0.57
N1	BL	-5.46	4.32	0.72	P2	BL	7.42	3.66	0.59
	PS	-6.71	4.17	0.70		PS	8.26	4.36	0.71
P1-N1	BL	18.79	8.27	1.38	N1-P2	BL	-15.40	5.85	0.95
	PS	20.86	8.73	1.46		PS	-16.70	6.80	1.10



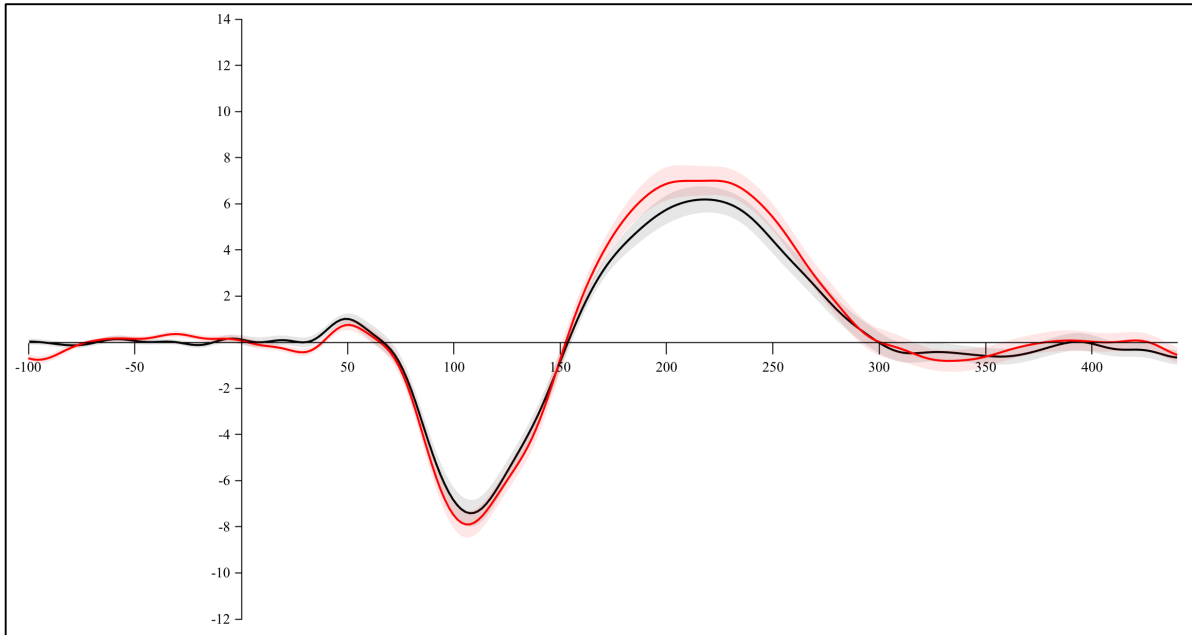
**Figure 3.1.** Box plots of component measures. The red horizontal line denotes the median value, whereas the blue box comprises data points in the 2<sup>nd</sup> and 3<sup>rd</sup> quartiles. The whiskers illustrate the range, and the red crosses mark outliers.



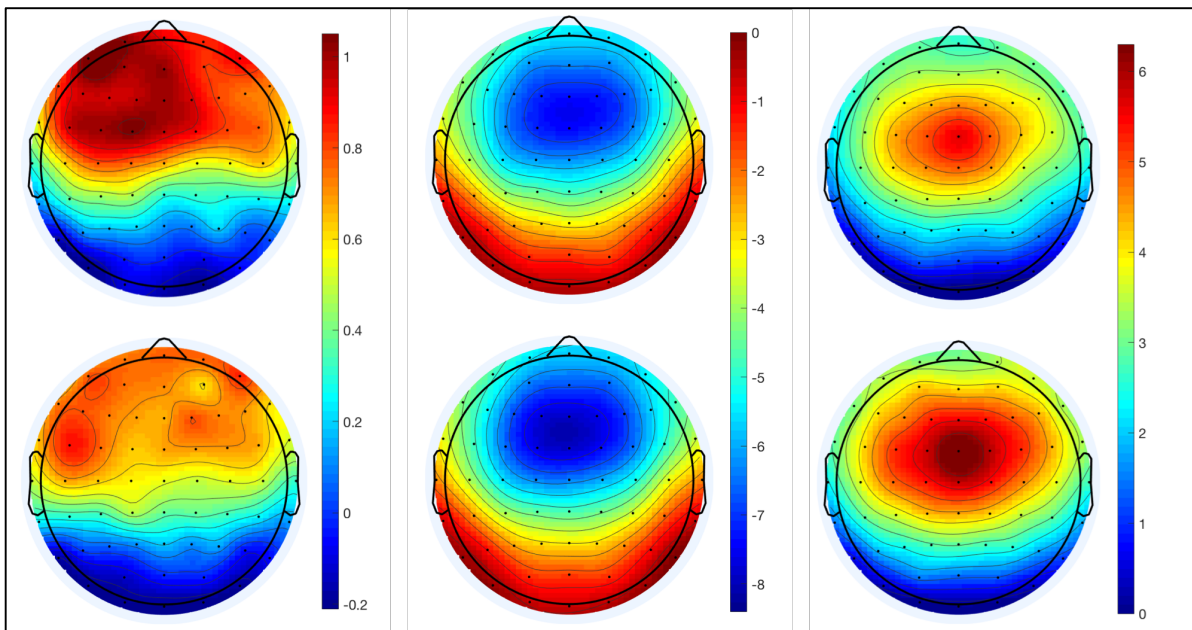
**Figure 3.2.** Grand average of all VEPs, as recorded from Oz, referenced to AFz. Baseline plotted in black, post-stimulation in red. Lighter coloured area represents each measurement's standard error of the mean (SEM).



**Figure 3.3.** Scalp amplitude topography for the VEP components. From left to right; C1, P1, N1. Baseline topography in top row, post-stimulation in bottom.



**Figure 3.4.** Grand average of all AEPs, as recorded from FCz, referenced to the mean of P9 and P10. Baseline plotted in black, post-stimulation in red. Lighter coloured area represents each measurement's standard error of the mean (SEM).



**Figure 3.5.** Scalp amplitude topography for the AEP components. From left to right; P50, N1, P2. Baseline topography in top row, post-stimulation in bottom.

### 3.1.2 Component amplitude modulation

In the V-SRM data, all the measured components were significantly altered in the post-stimulation block compared to pre-stimulation levels. The amplitudes of both P1 ( $M = 1.22 \mu\text{V}$ ,  $SE = 0.37$ , BCa 95 % CI [0.51, 1.96];  $t(35) = 3.33$ ,  $p = .002$ ,  $d = 0.18$ ) and N1 ( $M = 1.45 \mu\text{V}$ ,  $SE = 0.43$ , BCa 95 % CI [0.62, 2.32];  $t(35) = 3.50$ ,  $p = .001$ ,  $d = 0.30$ ) were significantly

increased. The absolute difference (peak-to-peak distance) between P1 and N1 was also significantly larger post-stimulation compared to baseline ( $M = 2.67 \mu\text{V}$ ,  $SE = 0.45$ , BCa 95 % CI [1.86, 3.55];  $t(35) = 6.08$ ,  $p = .000$ ,  $d = 0.31$ ). The C1 peak amplitude post-stimulation was decreased (i.e. less negative) relative to its pre-stimulation level ( $M = -1.28 \mu\text{V}$ ,  $SE = 0.36$ , BCa 95 % CI [-2.03, -0.67];  $t(35) = -3.60$ ,  $p = .001$ ,  $d = -0.27$ ). All effect sizes are in the range of small-to-medium magnitude (Sawilowsky, 2009). All effects survive Bonferroni multiple comparison correction ( $p < .0125$ ).

**Table 3.2.** Modulation of VEP components: Statistical assessment of differences between baseline and post-stimulation blocks; paired samples *t*-tests.

