DEPRESSION-RELATED ALTERATIONS IN DEVIANCE DETECTION ERPs IN THE AUDITORY AND SOMATOSENSORY MODALITY

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The brain's automatic electrophysiological responses to changes in the auditory and somatosensory environment represent potential tools for identifying depression-related neural markers. However, they have received scarce research attention to date. In this study, we used an oddball stimulus condition, in which a rare 'deviant stimulus' was interspersed with a frequent 'standard stimulus', to measure mismatch responses (MMN/MMR) and P3a component of event-related potentials (ERPs) to auditory intensity- and somatosensory location changes. We investigated whether these responses differentiate depressed patients from non-depressed controls. In addition, we investigated whether depression severity (overall depression severity, cognitive-affective symptom severity, or somatic symptom severity), as measured by the BDI-II, correlates with the ERPs.

A total of 57 participants aged between 18 and 62 years (18 depressed, 39 non-depressed), participated in the study. We found that none of the ERPs differentiated depressed patients from non-depressed controls. Furthermore, none of the depression severity indices correlated with the ERPs. The results indicate normal levels of automatic auditory- and somatosensory change detection among depressed patients, and therefore no biomarker potential was recognized in these ERPs. However, the results from this study should be considered preliminary due to the small sample size. More research is needed to assess the potential utility of ERPs as biomarkers of depression.

Keywords: depression, depression severity, auditory mismatch negativity (aMMN), somatosensory mismatch response (sMMR), auditory P3a (aP3a), somatosensory P3a (sP3a), event-related potential (ERP), oddball paradigm, intensity change, location change.

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Automaattisilla sähköfysiologisilla aivovasteilla mitatut kuulo- ja tuntoärsykemuutokset ovat potentiaalisia työkaluja masennuksen hermostollisten merkkien tunnistamiseksi. Kyseiset vasteet ovat kuitenkin saaneet osakseen vain vähän huomiota tutkimuskirjallisuudessa. Tässä tutkimuksessa käytimme oddball -paradigmaa (jossa harvinainen 'poikkeava ärsyke' annettiin 'toistettujen ärsykkeiden' sarjassa), mittaamaan auditiivisen intensiteettimuutoksen ja somatosensorisen lokaatiomuutoksen aiheuttamia tapahtumasidonnaisia herätevasteita (ERP), tarkemmin ottaen poikkeavuusnegatiivisuus- (MMN/MMR) ja P3a -vasteita. Tarkastelimme näiden herätevasteiden kykyä erotella masentuneet potilaat ei-masentuneista verrokeista. Lisäksi tutkimme korreloiko BDI-II-kyselyllä mitattu masennuksen vakavuusaste (kokonaisvakavuus, somaattisen oireilun vakavuus, tai kognitiivisaffektiivisen oireilun vakavuus) herätevasteiden kanssa.

Kaiken kaikkiaan 57 tutkittavaa, iältään 18–62 vuotta (18 masentunutta, 39 ei-masentunutta), osallistui tutkimukseen. Tämän tutkimuksen tulokset osoittivat, että yksikään herätevasteista ei erotellut masentuneita potilaita ei-masentuneista verrokeista. Lisäksi yksikään masennuksen vakavuusasteindekseistä ei korreloinut tapahtumasidonnaisten herätevasteiden kanssa. Tulokset viittaavat siihen, että muutoksen havaitseminen auditiivisessa ja somatosensorisessa ärsykeympäristössä on normaalilla tasolla masentuneilla potilailla, ja näin ollen kyseisistä tapahtumasidonnaisista herätevasteista ei löydetty potentiaalia masennuksen hermostollisten merkkien tunnistamiseksi. Pienestä otoskoosta johtuen tutkimuksen tuloksia tulisi kuitenkin pitää suuntaa antavina. Lisätutkimusta tarvitaan, jotta voitaisiin muodostaa luotettavia johtopäätöksiä tapahtumasidonnaisten herätevasteiden potentiaalista tunnistaa masennuksen hermostollisia merkkejä.

Avainsanat: masennus, masennuksen vakavuusaste, poikkeavuusnegatiivisuusvaste kuuloärsykkeissä (aMMN), poikkeavuusvaste tuntoärsykkeissä (sMMR), P3a kuuloärsykkeissä (aP3a), P3a tuntoärsykkeissä (sP3a), tapahtumasidonnainen herätevaste (ERP), oddball-paradigma, intensiteetinmuutos, lokaationmuutos.

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1 INTRODUCTION

Major depressive disorder, often referred to simply as depression, is a highly common mental disease that in numerous ways impairs an individual's ability to function efficiently (Otte et al., 2016; Käypä hoito, 2021). The etiology of Depression appears to involve interactions between genetic, environmental, and epigenetic factors (Otte et al., 2016), but our understanding of the more specific mechanisms underlying the disease remain far from being complete (Otte et al., 2016). Existing evidence does not point to a unified theory of the pathophysiology of depression (Hasler, 2010). Numerous theories of the pathophysiology of depression exist, but each theory seems to apply only to a subset of depressed patients and furthermore, the pathophysiology may undergo substantial change during the course of the illness (Hasler, 2010).

Depression has been linked to a variety of attentive higher order cognitive deficits (Otte et al., 2016). What is more unclear, is whether depression-related impairments can be found at the more fundamental level of pre-attentive and early attentive cognition. Pre-attentive information processing can be studied within the framework of predictive coding theory (Friston, 2005), which posits that the brain continuously monitors the outside world and attempts to make predictions of it. When a discrepancy between the prediction and sensory stimuli (‘a prediction error’) is detected, it can be measured by way of event-related potentials (ERPs) (Friston, 2005).

ERPs are averaged electroencephalogram (EEG) time-locked changes to external stimuli, in other words, measured brain responses arising from a specific sensory, motor, or cognitive event and they can be used to study the neural bases of human sensory processing and cognition non-invasively (Kähkönen et al., 2007). ERPs are cost-effective, have optimal temporal resolution, and the EEG equipment needed for measuring ERPs are widely available in hospitals (Kähkönen et al., 2007; Justo-Guillén et al., 2019; Ruohonen et al., 2020). Recent depression research has aimed at discovering useful biomarkers with the potential of furthering diagnostics and treatment, but not a single reliable biomarker of depression has yet surfaced. Studying early automatic information processing via ERPs could yield new insights into depression-related alterations in cognition, as well as pave the way for the discovery of useful depression biomarkers.