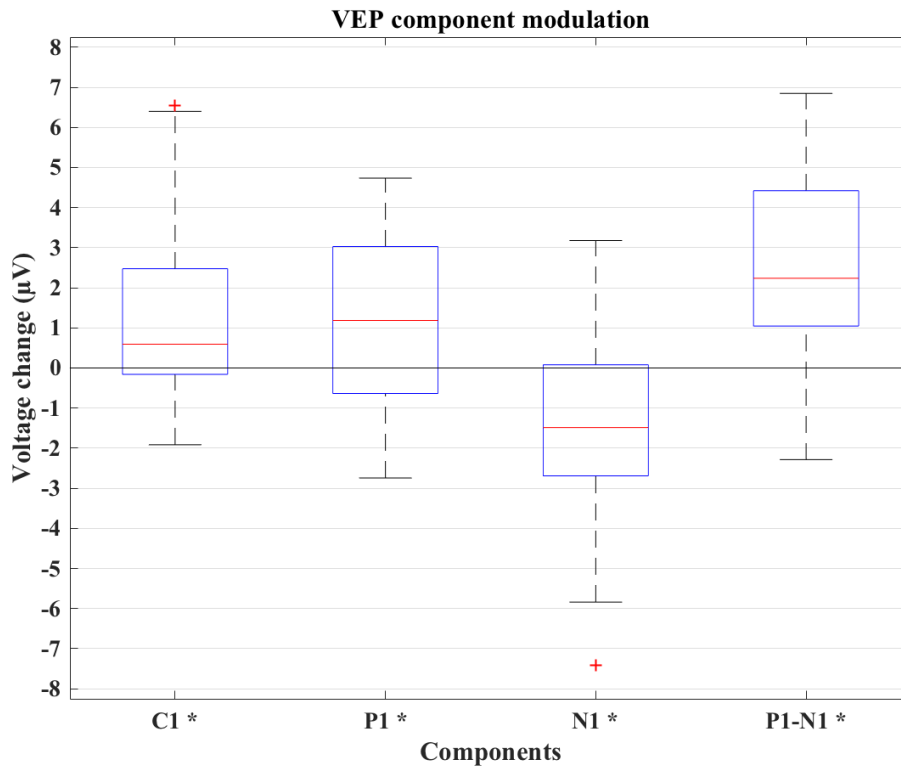
	<i>t</i> statistic	<i>p</i> (two-tailed)	Effect size ( <i>d</i> )	BCa 95 % C.I.
<i>C1</i>	-3.60	.001	-0.27	[-2.03 -0.67]
<i>P1</i>	3.33	.002	0.18	[0.51 1.96]
<i>N1</i>	3.50	.001	0.30	[0.62 2.32]
<i>P1 – N1 diff.</i>	6.08	.000	0.31	[1.86 3.55]

In the A-SRM data, of all the AEP components of interest, only P2 displayed a significant increase of amplitude post-stimulation as compared to baseline ( $M = 0.84 \mu\text{V}$ ,  $SE = 0.40$ , BCa 95 % CI [0.04, 1.65];  $t(37) = 2.10$ ,  $p = .043$ ,  $d = 0.23$ ). Neither P50 ( $M = -0.24 \mu\text{V}$ ,  $SE = 0.22$ , BCa 95 % CI [-0.62, 0.15];  $t(37) = -1.09$ ,  $p = .283$ ,  $d = -0.15$ ) or N1 ( $M = 0.46 \mu\text{V}$ ,  $SE = 0.29$ , BCa 95 % CI [-0.14, 1.03];  $t(37) = 1.59$ ,  $p = .121$ ,  $d = 0.13$ ) were significantly altered in the post-stimulation block relative to baseline values. However, the peak-to-peak distance between N1 and P2 were significantly larger post-stimulation compared to pre-stimulation ( $M = 1.30 \mu\text{V}$ ,  $SE = 0.49$ , BCa 95 % CI [0.35, 2.24];  $t(37) = 2.68$ ,  $p = .011$ ,  $d = 0.22$ ). The effect sizes are mainly small (Sawilowsky, 2009). Only the effect observed when comparing values of absolute difference between N1 and P2 survives Bonferroni multiple comparisons correction ( $p < .0125$ ).

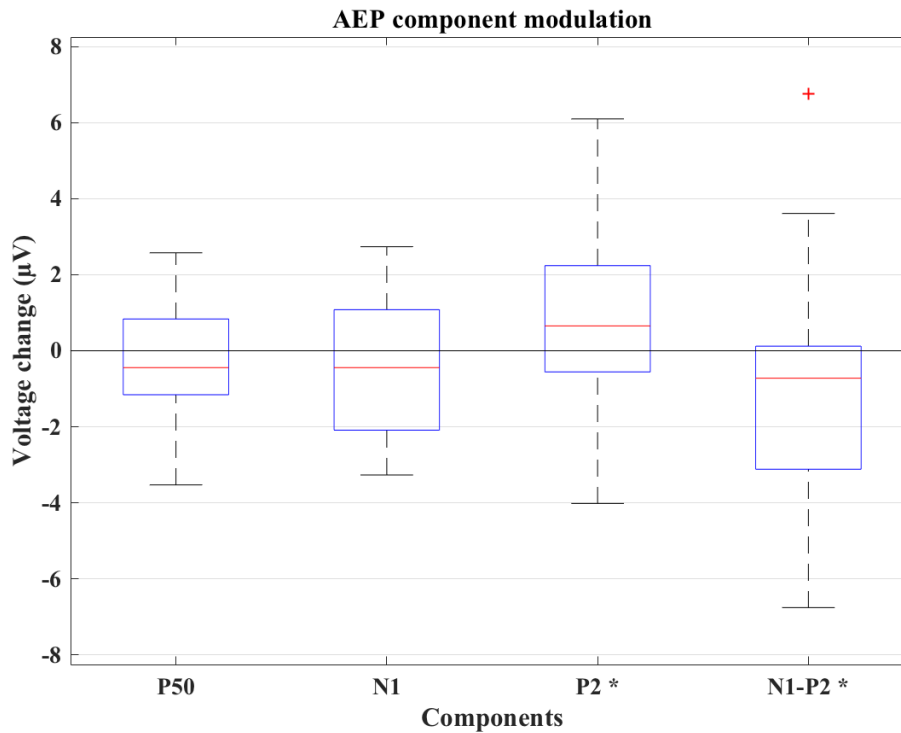
**Table 3.3.** Modulation of AEP components: Statistical assessment of differences between baseline and post-stimulation blocks; paired samples *t*-tests.

	<i>t</i> statistic	<i>p</i> (two-tailed)	Effect size ( <i>d</i> )	BCa 95 % C.I.
<i>P50</i>	-1.09	.283	-0.15	[-0.62 0.15]
<i>N1</i>	1.59	.121	0.13	[-0.14 1.03]
<i>P2</i>	2.10	.043	0.23	[0.04 1.65]
<i>N1 – P2 diff.</i>	2.68	.011	0.22	[0.35 2.24]





**Figure 3.6.** Box plots of VEP components voltage differences between baseline and post-stimulation. The red horizontal line denotes the median value, whereas the blue box comprises data points in the 2<sup>nd</sup> and 3<sup>rd</sup> quartiles. The whiskers illustrate the range, and the red crosses mark outliers. \* = significant at the .01  $\alpha$  level (not corrected for multiple comparisons).



**Figure 3.7.** Box plots of AEP components voltage differences between baseline and post-stimulation. The red horizontal line denotes the median value, whereas the blue box comprises data points in the 2<sup>nd</sup> and 3<sup>rd</sup> quartiles. The whiskers illustrate the range, and the red crosses mark outliers. \* = significant at the .05  $\alpha$  level (not corrected for multiple comparisons).

### 3.1.3 Statistical power

Table 3.4 contains *post hoc* analyses of statistical power.

**Table 3.4.** Analyses of statistical power: *Post hoc*  $\alpha = .05$ , one-tailed.

<i>Visual (n = 36)</i>	<i>Effect size (d)</i>	<i>Current power</i>	<i>Required n for 80 % power</i>
<i>C1</i>	-0.27	.48	87
<i>P1</i>	0.18	.28	193
<i>N1</i>	0.30	.55	71
<i>P1 – N1 diff.</i>	0.31	.57	66

#### *Auditory (n = 38)*

<i>P50</i>	-0.15	.23	277
<i>N1</i>	0.13	.20	368
<i>P2</i>	0.23	.40	119
<i>N1 – P2 diff.</i>	0.22	.38	130

## 3.2 Responder rates

Effect size-based responder rates for different criteria are given in table 3.5.

**Table 3.5.** Responder rates by criteria. Note that subjects defined as responders display an above-criterion change of component amplitude in the direction expected in regard to the hypotheses.

	<b>V-C1</b>	<b>V-P1</b>	<b>V-N1</b>	<b>V-P1-N1</b>	<b>A-P50</b>	<b>A-N1</b>	<b>A-P2</b>	<b>A-N1-P2</b>
<i>Mean vol. change</i>	67.6 %	67.6 %	76.5 %	85.3 %	61.8 %	58.8 %	64.7 %	73.5 %
<i>d &gt; 0.02</i>	61.8 %	67.6 %	76.5 %	85.3 %	52.9 %	55.9 %	58.8 %	70.6 %
<i>d &gt; 0.05</i>	50.0 %	64.7 %	70.6 %	82.4 %	50.0 %	52.9 %	52.9 %	58.8 %
<i>d &gt; 0.08</i>	44.1 %	47.1 %	61.8 %	76.5 %	35.3 %	44.1 %	50.0 %	52.9 %
<i>d &gt; 0.1</i>	41.2 %	47.1 %	50.0 %	73.5 %	32.4 %	44.1 %	47.1 %	41.2 %
<i>d &gt; 0.15</i>	38.2 %	38.2 %	47.1 %	58.8 %	23.5 %	32.4 %	41.2 %	38.2 %
<i>d &gt; 0.2</i>	32.4 %	32.4 %	38.2 %	52.9 %	11.8 %	23.5 %	26.5 %	29.4 %
<i>d &gt; 0.25</i>	23.5 %	26.5 %	29.4 %	44.1 %	2.9 %	14.7 %	20.6 %	23.5 %

## 3.3 Cross-modal effects

For the cross-modal analyses, only subjects with intact data from both SRM paradigms were included ( $n = 34$ , 25 females; mean age 31.3 years, SD 11.4 years, range 18-65 years).