It has been proposed that depression negatively affects the sensitivity and adaptability of the brain's predictive coding framework (Barrett et al., 2016; Sumner et al., 2020). In other words, the whole predictive coding apparatus might work inefficiently in depressed patients, highlighted by insensitivity towards prediction error which in turn may result in malfunctioning prediction update mechanisms and suboptimal predictions (Barrett et al., 2016; Sumner et al., 2020). However, this has

not been reliably verified through scientific research thus far (Barrett et al., 2016; Sumner et al., 2020). In our study, we explore whether ERPs could be used to discern differences in information processing between depressed patients and non-depressed controls. We focus on two different sensory modalities, the auditory and the somatosensory modality. As far as we know, the somatosensory modality has received scarce research attention thus far in the context of depression and change detection ERPs. The auditory modality on the other hand remains understudied, despite receiving more attention than its somatosensory counterpart. It is also important to note that existing literature is conflicted in terms of the association between depression and abnormalities in change detection ERPs. In addition to exploring differences between depressed patients and non-depressed controls, we investigate whether depression severity correlates with our chosen ERPs. The main objective of this study is to further the knowledge of depression-related effects on early automatic information processing.

1.1 Defining depression

In the Current Care Guidelines of 2021 (Käypä hoito, 2021), the term 'depression' is used as an umbrella term that covers the depressive episode (F32) subcategories and all of the recurrent depressive disorder (F33) subcategories as outlined in the 2019 version of International Statistical Classification of Diseases (ICD-10) (WHO, 2019). In the 2013 issue of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (APA, 2013), the broader term used to cover a variety of depression subcategories is 'major depressive disorder' (MDD). Despite the subtle differences between the DSM-5 and the ICD-10 approach in terms of terminology and diagnostics, for practical reasons we have decided to use the layman's term 'depression' throughout this study to refer to both the depressive episode (F32) and recurrent depressive episode (F33) subcategories, as well as MDD. This is done while recognizing that the ICD-10 and the DSM5 approaches towards depression are not entirely identical.[1]

Depression is a heterogeneous disease with a multitude of depressive phenotypes (Fitzgerald et al., 2009; Isometsä, 2013). These can involve vegetative symptoms such as alterations in appetite or sleep, and affective symptoms such as anxiety, sadness, and overall depressed mood (WHO, 2019). Furthermore, cognitive impairments in domains such as executive function, attention, and memory

[1] Comparisons between study results obtained under these different classification systems may not be quite as reliable as comparisons of results that have been obtained under the same classification framework.

are common (Rock et al., 2014; WHO, 2019). With reference to the 2019 version of the ICD-10 (WHO, 2019), a requirement for a depression diagnosis is the presence of at least four depression symptoms dating back a minimum of two weeks (WHO, 2019). Out of the required four symptoms, a minimum of two need to be primary symptoms of the disorder (WHO, 2019). According to the ICD-10 (WHO, 2019), the primary symptoms are depressed mood, fatigue, and loss of interest, whereas examples of secondary symptoms are exaggerated self-blame, disturbed sleep or appetite, and suicidal thoughts (WHO, 2019). In our study, the subjects in the depression group had all obtained a depression diagnosis under the ICD-10 framework.

1.2 Prevalence, societal costs, and treatment of depression

Globally, roughly one in five adults fall into a bout of depression in the course of their life and an estimated 6 % of the adult population are affected by the disease each year (Otte et al., 2016; Käypä hoito, 2021). The disease is almost twice as common among women as it is amongst men, both internationally (Otte et al., 2016) and in the Finnish population (Käypä hoito, 2021). In Finland, an estimated 5-7 % of the population suffer from depression each year (Käypä hoito, 2021). In addition to mental alterations, compelling evidence supports the notion that depression is linked to numerous physical diseases (Otte et al., 2016). Depression is estimated to be the second biggest contributing factor to global disease burden, defined by years lived with a disability (Otte et al., 2016, Käypä hoito, 2021) and it gives rise to some of the highest financial costs out of all major diseases (Otte et al., 2016; Käypä hoito, 2021). The costs are related to disability pension payments, sick day payments, decreased job performance, and health care costs to name a few (Otte et al., 2016; Käypä hoito, 2021).

Psychopharmacology and psychotherapy are the most common and most studied ways of treating depression, and they appear to be somewhat effective for most patients with the disease (Otte et al., 2016; Käypä hoito, 2021). However, an estimated 30 % of depressed patients seem to be resistant to modern psychopharmacological and psychotherapy interventions, which might be due to the large variation in symptom severity and other clinical features in the depressed population (Fitzgerald et al., 2009; Isometsä, 2013). A further clinical challenge is the comorbidity of depression and other psychiatric diseases. (Otte et al., 2016; Isometsä, 2013). In general terms, depression is highly recurrent, with an estimated 30-75 % of depressed having more than one depression episode during their lifetime (Richards, 2011). Factors like high symptom severity, a history of traumatic childhood experiences, and psychiatric comorbidity predict a less favorable course (Otte et al.,

2016). Yet, we are far from being able to explain fully and with certainty in what way current treatments of depression work, and why they work for some but not for others (Otte et al., 2016).

The high prevalence and recurrence rates of depression, the high societal costs and human suffering associated with it, and its diagnostics and treatment challenges highlight the need for better diagnostic tools and treatment that better responds to the unique and differing needs within the heterogenous depressed population (Otte et al., 2016; Käypä hoito, 2021).

1.3 Depression-related cognitive impairment

Depression is associated with impairments in both non-emotional and emotional-laden attentive cognition (Otte et al., 2016). In their meta-analysis of neuropsychological studies, Rock et al., (2014) identified memory, executive function, and attention as the primarily affected cognitive domains in depression. Impaired ability to stay focused while performing a task, often due to increased distractibility, is a common feature of depression (Kähkönen et al., 2007; Restuccia et al., 2016). Broadly speaking, even though cognitive function seems to return somewhat close to base level after remission, slight impairments can remain in a variety of domains (Otte et al., 2016). This suggests that cognitive impairment in depression is not solely the result of diminished motivation brought up by depressive mood (Otte et al., 2016). The brains of patients with depression tend to differ somewhat from the brains of non-depressed controls in several respects, such as in the function of neurotransmitter (e.g., serotonin, dopamine, adrenaline) systems, the hypothalamic-pituitary-adrenal (HPA) axis, and the default mode network (Rock et al., 2014; Otte et al., 2016). Dysfunctions in several brain areas, including the frontal and temporal cortices, have been shown to mediate cognitive performance-related abnormalities in depression (Rock et al., 2014; Otte et al., 2016). However, it must be noted that the neural mechanisms underlying depression-related cognitive deficits and the neural circuits responsible for changes in cognitive capacity are poorly understood (Rock et al., 2014; Otte et al., 2016).