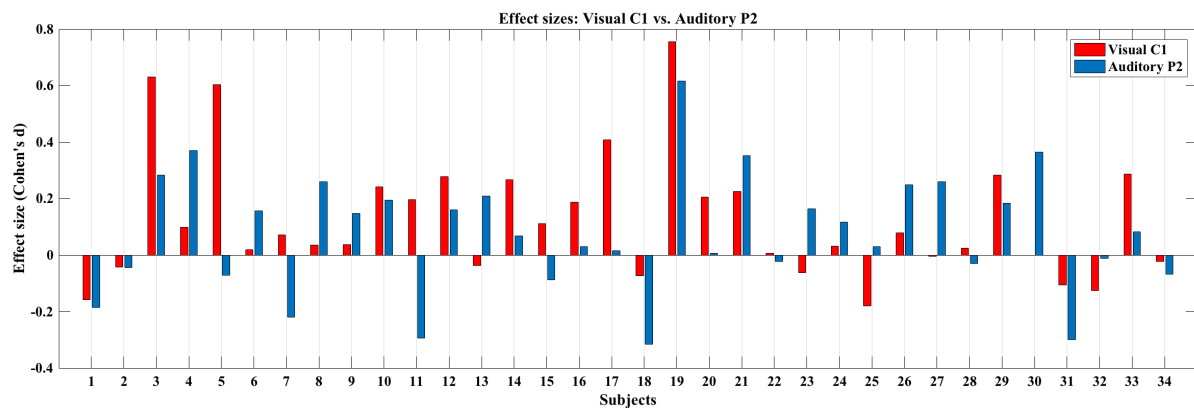
### 3.3.1 Correlational analysis: Within-subject effect sizes

In regard to cross-modal effects, the effect sizes of the amplitude changes at visual C1 and auditory P2 were correlated at a nominal significance threshold of  $p < .05$ ,  $r = .389$  BCa CI [-0.017, .663],  $p = .023$  (figure 3.8). The same holds true for visual C1 in relation to the auditory

N1-P2 peak-to-peak value,  $r = .368$  BCa CI  $[-.119, .687]$ ,  $p = .032$ . No between-modality correlations survived correcting for multiple comparisons (Bonferroni-corrected threshold:  $0.05/16 = 0.003125$ ). Several nominally significant within-modality correlations were also found (entries in *italic* in table 3.6).

**Table 3.6.** Correlation matrix for within-subject effect sizes (Cohen's  $d$ ). Pearson  $r$  and BCa 95 % confidence interval given for each bivariate correlation. Nominally significant cross-modal correlations in bold; nominally significant within-modal correlations in italics. \* nominally significant at the .05  $\alpha$  level (not corrected for multiple comparisons); \*\* nominally significant at the .01  $\alpha$  level (not corrected for multiple comparisons).

	<b>V-C1</b>																			
<b>V-C1</b>	1																			
		<b>V-P1</b>																		
<b>V-P1</b>	.322 <i>[-.085, .571]</i>	1																		
			<b>V-N1</b>																	
<b>V-N1</b>	<i>-.507**</i> <i>[-.741, -.161]</i>	<i>-.405*</i> <i>[-.650, -.061]</i>	1																	
				<b>V-P1-N1</b>																
<b>V-P1-N1</b>	<i>-.159</i> <i>[-.492, .202]</i>	<i>.533**</i> <i>[.208, .761]</i>	<i>.524**</i> <i>[.260, .722]</i>	1																
					<b>A-P50</b>															
<b>A-P50</b>	<i>-.096</i> <i>[-.467, .363]</i>	<i>-.100</i> <i>[-.414, .225]</i>	<i>-.037</i> <i>[-.432, .324]</i>	<i>-.165</i> <i>[-.490, .179]</i>	1															
						<b>A-N1</b>														
<b>A-N1</b>	<i>.004</i> <i>[-.381, .404]</i>	<i>.105</i> <i>[-.218, .405]</i>	<i>-.065</i> <i>[-.365, .271]</i>	<i>-.037</i> <i>[-.351, .260]</i>	<i>.166</i> <i>[-.145, .488]</i>	1														
							<b>A-P2</b>													
<b>A-P2</b>	<b>.389*</b> <b>[-.017, .663]</b>	<i>.014</i> <i>[-.359, .321]</i>	<i>.044</i> <i>[-.380, .508]</i>	<i>.083</i> <i>[-.274, .437]</i>	<i>-.332</i> <i>[-.609, .021]</i>	<i>-.231</i> <i>[-.588, .107]</i>	1													
								<b>A-N1-P2</b>												
<b>A-N1-P2</b>	<b>.368*</b> <b>[-.119, .687]</b>	<i>.114</i> <i>[-.292, .384]</i>	<i>-.024</i> <i>[-.495, .496]</i>	<i>.058</i> <i>[-.380, .494]</i>	<i>-.179</i> <i>[-.458, .168]</i>	<i>.495**</i> <i>[.195, .699]</i>	<i>.722**</i> <i>[.514, .836]</i>	1												



**Figure 3.8.** Visual representation of the relationship between visual C1 and auditory P2, in terms of within-subject effect sizes.

### 3.3.2 Cross-modality responder rates

Table 3.7 contains a cross-modality response matrix, indexing the percentage of subjects displaying an above-criterion component amplitude modulation in the expected direction, in both modalities. At criterion  $d > 0$ , 85.3 % of subjects displayed an above-criterion component amplitude modulation in the expected direction in at least one visual and one

auditory component (the auditory P50 was excluded, due to uncertain direction of effect). When the criterion was increased to  $d > 0.1$ , the percentage was 73.5 %. Due to the significant correlation between them, Cohen's kappa was calculated to assess agreement of response between visual C1 and auditory P2. At criterion  $d > 0$ , Cohen's kappa was .28, suggesting fair level of agreement (Landis & Koch, 1977).

**Table 3.7.** Cross-modality responder rates by within-subject effect size criteria. Percentage of subjects ( $n = 34$ ) with above-criterion effect sizes in both the specified visual and auditory component.

$d > 0$	A-P50	A-N1	A-P2	A-N1-P2
V-C1	41.2 %	44.1 %	50.0 %	55.9 %
V-P1	38.2 %	41.2 %	44.1 %	50.0 %
V-N1	47.1 %	44.1 %	55.9 %	58.8 %
V-P1-N1	52.9 %	50.0 %	58.8 %	67.6 %

$d > 0.1$	A-P50	A-N1	A-P2	A-N1-P2
V-C1	14.7 %	17.6 %	17.6 %	14.7 %
V-P1	14.7 %	17.6 %	17.6 %	14.7 %
V-N1	11.8 %	20.6 %	23.5 %	20.6 %
V-P1-N1	23.5 %	35.3 %	38.2 %	32.4 %

## **4 Discussion**

The current study yielded three main findings. First, a replication of previous findings on the visual SRM paradigm was evident, consisting of component amplitude decrease of C1, and increase of P1 and N1. Also, a significant modulation of the absolute difference between the two latter components was apparent. Second, the findings on the auditory SRM paradigm include a nominally significant component amplitude increase of P2, in addition to a robust modulation of the absolute difference between N1 and P2. Third, when correlating within-subject effect sizes across all components of interest, a nominally significant association between modulations of the visual C1 and auditory P2 emerged. These findings are discussed in detail below.

### **4.1 SRM-induced LTP-like plasticity**

#### **4.1.1 Modality-specific replication**

The principal target for the current replications was to validate the separate modality-specific SRM paradigms in a multi-modal context. A robust replication of the visual SRM findings from previous studies was evident, with significant tetanus-modulated amplitudes at all VEP components of interest: C1, P1, N1, and the absolute difference between the two latter components. These findings largely support the majority of previous work (e.g. Elvsåshagen et al., 2012; Kirk et al., 2010; Normann et al., 2007). The present findings of the auditory SRM paradigm however, differ from those of existing reports. In contrast to earlier demonstrations of an increase in auditory N1 component amplitude (Clapp, Kirk, et al., 2005), the sole significant SRM-induced modulation in the current experiment was a nominally significant increase of the P2 component amplitude. In addition, a robustly significant modulation of the absolute difference between N1 and P2 was evident. This latter finding has been demonstrated previously (Teo et al., 2014), but not immediately post-stimulation, as has been reported here.