The extent of attentive cognitive impairment has been shown to vary between depression features (Chen et al., 2015; Zaninotto et al., 2015; Otte et al., 2016). For example, depression severity (Otte et al., 2016), psychotic features (Zaninotto et al., 2015), and recurrence of depressive episodes (Chen et al., 2015) have been singled out as factors relevant for modulating the expression of higher order cognitive impairment. The pre-attentive sensory functions are associated with higher order attentive cognition (See for example Light et al., 2007 and Strömmer et al., 2017), and thus it might

be plausible that differences in more basic pre-attentive information processing can be found between different depression phenotypes.

1.4 Biomarkers of Depression

The term 'biomarker' refers to objective indicators of medical states that can be accurately measured and observed from outside of the patient (Strimbu & Tavel, 2010). Currently, important diagnostics and treatment related considerations utilise clinical interviews and self-reports as primary sources of information. This presents challenges in terms of differentiating between depression and other psychiatric disorders involving depressive symptoms as part of the symptom profile. Aspects interfering with the discovery of useful depression biomarkers include the fact that many other psychiatric diagnoses contain similar symptoms (APA, 2013; WHO, 2019), that depression is comorbid with a variety of mental and physical diseases (Isometsä, 2013; Otte et al., 2016), and that large variation in clinical features and underlying pathophysiology characterize patients with depression (Isometsä, 2013). Objective depression biomarkers are much needed to further depression diagnostics and treatment, but none have yet surfaced with enough scientific backing and overall suitability to be used extensively (McGrath et al., 2013; Kang & Cho, 2020).

Although predicting depression treatment response and recurrence can be a challenge in clinical work, many neuroimaging methods such as diffusion tensor imaging (DTI) and functional MRI (fMRI) have been used to address this issue (Kang & Cho, 2020). In addition to these, brain's event-related potentials (ERPs) represent a promising venue of biomarkers that may further the field of psychiatric disorder diagnostics and treatment. It is thought that ERPs could be used as neural markers for diagnostic purposes and for planning individualized treatment options for depression (Proudfit et al., 2015). ERPs could potentially help differentiate depression-related cognitive alterations from cognitive alterations related to other diseases. Furthermore, since a lack of motivation and concentration are common symptoms of depression (Käypä hoito, 2021; APA, 2013; WHO, 2019), event-related potentials could be useful, as they can be used to study the brains early automatic information processing without having to rely on the subject's motivation or attentional capacity (Kähkönen et al., 2007; Chen et al., 2015; Ruohonen, 2020).

The oddball condition has commonly been used to measure early automatic information processing (Kähkönen et al., 2007; He et al., 2010; Restuccia et al., 2016; Ruohonen & Astikainen, 2017; Ruohonen et al., 2020). The oddball procedure can be used for investigating early automatic responses that are elicited without attention (Näätänen & Picton, 1987) in auditory (Ritter et al.,

1992), visual (Horimoto et al., 2002), and somatosensory (Kangas et al., 2021) modalities to name a few. These processes have been studied by analysing mismatch negativity (MMN) and P3a component of the ERP (Justo-Guillén et al., 2019). Analysing early automatic information processing can be important for understanding attentive higher order cognitive functions. For example, Light et al., (2007) found that early central nervous system information processing as depicted by auditory MMN and P3a is strongly associated with cognitive and real-world psychosocial functioning. Strömmer et al., (2017) on the other hand found a link between somatosensory mismatch response (sMMR) and executive function. MMN/MMR and P3a are valuable tools for more objective assessment of the impact of different neuropsychiatric pathologies on involuntary attention (Näätänen et al., 2012; Chen et al., 2015). Additionally, it has been proposed that these ERPs have utility as alternative measures for early disease detection and disease progression tracking (Näätänen et al., 2012; Chen et al., 2015; Tseng et al., 2021).

1.4.1 Auditory and somatosensory MMN and P3a

Many cognitive processes such as memory, learning, and executive functions are influenced by attention. Raichle and Gusnard (2005: 168) suggest that much of the brain's energy expenditure is directed towards "the development and maintenance of [a] probabilistic model of anticipated events". This process is closely related to the predictive coding theory, which according to Friston (2005), posits that the brain attempts to predict and model future events based on previous sensory stimuli. Should the prediction fail, the 'prediction error' can be seen as a MMN component of the sensory ERP (Friston, 2005). MMN can be recorded from distal exteroceptive senses, such as auditory and visual senses, but also from proximal exteroceptive senses, such as somatosensory and olfactory senses (Herman et al., 2021). Auditory mismatch negativity (aMMN) has been observed as a negative polarity component of the ERP, which is detected when the brains elicit an automatic electrophysiological signal independent of conscious attention, to a deviating auditory stimulus from a series of standard ones (Näätänen, Gaillard, et al., 1978; Näätänen, Paavilainen, et al., 2007; Näätänen, Kujala, et al., 2011a). The involuntary attention switch elicited by the MMN is non-intentional and automatic, and it is related to detecting potentially relevant stimuli that are initially out of the organism's conscious focus (Justo-Guillen et al., 2019). Indeed, the MMN can be recorded without a behavioural task and even in the absence of the subject's attention, e.g., in sleeping infants (Huotilainen et al., 2003), sleeping adults (Sabri & Campbell, 2002), and comatose patients (Fischer and Luauté, 2005). MMN was first detected by Näätänen et al., (1978), using auditory signals

differing in pitch and volume, and several other studies have since found confirmatory results using varying types of auditory stimuli (e.g., Ritter et al., 1992; Chen et al., 2015; Kangas et al., 2021), olfactory stimuli (Krauel et al., 1999) as well as different types of visual stimuli, including visual bars (Astikainen et al., 2008), objects (Müller et al., 2010), and colours (Horimoto et al., 2002). In addition to using auditory, olfactory, and visual stimuli, MMN has also been found in studies using somatosensory stimuli (e.g., Naeije et al., 2018; Kangas et al., 2021). In the somatosensory domain, mismatch negativity has been found along with a positive polarity response, which is why the term 'somatosensory mismatch response' (sMMR) is also used (e.g., Akatsuka et al., 2005, Strömmer et al., 2017).