Importantly, the current report has deliberately been delimited to focus solely on the early-phase SRM effect. Consequently, plasticity effects sustained over a prolonged period of time are not considered. Such persistent plasticity effects, evident at least up to an hour after the sensory tetanic stimulation, has been regularly demonstrated in the context of the SRM protocol. The issue of early versus late SRM effects has been discussed by some authors

(Jahshan et al., 2017), although a definite account of their potentially differing neural substrates remains elusive. However, in the current study, attention is devoted to replication of short-term effects, and to cross-modal associations. As noted, the neuronal substrates of the SRM phenomenon are not entirely clear. This applies to both the visual and the auditory versions of the protocol. However, as documentation on the visual modality is more extensive compared to the scarcity characterising the auditory modality, the visual SRM phenomenon will be considered in the next section.

In terms of methods, *classic* LTP (LTP-induction in animal models and *in vitro* brain slices) and *sensory* LTP (i.e. the SRM effect) differ considerably. Classic LTP have been demonstrated on the level of the single synapse, a level of examination not available for non-invasive record. Sensory LTP on the other hand, as demonstrated in the current study, is evident at multiple time points in the VEP, strongly suggesting that plasticity processes are expressed in a multitude of synapses along the visual sensory processing pathway. Moreover, the equivalent current dipoles accountable for the amplitude variations in the early VEP components are known to be distributed across several modules of the visual pathway: C1 is considered to originate within the calcarine fissure of primary visual cortex; P1 and N1 in secondary/extrastriate cortices (Di Russo, Martínez, Sereno, Pitzalis, & Hillyard, 2002). Topographical representations of the VEP components in the current data, given in figure 3.3, are in compliance with these findings. The knowledge of the VEP components' electrophysiological origins, taken together with the current finding of robust SRM-driven modulation of all components of interest, suggests that SRM-induced plastic modulations of synapses are expressed in different modules of the visual sensory pathway. Interestingly, the current results implicate modulation of synaptic efficacy in both ascending thalamocortical pathways, in the case of C1 modulation (primary visual cortex), and bilateral local network activations, relating to N1 modulation (extrastriate areas) (Cavuş et al., 2012). Building on this line of reasoning, a possible future direction of SRM investigation could be to establish experimental control over the selective modulation of individual VEP components, promoting a means of localising areas of LTP-expression in the visual pathway. One possible approach to this issue would be to limit the tetanic stimulation to comprise only parts of the visual stimulus, e.g. selective tetanisation of horizontal/vertical lines of the checkerboard stimulus.

A related issue projecting from the noted methodological differences, concerns the nature of the networks which display enhancement of synaptic transmission. The expression of SRM-induced synaptic plasticity in the visual system is likely to involve a complex composition of interactions within and between serial and parallel networks with both excitatory and inhibitory properties. As of such, the precise role of LTP in the phenomenon invoked by the SRM paradigm, remains quite elusive. It is not unlikely that the SRM-induced plastic modulations of neural compounds in the visual sensory pathway also involves critical interactions between LTP processes and other plasticity mechanisms (Cooke & Bear, 2014). This is also discussed in the context of relevant terminology (Lahr et al., 2014), which will be discussed further in the context of responder rates below.

In contrast to the visual experiment, our findings related to the auditory SRM paradigm are less clear. Firstly, there are few relevant prior publications, and the available reports vary in regard to how modulation of AEP components is measured. The first demonstration (Clapp, Kirk, et al., 2005) reported an increase of the auditory N1 component amplitude, whereas the second study, which included an alternative, non-tetanised tone in addition to the tetanised one (Mears & Spencer, 2012), focused on persistent voltage shifts. In considering early post-tetanus plasticity effects, the latter effort was able to identify a positive voltage shift at left frontotemporal electrodes, and a negative shift at right temporal electrodes, both evident when voltage was averaged in the interval 60 to 350 ms. The most recent study (Lei et al., 2017) replicated the original N1 amplitude increase. However, the current data do not show an unambiguous increase of N1 amplitude, although a trend towards it is evident. Conversely, a significant post-tetanus amplitude increase of the P2 component is readily observable, in contrast to the noted reports. One study (Teo et al., 2014), however, reported a significant SRM-driven modulation of the absolute difference between N1 and P2. In contrast to the current study, this modulation was only evident 25 minutes after the tetanic stimulation, and not immediately post-stimulation, as has been demonstrated here. As the current report has not considered long-term aspects of the phenomenon, the relevance to the current study is not entirely clear. Moreover, it is not unlikely that the current modulation of N1-P2 absolute difference is accounted for by the selective modulation of the P2 amplitude, which is the stronger and more significant of the observed modulations. On the other hand, a frequently discussed topic in regard to the auditory evoked-potentials, is the interdependence of P2 on N1, i.e. whether both potentials are accounted for by the same neuronal population. Although available evidence indicate overlapping electrophysiological sources, bilaterally in the

superior and middle temporal gyri (STG/MTG) of the auditory cortex (Wang et al., 2014), N1 and P2 are generally considered functionally independent (Crowley & Colrain, 2004). Recently, the involvement of more frontal areas has been implicated for the generation of P2 (Ford, Roach, Palzes, & Mathalon, 2016). Intriguingly, in terms of functional characteristics, the P2 potential have recently been suggested as an index of learning in various auditory training protocols (Tremblay, Ross, Inoue, McClannahan, & Collet, 2014), possibly of relevance to the current effort. In sum, the roles of N1 and P2 in the auditory SRM paradigm remain unresolved, thus constituting a topic requiring further investigation.

Given that the current auditory SRM experiment was moulded from that of Clapp, Kirk, et al. (2005), a replication of the N1 amplitude modulation was expected. However, as discussed above, the current data yielded only a P2-dependent effect, observable as modulations to the P2 amplitude and the absolute difference between N1 and P2. The basic SRM protocol employed is not likely to be the cause of discrepancy from expectations. However, in considering the whole experimental session, some divergence of experimental design was evident. Most prominently, the current auditory SRM data were collected within a multi-modal framework, with the addition of another auditory experimental paradigm (LDAEP). Consequently, the subjects were exposed to a wider range of stimuli, as compared to other studies, increasing the likelihood of contamination from interference. The stimuli in the LDAEP protocol were of the same frequency (1 kHz) as the stimuli in the auditory SRM protocol, introducing a potential habituation/sensitisation factor. However, the last stimulus of the LDAEP was delivered several minutes before the onset of the first auditory SRM stimulus, which should constitute an interval long enough to obliterate such effects (Polich, Aung, & Dalessio, 1988). Moreover, attentional processes are known to modulate the amplitude of longer latency auditory sensory components, in this context the N1 and P2 (Woldorff & Hillyard, 1991). As noted, in the current experiment, the auditory SRM protocol was administered only after a considerable passage of time and other experimental protocols, introducing fatigue as a potential factor influencing attention. Also, in contrast to previous work, subjects in the current study were instructed to respond to an unrelated visual task during the auditory protocol, possibly altering attentional modulation.



### 4.1.2 Within-subject SRM: Responder rates

A prominent focus of the larger project of which the current thesis is a part, is to investigate within-subject properties of the SRM protocols. This issue is relevant in several regards. Most importantly, if the SRM effect truly reflects, at least to some degree, expression of LTP in stimulated synapses, an effect should be readily observable in the majority of healthy participants, given the role of LTP as a naturally occurring mechanism of synaptic plasticity. Next, in considering SRM as a potential biomarker of general LTP integrity in the brain, SRM expression in one modality should, to a respectable degree, be predictive of SRM expression in another modality. Conversely, without predictive power across modalities, the LTP-indexing properties of SRM would be severely limited, reflecting solely modality-selective mechanisms. A potentially enlightening approach to these issues, is to consider responder rates, i.e. the ratio of responders to non-responders. In addition, this investigation might provide some means to elucidate the nature of ERP-based measurements of the SRM phenomenon.

Previously, the term *potentiation* has been regularly employed in describing the alterations of sensory evoked potentials demonstrated within the frames of the SRM protocol. However, the current effort, building on the discussion of Lahr et al. (2014), promotes the term *modification* (or *modulation*) in its stead, accentuating the uncertainty regarding the nature of the plastic modulations of synapses reflected in sensory evoked potentials. As briefly introduced in the introduction, the components of a given ERP complex reflects equivalent current dipoles (i.e. simultaneous firing of enough equivalently oriented neurons) sufficiently strong to stand out from random voltage fluctuations. In this sense, it is perhaps natural to assume that a LTP-driven modulation of voltage is most likely to be reflected at such components, given that the individual neurons making up the equivalent current dipole in all likelihood support the same task. However, as discussed by Jahshan et al. (2017), there is no clear evidence ruling out that LTP-driven modulations might manifest independent of distinct ERP components. Moreover, it is not entirely clear that LTP-expressing synapses manifest as *increases* in sensory-evoked potential component amplitudes. The underlying cause of the SRM-driven modulations to component amplitudes might be influenced by other molecular or cellular mechanisms, distinct from, or interacting with, mechanisms of LTP.

The discussion of effect directionality emerged following reports of considerable heterogeneity in individual expression of protocols indexing LTP-like plasticity, including SRM and transcranial magnetic stimulation/paired-associate stimulation (TMS-PAS). One study (Müller-Dahlhaus et al., 2008), found that 52 % of participants displayed an increase in MEP amplitude over the course of the PAS protocol, whereas 48 % were characterised by a decrease. Another PAS study (Fratello et al., 2006) reported that approximately 78 % were MEP responders. Similarly, in a fMRI study of SRM (Lahr et al., 2014), increased activations following tetanic sensory stimulation were present for a third of the participants, whereas the remaining displayed decreased activations. As noted, few electrophysiological SRM studies have reported responder rates, with the notable exception of Klöppel et al. (2015), who reported that 76 % of participants displayed a post-tetanic increase of visual P1 amplitude. In the current report, single-subject effect sizes have been computed, and subsequently contrasted to a selection of criteria, in order to further elaborate on the issue of inter-subjective variability in SRM-expression. The auditory data are particularly interesting in this respect, due to the absence of an unequivocal main effect. In regard to the visual data, although difference testing reveals robust effects on all components, the corresponding responder rates warrant considerable caution in their interpretation. Generally, the fraction of individuals displaying either visual or auditory SRM response is low, particularly when the effect size-based criterion increases. Moreover, in accordance with expectation, the rates vary across components, and decline as the threshold value of  $d$  increases (table 3.5). At the most liberal of criteria, the occurrence of any tetanus-driven modulation of mean amplitude in the hypothesised direction, the current visual responder rates at any individual component are consistent with those previously reported (Klöppel et al., 2015), although slightly lower. In the auditory data, the corresponding rates are unanimously lower than their visual counterparts. However, the peak-to-peak measures of visual P1-N1 and auditory N1-P2 are notably higher, suggesting that these measures might provide better sensitivity in characterising responders, although possibly at the expense of the corresponding specificity. The definition of a responder, in regard to standardised measurement and criterion, is an issue that demands further attention, requiring investigators to report responder rates for future comparison.

Importantly, in the results presented in the current report, a positive effect size reflects a change of amplitude in the hypothesised direction, thus implicitly ruling out the relevance of amplitude modulations of the opposite bearing. Consequently, the polarity (i.e. the *increase*

or *decrease*) of amplitude changes, over the course of the SRM protocol, remains an intriguing topic for discussion. One way of looking at this issue, is to conclude that the absence of a *positive effect* (i.e. amplitude modulation in the expected direction) characterises non-responding individuals. However, given that the SRM paradigm truly indexes LTP-expression and that mechanisms of LTP are mostly intact in the current sample, an explanation for the high count of non-responders is not readily available, particularly regarding the auditory protocol. One possible interpretation of these findings (Lahr et al., 2014) is that such *negative effects* (in the current context) might reflect equivalent LTP mechanisms, although expressed in synapses different from those potentiated when a positive effect is observed. As previously noted, it is likely that SRM-induced LTP may be expressed in synapses of either excitatory or inhibitory networks, which may in turn play a role in determining the polarity of an alteration of a specific amplitude. Thus, functional characteristics of the individual brain might well contribute to the shaping of individual SRM-induced synaptic plasticity expression. Similarly, in considering individual brain morphology, variation in the locations and orientations of the equivalent current dipoles contributing to the electrophysiological potentials of interest, is also likely to be an influential factor (Elvsåshagen et al., 2015). From this perspective, the direction of the individual SRM-induced amplitude modulations becomes irrelevant, leading to a greater ratio of SRM-responders to non-responders. However, the current low responder rates may simply be attributable to error, both random and systematic, in the data. This issue should be addressed in a larger sample than the current.

### **4.1.3 Cross-modality correlation**

The principal aim of the current study was to determine if the expression of SRM-induced LTP in one sensory modality can predict expression in another sensory modality. Of notable relevance, Klöppel et al. (2015) have compared effect sizes of visual SRM to those of the PAS protocol, identifying a correlation between the two presumed measures of LTP-expression. In their report, the conclusion nevertheless states that LTP-like plasticity effects are likely to differ across the motor and the visual sensory systems, due to poor agreement between the variables. Importantly, the two paradigms in question differ considerably, and their direct comparison warrants caution. Conversely, in the current approach, the two protocols are constructed as modality-dependent equivalents, presumably facilitating the validity of direct comparison.

Effect sizes, indexing amplitude alteration from baseline blocks to post-stimulation blocks, across all visual and auditory components, were subjected to bivariate correlational analyses. The resulting correlational matrix includes several apparent within-modality correlations, and two nominally significant between-modality associations. The SRM-driven decrease of the visual C1 component amplitude appears associated with the equivalent increase of the auditory P2 component amplitude. The correlation is also evident when auditory P2 is substituted with the N1-P2 absolute difference. This is, to the best of our knowledge, the first demonstration of a within-subject association between SRM-induced LTP-expression in visual and auditory modality. However, due to limitations in terms of statistical power in the current study, it must be emphasised that caution is warranted in the interpretation of the finding. It should be noted, however, that few prior studies of the SRM phenomenon exceed the current effort in terms of statistical power (see table 1.1 for  $n$  of a selection of relevant studies). The current correlation coefficient is not of a convincing magnitude, and its significance did not survive a stringent control for multiple comparisons. One possible explanation for this concerns the unbalanced state of robustness between the two modalities. As expected from existing literature, the visual SRM effect comes out considerably more robust than its auditory counterpart, somewhat blurring the cross-modal picture. Particularly, the current finding of an auditory P2 amplitude increase, and the absence of the previously demonstrated N1 equivalent, makes the implications of the association more difficult to disentangle. However, agreement between within-subject visual C1 responses and auditory P2 responses, assessed using Cohen's kappa, was significantly stronger compared to Klöppel et al. (2015). Taking all into account, the current data indicate a possible common mechanism for the expression of SRM-induced LTP in both the visual and auditory modality, thus providing some evidence for the hypothesis of the SRM effect as an index of the generalised integrity of LTP-based synaptic plasticity processes. Importantly, the current finding does not provide any direct insight regarding the neuronal mechanisms underpinning the SRM phenomenon, but it does support the notion that individual capacity for displaying the effect may be common to multiple sensory systems, and thus not merely be of a modality-specific nature.

Despite the discussed factors warranting caution in interpretation, the correlation between the visual C1 and auditory P2 amplitude changes is considered noteworthy. Importantly, an association between two unexpected variables was found. The visual C1 component peaks

considerably earlier (~70-90 ms) in the visual evoked potential than the auditory P2 does (~180-220 ms) in the auditory equivalent, eliminating the potential for a temporal association. Due to their temporal discrepancy, the functional significance of the two components are also likely to be of diverging nature. The visual C1 originates in the calcarine fissure of the primary visual cortex, likely reflecting ascending thalamocortical pathways, whereas the auditory P2, in comparison, emerges later in the processing stream. As the functional significance of the auditory P2 is poorly understood (Crowley & Colrain, 2004), the disentangling of a potential functional association between visual C1 and auditory P2 requires a broader perspective than the current. Conversely, it should also be noted that functional association between modules of the two sensory modalities, is not given. The SRM-driven modulations of the two components might be functionally unrelated, yet share some cross-modal LTP-dependent mechanism, accounting for their co-variation. Consequently, the nature of the current cross-modal association remains elusive. Further understanding of the different aspects of electrophysiological signals in SRM-expression are required, including, but not limited to, the significance of component amplitude modulations.

## **4.2 Methodological considerations**

The current study measured SRM-induced LTP-like plasticity effects using the event-related potential (ERP) technique. However, there exists no golden standard related to how ERP measures are best quantified and analysed (Luck, 2014). The current data consist of absolute measures of voltage at specified amplitude peaks, i.e. voltage at one latency. Conversely, measures of mean voltage in pre-defined latency windows might in some cases yield more robust indices. A wide range of quantification approaches are available. Similarly, measures of voltage may be standardised prior to data extraction, thus facilitating direct comparison of measures from different subjects. In the current context, the process of standardisation was performed in the case of within-subject tetanus-driven changes of amplitude, providing effect sizes comparable at the between-subject level. These effect sizes were subsequently used in determining responder rates, and in identifying between-modality correlations. However, it is not guaranteed that this approach is the most valid. Optional approaches include the use of absolute differences of voltage, and percentwise modulation.