MMN depicts the pre-attentive index of deviance detection in the ERP, whereas P3a portrays the attention orienting response during task processing, in other words, the resulting involuntary grabbing of attention produced by the change (Friedman et al., 2001; Light et al., 2007; Chen et al., 2015). As mentioned by Chen et al., (2015), mostly unconscious conditions have been used to measure MMN, whereas P3a has mostly been elicited by using active conditions with task requirements (such as counting). They also note that the P3a response can be obtained concurrently with MMN.

1.4.2 Neurobiological basis and practical application of MMN and P3a

In a review on ERP in depression research, Bruder et al., (2012) suggest that it is necessary to separate subcomponents, such as MMN from the N1 and P3a from the P300, in order to better understand how the pathology of depression impacts specific phases of cognitive processing. The MMN and P3a components are sequential and co-occur with MMN appearing before P3a (Light et al., 2007; Chen et al., 2015). Peak aMMN is elicited around 150-250 ms after the onset of a stimulus deviating in different properties, such as intensity, duration, or location (Näätänen et al., 2007). sMMR on the other hand is generally elicited 100-200 ms after the onset of for example a duration (Akatsuka et al., 2005) or spatial location (Strömmer et al., 2014; Kangas et al., 2021) deviant stimulus. To our knowledge, not a single study has found an intensity deviant sMMR. As Kangas et al. (2021) notes, intensity deviants may not be as suitable as location deviants for studying pre-attentive somatosensory processing as indexed by sMMR. P3a component of ERP occurs slightly after MMN, approximately 250-300 ms after stimulus onset (Light et al., 2007; Kiang et al., 2009; Hermens et al., 2010; Kangas et al., 2021).

As suggested by previous studies, the generation of both aMMN and sMMR happens in their own sensory modality-specific neural networks (Naeije et al., 2016, 2018). Auditory MMN consists of two overlapping subcomponents; the supra-temporal subcomponent and the frontal subcomponent (Qiao et al., 2013). The supra-temporal subcomponent relates to unconscious change detection, while the alterations in the sensory stimuli that cause an involuntary attention switch are associated with the frontal subcomponent (Qiao et al., 2013). Similarly to aMMN, somatosensory MMR also seems to have sensory-specific-, as well as frontal subcomponents (Restuccia et al., 2009; Spackman et al., 2010). As with aMMN, the sensory-specific components (centro-parietal regions for sMMR) have been suggested to reflect the mismatch detection, whereas the frontal subcomponents are thought to reflect covert attention switch toward an unnoticed stimulus (Näätänen & Michie, 1979). As opposed to MMN/MMR, the P3a response is thought of being less sensory modality-specific, with the interaction between the hippocampus, temporal-parietal areas, and the frontal lobes being most crucial (e.g., Friedman et al., 2001; Knight, 1996; Wronka et al., 2012).

Several previous studies suggest that MMN and P3a can be concurrently obtained in a passive oddball experimental model (e.g., Chen et al., 2015), such as the one used in our study. Because MMN is highly stable over time and can be rapidly assessed (Pekkonen et al., 1995; Kujala et al., 2001; Light & Braff, 2005) without attentional and motivational confounders (Braff & Light, 2004), MMN could be used as a potential neural marker of early automatic information processing with clinical utility. Several previous studies have linked changes in MMN and P3a to different neuropsychiatric conditions, and cognitive and psychosocial functioning (Hermens et al., 2010; Kaur, Battisti, Lagopoulos, et al., 2011; Kaur, Battisti, Ward, et al., 2012; Naismith et al., 2012). An increase in MMN amplitude may for instance precede improvement in clinical severity, suggesting that MMN could be used as an indicator of treatment efficacy (Näätänen et al., 2012). However, because several disorders can affect MMN, it has been suggested that MMN provides a generic illness measure that is useful for assessing illness severity (Banati & Hickie, 2009; Näätänen et al., 2012). Indeed, our understanding of different neuropsychiatric disorders and their mechanisms are expanding as MMN paradigms are increasingly being used to address a range of clinical questions (Näätänen et al., 2014).

1.5 Depression-related effects on MMN/MMR and P3a amplitude

Sumner et al., (2020) theorise that the brains of depressed patients might respond insensitively to prediction errors at least in part due to fatigue and/or frequent ruminations, which both are common features of depression (Barrett et al., 2016). On the other hand, rigid repetitive thinking, heightened

self-focus, and rumination commonly observed in depressed patients, are thought of as being the byproduct of the depression-related overactive default mode network (DMN) and associated problems in the dynamic modulation of this system (Barrett et al., 2016; Otte et al., 2016). Some ERP studies have found that depression-related bias in information processing is not restricted to the processing of emotional stimuli but extends also to the processing of non-emotional sensory information (e.g., Kähkönen et al., 2007; Chang et al., 2011).

In the following sections, we will discuss depression-related effects on auditory and somatosensory MMN/MMR and P3a. We begin with the auditory realm and from there on we proceed to the somatosensory realm. Finally, we touch upon more specific depression features in relation to our chosen ERPs.

1.5.1 Research linking Depression to auditory MMN and P3a alterations

Serotonergic function has been closely linked to both depression (Maes, 1995; Leonard, 2000) and the function of the primary auditory cortex (Hegerl et al., 2001). This indicates that investigating the connection between sound intensity change detection and depression could be useful. In general, it seems like most of the scientific endeavours relevant to our chosen subject have focused on the link between depression and auditory MMN, traditionally by way of using frequency or duration deviants. In recent years, more studies employing intensity deviants in the oddball condition have surfaced (Ruohonen & Astikainen, 2017; Bissonnette et al., 2020; Ruohonen et al., 2020). Out of major psychiatric diseases, schizophrenia has most robustly been linked to changes in aMMN and aP3a (for a review see e.g., Näätänen et al., 2016). There is more uncertainty in terms of depression-related effects on aMMN and aP3a.