### **4.3 Limitations**

One methodological limitation was the non-randomised design of the experimental procedure. Due to the role of attention and alertness in the recording of sensory-evoked potentials, randomisation of the sequential order of presented paradigms might have influenced the results. Given the likely decline of subjective alertness, and increase of fatigue, over the relatively long experimental session, the auditory evoked potentials are more likely to be contaminated, relative to the visual evoked potentials. However, participants were required to respond to the same visual cue across both modalities, hence controlling for effects of attentional decline. Previous studies have suggested that the SRM effect may be influenced by levels of physical activity (Smallwood et al., 2015) and genetics (Lamb et al., 2015). However, these factors were not accounted for in the current study. Moreover, since effect sizes were generally in the small to medium range, a larger sample size will likely be necessary in order to have sufficient power to robustly detect these subtle effects, as suggested by the post-hoc power analyses (table 3.4).

### **4.4 Themes for future research**

The current report raises several questions, both methodological and conceptual, in regard to the SRM protocol. Most prominently is the need for replication of the current cross-modal finding of a nominally significant association between the SRM-driven modulation of visual C1 and auditory P2. Second, further investigation into SRM responder rates is required, particularly concerning the current polarity-dependant definition of response. Future research, preferably with more statistical power, should aim to elucidate the nature of ERP-based measures of SRM. Third, as the auditory SRM protocol yields ambiguous effects, further methodological inquiries are advisable. Finally, the current validation of a multi-modal approach to SRM, also pave the way for methodological considerations in regard to data processing and measurement. Alternatives to component amplitude measures are available, and these should be subject to scrutiny. Also, the use of independent component analysis (ICA) and dipole analyses are relevant.

## 5 Conclusion

The current study is the first to demonstrate the efficacy of a multi-modal stimulus-selective response modification paradigm (SRM). Within the same experimental session, this dual-modality approach effectively indexes LTP-like plasticity in separate sensory systems. The phenomenon was evident in both the visual and the auditory modality separately, although the expression of the effect in the auditory protocol remains somewhat ambiguous, compared to some prior reports. Moreover, the within-subject effect sizes indexing the SRM-driven amplitude modulation at the visual C1 and at the auditory P2, appeared associated. However, due to limited statistical power, caution in interpretation is warranted. Regardless, the finding is considered of promising, providing some evidence for the study's principle hypothesis of a cross-modal SRM-related association. The nature of this finding, consisting of an early visual component associated with a late auditory component, remains elusive. Thus, the implications of this cross-modal effect are not entirely clear.

Another prominent focus of the current work was to probe the issue of responder rates within the SRM framework. Only rarely have previous efforts discussed the constituents that make up the definition of the individual responder. We found responder rates in line with a previous study (Klöppel et al., 2015), and subsequently discussed the plausibility and possible implications of a polarity-independent definition of SRM-response.

In summary, the current study provides the first promising evidence for a cross-modal association of sensory-induced LTP-like plasticity within the SRM framework. Future studies utilising larger samples will be needed to replicate these findings and resolve remaining methodological and conceptual ambiguities.

# References

- Abraham, W. C., Logan, B., Greenwood, J. M., & Dragunow, M. (2002). Induction and experience-dependent consolidation of stable long-term potentiation lasting months in the hippocampus. *The Journal of Neuroscience*, *22*(21), 9626-9634.
- Beck, H., Goussakov, I. V., Lie, A., Helmstaedter, C., & Elger, C. E. (2000). Synaptic plasticity in the human dentate gyrus. *The Journal of Neuroscience*, *20*(18).
- Bhandari, A., Voineskos, D., Daskalakis, Z. J., Rajji, T. K., & Blumberger, D. M. (2016). A Review of Impaired Neuroplasticity in Schizophrenia Investigated with Non-invasive Brain Stimulation. *Frontiers in Psychiatry*, *7*, 45. doi:10.3389/fpsy.2016.00045
- Bigdely-Shamlo, N., Mullen, T., Kothe, C., Su, K.-M., & Robbins, K. A. (2015). The PREP pipeline: standardized preprocessing for large-scale EEG analysis. *Frontiers in Neuroinformatics*, *9*, 16. doi:10.3389/fninf.2015.00016
- Bliss, T. V. P., & Collingridge, G. L. (1993). A synaptic model of memory: long-term potentiation in the hippocampus. *Nature*, *361*(6407), 31-39. doi:10.1038/361031a0
- Bliss, T. V. P., & Lømo, T. (1973). Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *The Journal of Physiology*, *232*(2), 331-356. doi:10.1113/jphysiol.1973.sp010273
- Cantarero, G., Lloyd, A., & Celnik, P. (2013). Reversal of Long-Term Potentiation-Like Plasticity Processes after Motor Learning Disrupts Skill Retention. *The Journal of Neuroscience*, *33*(31), 12862-12869. doi:10.1523/JNEUROSCI.1399-13.2013
- Castrén, E. (2013). Neuronal Network Plasticity and Recovery From Depression. *JAMA Psychiatry*, *70*(9), 983-989. doi:10.1001/jamapsychiatry.2013.1
- Cavuş, I., Reinhart, R. M., Roach, B. J., Gueorguieva, R., Teyler, T. J., Clapp, W. C., . . . Mathalon, D. H. (2012). Impaired visual cortical plasticity in schizophrenia. *Biological psychiatry*, *71*(6), 512-520. doi:10.1016/j.biopsych.2012.01.013
- Chaumon, M., Bishop, D., & Busch, N. A. (2015). A practical guide to the selection of independent components of the electroencephalogram for artifact correction. *Journal of Neuroscience Methods*, *250*, 47-63. doi:10.1016/j.jneumeth.2015.02.025
- Chen, W. R., Lee, S., Kato, K., Spencer, D. D., Shepherd, G. M., & Williamson, A. (1996). Long-term modifications of synaptic efficacy in the human inferior and middle temporal cortex. *Proceedings of the National Academy of Sciences*, *93*(15), 8011-8015. doi:10.1073/pnas.93.15.8011



- Clapp, W. C., Hamm, J. P., Kirk, I. J., & Teyler, T. J. (2012). Translating long-term potentiation from animals to humans: a novel method for noninvasive assessment of cortical plasticity. *Biological psychiatry*, *71*(6), 496-502.  
doi:10.1016/j.biopsych.2011.08.021
- Clapp, W. C., Kirk, I. J., Hamm, J. P., Shepherd, D., & Teyler, T. J. (2005). Induction of LTP in the human auditory cortex by sensory stimulation. *European Journal of Neuroscience*, *22*(5), 1135-1140. doi:10.1111/j.1460-9568.2005.04293.x
- Clapp, W. C., Zaehle, T., Lutz, K., Marcar, V. L., Kirk, I. J., Hamm, J. P., . . . Jancke, L. (2005). Effects of long-term potentiation in the human visual cortex: a functional magnetic resonance imaging study. *Neuroreport*, *16*(18), 1977-1980.  
doi:10.1097/00001756-200512190-00001
- Cooke, S. F., & Bear, M. F. (2010). Visual Experience Induces Long-Term Potentiation in the Primary Visual Cortex. *The Journal of Neuroscience*, *30*(48), 16304-16313.  
doi:10.1523/JNEUROSCI.4333-10.2010
- Cooke, S. F., & Bear, M. F. (2012). Stimulus-Selective Response Plasticity in the Visual Cortex: An Assay for the Assessment of Pathophysiology and Treatment of Cognitive Impairment Associated with Psychiatric Disorders. *Biological psychiatry*, *71*(6), 487-495. doi:10.1016/j.biopsych.2011.09.006
- Cooke, S. F., & Bear, M. F. (2014). How the mechanisms of long-term synaptic potentiation and depression serve experience-dependent plasticity in primary visual cortex. *Philosophical Transactions of the Royal Society of London B: Biological Sciences*, *369*(1633), 20130284. doi:10.1098/rstb.2013.0284
- Cooke, S. F., & Bliss, T. V. P. (2006). Plasticity in the human central nervous system. *Brain*, *129*(7), 1659-1673. doi:10.1093/brain/awl082
- Crowley, K. E., & Colrain, I. M. (2004). A review of the evidence for P2 being an independent component process: age, sleep and modality. *Clinical Neurophysiology*, *115*(4), 732-744. doi:10.1016/j.clinph.2003.11.021
- de Gobbi Porto, F. H., Fox, A., Tusch, E. S., Sorond, F., Mohammed, A. H., & Daffner, K. R. (2015). In vivo evidence for neuroplasticity in older adults. *Brain Research Bulletin*, *114*. doi:10.1016/j.brainresbull.2015.03.004
- Delorme, A., & Makeig, S. (2004). EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods*, *134*(1), 9-21. doi:10.1016/j.jneumeth.2003.10.009