Some studies comparing depressed participants to non-depressed controls have indicated increased aMMN amplitudes for frequency changes (Kähkönen et al., 2007; He et al., 2010; Restuccia et al., 2016), while others have demonstrated the exact opposite: reduced aMMN amplitudes for frequency (e.g., Hirakawa et al., 2017) and duration (Naismith et al., 2012; Qiao, Yu, et al., 2013; Qiao, Yang, et al., 2015; Chen et al., 2015) deviants, as well as reduced aMMN amplitudes for both duration and frequency changes within a single study (Takei et al., 2009). Furthermore, other studies examining duration and frequency changes (Umbricht et al., 2003; Bissonnette et al., 2020) or intensity changes (Ruohonen & Astikainen, 2017; Ruohonen et al., 2020) found no depression-related effects on aMMN amplitude. On the other hand, Bissonette et al., (2020) used an intensity change paradigm quite like the aforementioned intensity change studies and found an increased aMMN

amplitude in depressed patients compared to non-depressed controls (Bissonnette et al., 2020). Bissonette et al., (2020) also found increased aMMN amplitudes in the depressed group when employing an auditory location deviant.

In most depression studies utilising ERPs, aP3a has been explored separately from aMMN, and to a lesser extent. The studies by Kähkönen et al., (2007) and Chen et al., (2015) represent a rarity in this regard, since they investigated auditory MMN and P3a simultaneously in depressed adults. Hypothetically, the scarceness of studies investigating the link between depression and aP3a might partially be due to a commonly held assumption that MMN alterations automatically transfer over into the subsequent P3a response, resulting in a view that focusing on aP3a might not be that fruitful. The results from Jaworska et al., (2013), Kähkönen et al., (2007), and Bruder et al., (2009) among others seem to contradict this assumption, instead supporting the notion that studying the link between depression and aP3a might be worthwhile. Jaworska et al., (2013) explored whether aP3a might be useful in predicting antidepressant treatment response and their results suggest that greater baseline aP3a amplitudes are associated with a positive antidepressant response (Jaworska et al., 2013). Kähkönen et al., (2007) on the other hand found depression-related effects on frequency aMMN but not on frequency aP3a. There are also reports of decreased novelty sound deviant P3 (considered identical to aP3a) amplitude in depressed patients compared to non-depressed controls in a tree stimuli novelty oddball setting (standard sound, deviant sound, and e.g., animal or environment sounds as novelty) (Bruder et al., 2009; Lv et al., 2010; Tenke et al., 2010).

1.5.2 Depression in relation to somatosensory MMR and P3a

Depression commonly correlates with severe homeostatic disturbance (Harshaw, 2015) and often involves a wide variety of somatic symptoms (Simon et al., 1999; Kirmayer, 2001; Harshaw, 2015; Dunlop et al., 2020). Depression has been linked to abnormalities in interoception (Harshaw, 2015), and somatosensory information processing can be seen as a sense that is part of interoception (e.g., Horváth et al., 2021). Existing evidence also shows that interoceptive and somatosensory processing partly activate the same brain areas (Herman et al., 2021). In addition, somatosensory amplification (in other words, a tendency to focus on certain weak and infrequent bodily sensations, and to assess those as pathological and symptomatic of disease), has been noted in depression (Sayar et al., 2003). Indeed, a link between depression and structural (Kropf et al., 2018), metabolic (Kropf et al., 2018), and functional connectivity (Kropf et al., 2018; Kang et al., 2018) alterations of the somatosensory

cortex have been discovered. The above-mentioned aspects indicate that a link between depression and somatosensory change detection ERPs might exist.

To our knowledge, few studies to date have investigated the link between depression and somatosensory ERPs. Findings outside the oddball paradigm have shown increased amplitudes of late ERP components (such as P200 and P300) in depressed patients compared to non-depressed controls (e.g., Dietl et al., 2001). However, as far as we know, the link between depression and somatosensory MMR/P3a remains unstudied in a passive oddball paradigm. Most existing ERP studies in the somatosensory modality have merely focused on eliciting sMMR (e.g., Shen, Smyk, et al., 2018; Shen, Weiss, et al., 2018) and less than a handful of studies appear to have investigated the link between sMMR and ageing (The only ones we could find were Strömmer et al., 2014 and Strömmer et al., 2017). Both Strömmer et al., (2017) and Strömmer et al., (2014) found an attenuation of sMMR amplitude in older adults compared to young adults, which suggests an age-related cognitive decline. As for sP3a amplitudes, Strömmer et al., (2017) did not find group differences, but in older adults, an association with physical fitness and sP3a was found. Ageing-related findings in this regard can be considered relevant due to ageing and depression involving somewhat similar cognitive deficiencies (see Lee et al., 2012 for depression, and Harada et al., 2013 for ageing). Given the above-mentioned aspects, and that depression-related changes in MMN and P3a amplitudes have been found within the auditory realm, exploring the link between depression and somatosensory MMR and P3a might prove useful.

In the next section, we take a closer look at studies highlighting the relationship between specific depression features and our chosen ERPs.

1.5.3 Depression severity and other depression features in relation to MMN/MMR and P3a

Several depression characteristics have been identified and associated with different underlying pathophysiologies (see e.g., Musliner et al., 2016). However, a knowledge gap seems to exist in terms of which depression associated factors, and in what way, are related to changes in aMMN response (Tseng et al., 2021), and the same seems to apply for aP3a response. The links between depression and sMMR/sP3a on the other hand, remain unstudied. Some existing evidence supports the notion that intensity processing (LDAEP) could be used as a marker for distinguishing between different phenotypes of depression (e.g., Fitzgerald et al., 2009; Lee et al., 2014;). Even if the evidence in this

regard would be more robust, it would only provide a slight hint that aMMN and/or aP3a might express differences in more precise depression features.

Tseng et al., (2021) bring up a few potential moderating factors of aMMN response, such as illness severity, recurrence, the more precise symptom profile, and the duration of the current depressive episode. Although some studies addressing these issues exist, they are few in number, with illness severity and recurrence appearing to be the most addressed thus far. Bissonette et al., (2020) found that the more severe the depression, the larger the location deviant aMMN, whereas Mu et al., (2016) did not find a significant correlation between depression severity and location deviant aMMN. Furthermore, there are reports of no correlation between depression severity and frequency deviant aMMN (Takei et al., 2009; He et al., 2010; Bissonette et al., 2020), duration deviant aMMN (Takei et al., 2009; Naismith et al., 2012; Qiao et al., 2013; Chen et al., 2015; Bissonette et al., 2020), and intensity deviant aMMN (Mu et al., 2016; Bissonnette et al., 2020). Chen et al., (2015) on the other hand found that the severity of the depression was correlated with a decrease in duration aP3a whereas e.g., Bruder et al., (2009) reported no correlation between the aforementioned factors.