- Delorme, A., Palmer, J., Onton, J., Oostenveld, R., & Makeig, S. (2012). Independent EEG Sources Are Dipolar. *PLoS ONE*, 7(2). doi:10.1371/journal.pone.0030135
- Di Russo, F., Martínez, A., Sereno, M. I., Pitzalis, S., & Hillyard, S. A. (2002). Cortical sources of the early components of the visual evoked potential. *Human Brain Mapping*, 15(2). doi:10.1002/hbm.10010
- Dinse, H. R., & Tegenthoff, M. (2015). Evoking plasticity through sensory stimulation: Implications for learning and rehabilitation. *e-Neuroforum*, 6(1), 11-20. doi:10.1007/s13295-015-0003-1
- Eckert, M. J., Guévremont, D., Williams, J. M., & Abraham, W. C. (2013). Rapid visual stimulation increases extrasynaptic glutamate receptor expression but not visual - evoked potentials in the adult rat primary visual cortex. *European Journal of Neuroscience*, 37(3), 400-406. doi:10.1111/ejn.12053
- Elvsåshagen, T., Moberget, T., Bøen, E., Boye, B., Englin, N. O., Pedersen, P. Ø., . . . Andersson, S. (2012). Evidence for impaired neocortical synaptic plasticity in bipolar II disorder. *Biological psychiatry*, 71(1), 68-74. doi:10.1016/j.biopsych.2011.09.026
- Elvsåshagen, T., Moberget, T., Bøen, E., Hol, P. K., Malt, U. F., Andersson, S., & Westlye, L. T. (2015). The surface area of early visual cortex predicts the amplitude of the visual evoked potential. *Brain Structure and Function*, 220(2), 1229-1236. doi:10.1007/s00429-013-0703-7
- Faul, F., Erdfelder, E., Buchner, A., & Lang, A.-G. (2009). Statistical power analyses using G\*Power 3.1: Tests for correlation and regression analyses. *Behavior Research Methods*, 41(4), 1149-1160. doi:10.3758/BRM.41.4.1149
- Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A. (2007). G\*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*, 39(2), 175-191. doi:10.3758/BF03193146
- Feldman, D. E. (2009). Synaptic Mechanisms for Plasticity in Neocortex. *Annual review of neuroscience*, 32(1), 33-55. doi:10.1146/annurev.neuro.051508.135516
- Field, A. (2013). *Discovering Statistics Using IBM SPSS Statistics* (4 ed.). London: SAGE Publications Ltd.
- Ford, J. M., Roach, B. J., Palzes, V. A., & Mathalon, D. H. (2016). Using concurrent EEG and fMRI to probe the state of the brain in schizophrenia. *NeuroImage: Clinical*, 12, 429-441. doi:10.1016/j.nicl.2016.08.009

- Forsyth, J. K., Bachman, P., Mathalon, D. H., Roach, B. J., & Asarnow, R. F. (2015). Augmenting NMDA receptor signaling boosts experience-dependent neuroplasticity in the adult human brain. *Proceedings of the National Academy of Sciences*, *112*(50), 15331-15336. doi:10.1073/pnas.1509262112
- Frantseva, M. V., Fitzgerald, P. B., Chen, R., Möller, B., Daigle, M., & Daskalakis, Z. J. (2008). Evidence for Impaired Long-Term Potentiation in Schizophrenia and Its Relationship to Motor Skill Learning. *Cerebral Cortex*, *18*(5), 990-996. doi:10.1093/cercor/bhm151
- Fratello, F., Veniero, D., Curcio, G., Ferrara, M., Marzano, C., Moroni, F., . . . Gennaro, L. (2006). Modulation of corticospinal excitability by paired associative stimulation: Reproducibility of effects and intraindividual reliability. *Clinical Neurophysiology*, *117*(12), 2667-2674. doi:10.1016/j.clinph.2006.07.315
- Hebb, D. O. (1949). *The organization of behavior : a neuropsychological theory*. New York: John Wiley.
- Hillyard, S. A., & Anllo-Vento, L. (1998). Event-related brain potentials in the study of visual selective attention. *Proceedings of the National Academy of Sciences*, *95*(3), 781-787. doi:10.1073/pnas.95.3.781
- Jahshan, C., Wynn, J. K., Mathalon, D. H., & Green, M. F. (2017). Cognitive correlates of visual neural plasticity in schizophrenia. *Schizophrenia Research*. doi:10.1016/j.schres.2017.03.016
- Karns, C. M., & Knight, R. T. (2009). Intermodal Auditory, Visual, and Tactile Attention Modulates Early Stages of Neural Processing. *Journal of Cognitive Neuroscience*, *21*(4), 669-683. doi:10.1162/jocn.2009.21037
- Kirk, I. J., McNair, N. A., Hamm, J. P., Clapp, W. C., Mathalon, D. H., Cavus, I., & Teyler, T. J. (2010). Long-term potentiation (LTP) of human sensory-evoked potentials. *Wiley Interdisciplinary Reviews: Cognitive Science*, *1*(5), 766-773. doi:10.1002/wcs.62
- Kirkwood, A., & Bear, M. F. (1994). Hebbian synapses in visual cortex. *The Journal of Neuroscience*, *14*(3 Pt 2).
- Kleiner, M., Brainard, D., Pelli, D., Ingling, A., Murray, R., & Broussard, C. (2007). What's new in Psychtoolbox-3. *Perception*, *36*(14).
- Klöppel, S., Lauer, E., Peter, J., Minkova, L., Nissen, C., Normann, C., . . . Lahr, J. (2015). LTP-like plasticity in the visual system and in the motor system appear related in

- young and healthy subjects. *Frontiers in Human Neuroscience*, 9, 506.  
doi:10.3389/fnhum.2015.00506
- Lahr, J., Peter, J., Bach, M., Mader, I., Nissen, C., Normann, C., . . . Klöppel, S. (2014). Heterogeneity of stimulus-specific response modification-an fMRI study on neuroplasticity. *Frontiers in Human Neuroscience*, 8, 695.  
doi:10.3389/fnhum.2014.00695
- Lamb, Y. N., McKay, N. S., Thompson, C. S., Hamm, J. P., Waldie, K. E., & Kirk, I. J. (2015). Brain - derived neurotrophic factor Val66Met polymorphism, human memory, and synaptic neuroplasticity. *Wiley Interdisciplinary Reviews: Cognitive Science*, 6(2), 97-108. doi:10.1002/wcs.1334
- Landis, R. J., & Koch, G. G. (1977). The Measurement of Observer Agreement for Categorical Data. *Biometrics*, 33(1), 159. doi:10.2307/2529310
- Lei, G., Zhao, Z., Li, Y., Yu, L., Zhang, X., Yan, Y., . . . Yang, S. (2017). A method to induce human cortical long-term potentiation by acoustic stimulation. *Acta Oto-Laryngologica*, 1-8. doi:10.1080/00016489.2017.1332428
- List, J., Duning, T., Kürten, J., Deppe, M., Wilbers, E., & Flöel, A. (2013). Cortical plasticity is preserved in nondemented older individuals with severe ischemic small vessel disease. *Human Brain Mapping*, 34(6), 1464-1476. doi:10.1002/hbm.22003
- López-Alonso, V., Cheeran, B., Río-Rodríguez, D., & Fernández-del-Olmo, M. (2014). Inter-individual Variability in Response to Non-invasive Brain Stimulation Paradigms. *Brain Stimulation*, 7(3), 372-380. doi:10.1016/j.brs.2014.02.004
- Lopez-Calderon, J., & Luck, S. J. (2014). ERPLAB: an open-source toolbox for the analysis of event-related potentials. *Frontiers in Human Neuroscience*, 8, 213.  
doi:10.3389/fnhum.2014.00213
- Luck, S. J. (2014). *An Introduction to the Event-Related Potential Technique* (2 ed.): MIT Press.
- Lüscher, C., & Frerking, M. (2001). Restless AMPA receptors: implications for synaptic transmission and plasticity. *Trends in Neurosciences*, 24(11), 665-670.  
doi:10.1016/S0166-2236(00)01959-7
- Lømo, T. (1966). Frequency Potentiation of Excitatory Synaptic Activity in the Dentate Area of the Hippocampal Formation. *Acta Physiologica Scandinavica*, 68.  
doi:10.1111/j.1748-1716.1966.tb03476.x