In terms of recurrence, Chen et al., (2015) and Ruohonen & Astikainen., (2017) found no difference in aMMN amplitude between patients with first-episode major depression (FMD) and patients with recurrent major depression (RMD). Notably, in the study by Chen et al., (2015), RMD patients had significantly lower aP3a amplitudes than FMD patients. In addition, the reductions in aP3a amplitude were related to the RMD patients' number of previous depressive episodes (Chen et al., 2015).

In previous depression research, a common depression phenotype distinction has been made between the somatic and cognitive-affective phenotypes (e.g., Thombs et al., 2010; de Miranda Azevedo et al., 2014; Kupper et al., 2012). However, as far as we know, not a single study has yet investigated whether somatic and/or cognitive-affective symptom severity score correlates with one or more of our chosen ERPs. Therefore, we have decided to explore this issue. This might be fruitful, seeing as depression is a highly heterogeneous disease and it has been suggested that using different kinds of treatments may benefit patients with different depression phenotypes (for a review, see Stewart et al., 2007).

1.6 Research questions and hypotheses

In this study, we focus on investigating whether depression-related effects are observable in MMN/MMR and P3a amplitudes within the auditory and somatosensory realm. We make use of an

intensity deviant setting in the auditory modality. This decision is partly motivated by the fact that intensity deviants have been less studied than duration and frequency deviants. Furthermore, the processing of sound intensity could be expected to reflect depression-related alterations because both sound intensity processing and depression have been associated with serotonergic function (Hegerl & Juckel, 1993; Hegerl et al., 2001). We decided to employ a location deviant setting in the somatosensory modality, because location deviants have been suggested as more suitable than intensity deviants for exploring somatosensory change detection ERPs (Kangas et al., 2021). Furthermore, ageing-related effects (somewhat similar to depression-related effects) (see Lee et al., 2012 for depression, and Harada et al., 2013 for ageing) on sMMR have been found with location deviants (Strömmer et al., 2014; Strömmer et al., 2017).

Both modality-specific experiments will be done within a passive oddball paradigm. We will also investigate whether depression severity (the total score) and/or the somatic and/or cognitive-affective index scores (as outlined by Thombs et al., 2010) as measured with the Finnish translation of the Beck Depression Inventory II (BDI-II) questionnaire (Psykologian Kustannus Oy, 2004), correlate with the deviance detection ERP amplitudes in the auditory (aMMN and aP3a) and/or the somatosensory (sMMR and sP3a) modality.

Theoretically it has been proposed that the whole predictive coding apparatus works inefficiently in depressed patients, highlighted by insensitivity towards prediction error which in turn may result in malfunctioning prediction update mechanisms and suboptimal predictions (Barrett et al., 2016; Sumner et al., 2020). A malfunctioning predictive coding apparatus in turn might be assumed to influence change detection as expressed by aMMN, aP3a, sMMR and sP3a.

Our research questions and hypotheses are:

1. **Does the depressed group differ from the non-depressed control group**

   a) in terms of aMMN and/or aP3a amplitudes?

   Due to the hypothetical link between depression and malfunction in the predictive coding apparatus (Sumner et al., 2020), we expect that intensity aMMN and aP3a amplitudes distinguish the depressed group from the non-depressed control group. However, previous studies that have utilised an intensity deviant oddball setting similar to ours and haven't found support for the notion that aMMN amplitude distinguishes depressed patients from non-depressed controls (Ruohonen & Astikainen, 2017; Ruohonen et al., 2020), outnumber those that have (Bissonette et al., 2020). Research appears to be nonexistent to date in terms of the

ability of intensity aP3a amplitude to distinguish between depressed patients and non-depressed controls.

b) in terms of sMMR and/or sP3a amplitudes?

The link between ageing and sMMR (Strömmer et al., 2014; Strömmer et al., 2017) would imply that an association between depression and sMMR exists. Considering that late somatosensory ERP components have been shown to differentiate depressed patients from non-depressed controls (e.g., Dietl et al., 2001), it seems plausible that sP3a does the same. Based on the above-mentioned aspects coupled with a potentially suboptimally functioning predictive coding apparatus (Sumner et al., 2020), as well as the somatic (Simon et al., 1999; Kirmayer 2001; Harshaw 2015; Dunlop et al., 2020) and interoceptive (Harshaw, 2015) abnormalities associated with depression, we expect sMMR and sP3a amplitudes to differentiate the depressed group from the non-depressed control group. However, to our knowledge no previous studies exploring this particular question exist to date.

2. **Is there a correlation between depression severity (total score on the BDI-II questionnaire) and**

a) aMMN and/or aP3a amplitudes in the depressed group?

Hypothesizing that depression is characterised by deficiency in the predictive coding system, one could make a further assumption that the more severe the depression, the more functional deficiency in the predictive coding apparatus. Therefore, we expect to find a correlation between depression severity and intensity deviance aMMN and aP3a amplitudes, in the depressed group.

b) sMMR and/or sP3a amplitudes in the depressed group?

Based on the assumption that depression severity correlates negatively with optimal functioning of the predictive coding apparatus, we expect to find a correlation between depression severity and sMMR and sP3a amplitudes. The link between ageing and sMMR (Strömmer et al., 2014; Strömmer et al., 2017), and the correlative findings in terms of depression severity and aMMN (e.g., Bissonette et al., 2020) and aP3a (e.g., Chen et al., 2015)

would suggest that depression severity might correlate with sMMR and sP3a amplitudes. However, it is worth noting that to our knowledge no previous studies exploring the association between depression severity and sMMR and/or P3a exist.

3. **Is there a correlation between the somatic and/or cognitive affective index scores of the BDI-II and**

   a) aMMN and/or aP3a amplitudes (within the depressed group)?
   b) sMMR and/or sP3a amplitudes (within the depressed group)?

   Several symptom profiles of depression have been identified, and they have been associated with different underlying neurobiological and pathophysiological backgrounds (see e.g., Musliner et al., 2016). This indicates that the more precise symptomatic profile of depression might be linked to the generation of aMMN/sMMR and aP3a/sP3a. We have decided to investigate this issue exploratively.