- Lømo, T. (2012). Plastisitet i hjernen: mekanismer og betydning. In T. Fladby, S. Andersson, & L. Gjerstad (Eds.), *Nevropsykiatri: Metoder og kliniske perspektiver*. Oslo: Gyldendal Akademisk.
- Makeig, S., & Onton, J. (2012). ERP Features and EEG Dynamics: An ICA Perspective. In S. J. Luck & E. S. Kappenman (Eds.), *The Oxford Handbook of Event-Related Potential Components*: Oxford University Press.
- Malinow, R. (2003). AMPA receptor trafficking and long-term potentiation. *Philosophical Transactions of the Royal Society of London B: Biological Sciences*, 358(1432), 707-714. doi:10.1098/rstb.2002.1233
- Marsden, W. N. (2013). Synaptic plasticity in depression: Molecular, cellular and functional correlates. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 43, 168-184. doi:10.1016/j.pnpbp.2012.12.012
- McNair, N. A., Clapp, W. C., Hamm, J. P., Teyler, T. J., Corballis, M. C., & Kirk, I. J. (2006). Spatial frequency-specific potentiation of human visual-evoked potentials. *Neuroreport*, 17(7), 739-741.
- Mears, R. P., & Spencer, K. M. (2012). Electrophysiological Assessment of Auditory Stimulus-Specific Plasticity in Schizophrenia. *Biological psychiatry*, 71(6), 503-511. doi:10.1016/j.biopsych.2011.12.016
- Miller, J., Patterson, T., & Ulrich, R. (1998). Jackknife - based method for measuring LRP onset latency differences. *Psychophysiology*, 35(1), 99-115. doi:10.1111/1469-8986.3510099
- Milner, B., Squire, L. R., & Kandel, E. R. (1998). Cognitive Neuroscience and the Study of Memory. *Neuron*, 20(3), 445-468. doi:10.1016/S0896-6273(00)80987-3
- Müller-Dahlhaus, F. J. M., Orekhov, Y., Liu, Y., & Ziemann, U. (2008). Interindividual variability and age-dependency of motor cortical plasticity induced by paired associative stimulation. *Experimental Brain Research*, 187(3), 467-475. doi:10.1007/s00221-008-1319-7
- Nicoll, R. A. (2017). A Brief History of Long-Term Potentiation. *Neuron*, 93(2), 281-290. doi:10.1016/j.neuron.2016.12.015
- Nolan, H., Whelan, R., & Reilly, R. B. (2010). FASTER: Fully Automated Statistical Thresholding for EEG artifact Rejection. *Journal of Neuroscience Methods*, 192(1), 152-162. doi:10.1016/j.jneumeth.2010.07.015

- Normann, C., Schmitz, D., Fürmaier, A., Döing, C., & Bach, M. (2007). Long-Term Plasticity of Visually Evoked Potentials in Humans is Altered in Major Depression. *Biological psychiatry*, *62*(5), 373-380. doi:10.1016/j.biopsych.2006.10.006
- Pearson-Fuhrhop, K. M., Kleim, J. A., & Cramer, S. C. (2009). Brain plasticity and genetic factors. *Topics in stroke rehabilitation*, *16*(4), 282-299. doi:10.1310/tsr1604-282
- Player, M. J., Taylor, J. L., Alonzo, A., & Loo, C. K. (2012). Paired associative stimulation increases motor cortex excitability more effectively than theta-burst stimulation. *Clinical Neurophysiology*, *123*(11), 2220-2226. doi:10.1016/j.clinph.2012.03.081
- Polich, J., Aung, M., & Dalessio, D. J. (1988). Long latency auditory evoked potentials. *The Pavlovian Journal of Biological Science*, *23*(1), 35-40. doi:10.1007/BF02910543
- Pratt, H. (2012). Sensory ERP Components. In S. J. Luck & E. S. Kappenman (Eds.), *The Oxford Handbook of Event-Related Potential Components*: Oxford University Press.
- Proverbio, A. M., Zotto, M., & Zani, A. (2010). Electrical neuroimaging evidence that spatial frequency-based selective attention affects V1 activity as early as 40-60 ms in humans. *BMC Neuroscience*, *11*(1), 1-13. doi:10.1186/1471-2202-11-59
- Reis, J., Schambra, H. M., Cohen, L. G., Buch, E. R., Fritsch, B., Zarahn, E., . . . Krakauer, J. W. (2009). Noninvasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation. *Proceedings of the National Academy of Sciences*, *106*(5), 1590-1595. doi:10.1073/pnas.0805413106
- Ross, R. M., McNair, N. A., Fairhall, S. L., Clapp, W. C., Hamm, J. P., Teyler, T. J., & Kirk, I. J. (2008). Induction of orientation-specific LTP-like changes in human visual evoked potentials by rapid sensory stimulation. *Brain Research Bulletin*, *76*(1-2), 97-101. doi:10.1016/j.brainresbull.2008.01.021
- Sale, M. V., Ridding, M. C., & Nordstrom, M. A. (2007). Factors influencing the magnitude and reproducibility of corticomotor excitability changes induced by paired associative stimulation. *Experimental Brain Research*, *181*(4), 615-626. doi:10.1007/s00221-007-0960-x
- Sawilowsky, S. S. (2009). New Effect Size Rules of Thumb. *Journal of Modern Applied Statistical Methods*, *8*(2), 597-599. doi:10.22237/jmasm/1257035100
- Schloesser, R. J., Huang, J., Klein, P. S., & Manji, H. K. (2007). Cellular Plasticity Cascades in the Pathophysiology and Treatment of Bipolar Disorder. *Neuropsychopharmacology*, *33*(1), 110-133. doi:10.1038/sj.npp.1301575
- Smallwood, N., Spriggs, M. J., Thompson, C. S., Wu, C. C., Hamm, J. P., Moreau, D., & Kirk, I. J. (2015). Influence of Physical Activity on Human Sensory Long-Term

- Potentiation. *Journal of the International Neuropsychological Society*, 21(10), 831-840. doi:10.1017/S1355617715001095
- Soeiro-de-Souza, M. G., Dias, V. V., Figueira, M. L., Forlenza, O. V., Gattaz, W. F., Zarate, C. A., & Machado - Vieira, R. (2012). Translating neurotrophic and cellular plasticity: from pathophysiology to improved therapeutics for bipolar disorder. *Acta Psychiatrica Scandinavica*, 126(5), 332-341. doi:10.1111/j.1600-0447.2012.01889.x
- Spriggs, M. J., Cadwallader, C. J., Hamm, J. P., Tippett, L. J., & Kirk, I. J. (2017). Age-related alterations in human neocortical plasticity. *Brain Research Bulletin*, 130, 53-59. doi:10.1016/j.brainresbull.2016.12.015
- Stefan, K., Wycislo, M., & Classen, J. (2004). Modulation of Associative Human Motor Cortical Plasticity by Attention. *Journal of Neurophysiology*, 92(1), 66-72. doi:10.1152/jn.00383.2003
- Teo, J. T. H., Bentley, G., Lawrence, P., Soltesz, F., Miller, S., Willé, D., . . . Nathan, P. J. (2014). Late cortical plasticity in motor and auditory cortex: role of met-allele in BDNF Val66Met polymorphism. *International Journal of Neuropsychopharmacology*, 17(5), 705-713. doi:10.1017/S1461145713001636
- Teyler, T. J., Hamm, J. P., Clapp, W. C., Johnson, B. W., Corballis, M. C., & Kirk, I. J. (2005). Long - term potentiation of human visual evoked responses. *European Journal of Neuroscience*, 21(7), 2045-2050. doi:10.1111/j.1460-9568.2005.04007.x
- Tremblay, K. L., Ross, B., Inoue, K., McClannahan, K., & Collet, G. (2014). Is the auditory evoked P2 response a biomarker of learning? *Frontiers in Systems Neuroscience*, 8, 28. doi:10.3389/fnsys.2014.00028
- Wang, J., Mathalon, D. H., Roach, B. J., Reilly, J., Keedy, S. K., Sweeney, J. A., & Ford, J. M. (2014). Action planning and predictive coding when speaking. *NeuroImage*, 91, 91-98. doi:10.1016/j.neuroimage.2014.01.003
- Widmann, A., Schröger, E., & Maess, B. (2015). Digital filter design for electrophysiological data - a practical approach. *Journal of Neuroscience Methods*, 250, 34-46. doi:10.1016/j.jneumeth.2014.08.002
- Winkler, I., Debener, S., Muller, K.-R., & Tangermann, M. (2015). On the influence of high-pass filtering on ICA-based artifact reduction in EEG-ERP. *Engineering in Medicine and Biology Society (EMBC), 2015 37th Annual International Conference of the IEEE, 2015*, 4101-4105. doi:10.1109/EMBC.2015.7319296

- Woldorff, M. G., & Hillyard, S. A. (1991). Modulation of early auditory processing during selective listening to rapidly presented tones. *Electroencephalography and Clinical Neurophysiology*, 79(3), 170-191. doi:10.1016/0013-4694(91)90136-R
- Xu, T., Yu, X., Perlik, A. J., Tobin, W. F., Zweig, J. A., Tennant, K., . . . Zuo, Y. (2009). Rapid formation and selective stabilization of synapses for enduring motor memories. *Nature*, 462(7275), 915-919. doi:10.1038/nature08389
- Zaehle, T., Clapp, W. C., Hamm, J. P., Meyer, M., & Kirk, I. J. (2007). Induction of LTP-like changes in human auditory cortex by rapid auditory stimulation: an fMRI study. *Restorative neurology and neuroscience*, 25(3-4).



# Appendix

There is no appended content.