2 MATERIALS AND METHODS

2.1 Participants

This study was part of a larger research project (InfoDepPro) exploring depression-related changes in exteroceptive and interoceptive information processing. The ethical committee of the Central Finland Health Care District approved the ethical aspects of the research project, and the study was conducted in accordance with the declaration of Helsinki. The declaration of Helsinki outlines standards for guaranteeing participant safety, for informing participants, and for obtaining informed consent from each participant. Written informed consent was obtained from each participant prior to their participation in the study. A significant part of this study's methods were similar to the ones in a recently published article by Kangas et al., (2021). The target population of this study consisted of 18-60-year-old individuals with a depression diagnosis (ICD-10: F32, F33 and F34.1). The depressed participants were recruited via multiple channels; through the Central Finland Health Care District (CFHCD) psychiatric polyclinic, through health care professionals treating depression, and through the Finnish Student Health Service (FSHS) Jyväskylä office. Furthermore, recruitment ads in newspapers and notice board advertisements in public places were utilised. The control group consisted of 18-60-year-old non-depressed participants and were recruited via email lists of the University of Jyväskylä, different volunteer organisations, and notice board advertisements in public places.

The initial interview with both depressed and non-depressed participants was conducted via a phone call to determine the eligibility of each potential participant. In addition, questionnaires were used to collect information regarding the inclusion and exclusion criteria. Eligible participants for both groups were right-handed individuals who were not pregnant, not breastfeeding, who had no self-reported significant health-related issues such as neurological diseases (excluding symptomless migraine and fibromyalgia) or brain damage, and no significant deterioration in hearing, sight (use of eyeglasses was permitted), cognitive function, or motor function. The hearing thresholds were measured prior to the auditory EEG experiment for the left and right ear individually using an SA-51 audiometer (Mediroll Medico-Technical Limited) before the start of EEG recordings. The adopted exclusion criterion was a threshold above 20dB for 1000 Hz sounds. Further universal exclusion criteria were drug or alcohol abuse and heavy alcohol use (for men, more than 24 portions a week, for women, more than 16 portions a week).

The inclusion criteria specific for depressed participants included the absence of any other psychiatric disease besides depression. Control specific inclusion criteria included basic health, no current or previous depression diagnosis or other psychiatric diagnoses, no self-reported depressive symptoms (BDI-II<10), no medication that affects the central nervous system, and no medication abuse. Seeing as one of the inclusion criteria for controls was the absence of a depression diagnosis in conjunction with a lack of self-reported depression symptoms, the BDI-II questionnaire was verbally administered to potential controls during the initial phone interview. In addition to this, both the depressed patients and control participants were asked to complete a printed version of the BDI-II questionnaire at home.

The study consisted of a total of 57 participants (18 in the depressed group and 39 in the control group) who had filled the questionnaires. The depressed group consisted of 4 males and 14 females, whereas the control group consisted of 11 males and 28 females. Out of the grand total of 57 participants in our study, auditory data could be obtained from 55 participants (17 depressed participants and 38 non-depressed participants) and somatosensory data from 52 participants (16 depressed participants and 36 non-depressed participants). We decided to include all possible participants in the analyses to gain the advantage of more data, which meant that the size of the depressed group was roughly half the size of the non-depressed control group across all between-group comparisons. It also meant that the number of participants varied between the auditory and the somatosensory experiment. We were unable to obtain auditory data from two participants (one depressed participant and one non-depressed control) due to technical issues, and somatosensory data from five participants (two depressed participants and three non-depressed control participants) due to technical difficulties, arrhythmia, or unwillingness to participate. The exclusion of one depressed and one non-depressed participant from the somatosensory data were due to technical difficulties, whereas one depressed and one non-depressed participant were not able to participate in the somatosensory experiment due to arrhythmia. One non-depressed participant chose not to participate in the somatosensory condition.

Independent samples t-tests revealed no significant difference in age between the depressed group and the non-depressed control group in neither the auditory ($t(53) = .967$, $p = .338$, $d = 0.282$) nor the somatosensory ($t(50) = .763$, $p = .449$, $d = .229$) experiment. Chi- square tests on the other hand revealed no significant differences in gender distribution between the depressed group and the non-depressed control group in neither the auditory (X^2 (1, $N = 55$) = .048, $p = .826$, Cramer's V = .030) nor the somatosensory (X^2 (1, $N = 52$) = .785, $p = .376$, Cramer's V = .123) experiment. For more precise demographic and clinical variables, refer to Table 1 below.

Table 1. Frequencies for gender, medication, and age in years.

	Questionnaires (n=57)		**Auditory Experiment (n=55)**		**Somatosensory Experiment (n=52)**	
Variable	*Depression Group*	*Non-depressed group*	*Depression group*	*non-depressed group*	*Depression group*	*non-depressed group*
Total (n)	18	39	17	38	16	36
females (n)	14	28	13	28	13	25
males (n)	4	11	4	10	3	11
Age M ± SD (range)	34.83 ± 14.09 (20-58)	32.41 ± 13.35 (19-60)	36.65 ± 14.08 (20-58)	31.87 ± 13.09 (19-60)	34.38 ± 13.66 (20-58)	31.42 ± 12.56 (19-60)
Depression Medication (n)	15	N/A	14	N/A	13	N/A

2.2 Procedure

The study procedure consisted of two different measurement types: EEG measurements and a questionnaire measuring depression symptoms (BDI-II). The auditory and the somatosensory EEG experiments were conducted during a single measurement day, whereas a printed version of the BDI-II was either sent to the depressed participants prior to the measurement day via mail or handed to them during the measurement day. For the EEG measurements, the participants were asked to sit in a dimly lit room that was soundproofed and electrically shielded. To minimise the chance of muscle artefacts from occurring, they were instructed to avoid excess movements and facial expressions. The participants were also instructed to ignore the somatosensory and auditory stimuli and instead focus their attention on a silent movie playing on the screen. During the measurement, the researchers could monitor the participants via an audio and video feed.

2.3 Beck Depression Inventory-II

The Finnish version of the 21-item BDI-II inventory (Psykologian Kustannus Oy, 2004) was used to assess the depression symptoms. In previous studies, the BDI-II has been successfully used to distinguish between patients with a depression diagnosis and non-depressed controls, as well as between patients with mild, moderate, and severe depression (Beck et al., 1996). Each of the 21 items consists of four answer options/statements and are scored between 0 and 3, with higher scores signifying a rise in symptom severity (Psykologian Kustannus Oy, 2004). Total scores range from 0 to 63, with different scores indicating a different level of depressive symptoms (0-13 points: lack of depression, 14-19 points: mild depression, 20-28 points: moderate depression, 29-63 points: severe depression) (Psykologian Kustannus Oy, 2004). In the questionnaire, respondents are asked to describe the way they have been feeling during the past 2 weeks. According to Thombs et al., (2010), extensive evidence exists in terms of the validity and reliability of the BDI–II in both psychiatric and non-psychiatric populations. Beck et al., (1996) point out that previous research has found test-retest reliabilities as high as .93 (time window of one week between tests) for the BDI-II and an average inner split-half consistency of .86. A strong correlation between BDI-II scores and other depression assessment instruments has also been noted (Hamilton Rating Scale .71; Symptom Checklist -90-R .89) (Beck et al., 1996). Furthermore, a strong correlation between BDI-II scores and evaluations based on psychiatric interviews has been found (Viinamäki et al., 2004).

In our study, the depressed group in the auditory experiment had a mean BDI-II total score of 26.56 (moderate depression), and the depressed group in the somatosensory experiment had a mean BDI-II total score of 27.00 (moderate depression). The depressed group in the auditory experiment (n=17) consisted of two participants with no depression, three participants with mild depression, three participants with moderate depression, and nine participants with severe depression. The depressed group in the somatosensory experiment (n=16) consisted of three participants with no depression, two participants with mild depression, three participants with moderate depression, and eight participants with severe depression.

As noted by Thombs et al., (2010), studies have reported several different factor structures for the BDI–II. We decided to use the same cognitive-affective and somatic symptom profile division of the BDI-II as the one used by Thombs et al., (2010). We summed the scores of items 1–14 (sadness, pessimism, past failure, loss of pleasure, guilty feelings, punishment feelings, self-dislike, self-criticalness, suicidal ideation, crying, agitation, loss of interest, indecisiveness, and worthlessness) to calculate the cognitive-affective scores. Somatic scores were calculated by summing the scores of

items 15–21 (loss of energy, sleep problems, irritability, appetite problems, concentration, fatigue, and loss of interest in sex). In our study, the depressed group in the auditory experiment had a mean cognitive-affective index score of 16.71 whereas the depressed group in the somatosensory experiment had a mean cognitive-affective index score of 15.94. The mean somatic index score for the depressed group was 10.29 in the auditory and 10.62 in the somatosensory experiment.

2.4 EEG measurements

EEG was used to measure brain responses in two experiments that used either auditory or somatosensory stimuli: the auditory experiment and the somatosensory experiment. In the auditory experiment, an intensity deviance detection condition was used, whereas in the somatosensory experiment, a location deviance detection condition was used. In both experiments, the stimuli were presented in an oddball paradigm using a pseudorandom order, meaning that between the deviant stimuli there were at least two standard stimuli presented. In the auditory experiment, a total of 2000 stimuli were presented through a loudspeaker situated approximately one metre above the participant. The stimuli were 1000 Hz sinusoidal sounds lasting 100 ms (with a 10-ms onset and offset time). The auditory experiment consisted of an increment condition and a decrement condition, where the deviant and standard stimuli varied in intensities of 60 dB and 80dB (sound pressure level; SPL), depending on the condition. A sound level metre (type 2235, Büel and Kjaer, Naerum, Denmark) with A-weighting was used to measure the SPLs. In the increment condition, the deviant stimuli were 80 dB (SPL) and the standard stimuli were 60dB (SPL), whereas in the decrement condition the intensities were reversed. In accordance with the study by Kangas et al. (2021), the probability of the deviant stimuli was 10 %.

In the somatosensory experiment, the stimuli were generated by a constant current stimulator (Digitimer Ltd, model DS7A, Welwyn Garden City, UK). The stimuli were faint electric currents delivered to the left forefinger and little finger through flexible metal ring electrodes by stimulating the anode around the distal phalanx and the cathode around the proximal phalanx. The electrodes were moistened by conductive jelly in order to reduce impedance, and a piece of gauze was placed on the finger between the electrodes to prevent conductivity between the two electrodes in the same finger. Before the EEG recording, subjective somatosensory thresholds were determined for each participant for both the forefinger and the little finger in order to find an optimal stimulus intensity. The stimulus intensity was set at 1.5 times the individual somatosensory threshold. The experiment

consisted of two different stimulus conditions: in one condition, the deviant stimuli were presented to the little finger and the standard stimuli were presented to the forefinger, whereas in the other condition this was reversed. A total of 1680 stimuli were presented, with the deviant stimuli probability being 14 %.

In both the auditory and the somatosensory experiments, a randomised Stimulus Onset Asynchrony (SOA) was used. For the auditory experiment it was randomly set at 530 ms, 580 ms, or 630 ms. For the somatosensory experiment it was randomly set at 406 ms, 456 ms, or 506 ms. E-prime 2.0 software (Psychology Software Tools Inc., Sharpsburg, MD, USA) was used to control the stimulus presentation for both experiments.

2.5 EEG Data acquisition

A high-impedance amplifier (NeurOne Bittium Biosignal, Ltd.) with a 128-channel sensor Net (Electrical Geodesic Inc., HydroCel GSN 128, 1.0) with an online filtering from 0.01 to 250 Hz and a sampling rate of 1000 Hz was used to record the EEG data. Impedances below 20 kΩ were used and the data was referenced to a vertex electrode (Cz) during the recording.

2.6 EEG Data Processing

We analysed the EEG data with Brain Vision Analyzer 2.2 software (Brain Products GmbH, Münich, Germany) and applied as a new reference a calculated average over all channels. Noisy channels were interpolated with a spherical spline model and the data was filtered with a low cut-off at 0.1 Hz and a high cut-off at 30 Hz, as well as with a notch filter of 50Hz with a roll-off of 24 dB/octave. To allow for the same number of segments and a similar signal-to-noise ratio for standard and deviant responses, averages of amplitudes for responses to standard stimuli were calculated only for stimuli immediately preceding the deviant stimuli. The Gratton and Coles method (Gratton et al., 1983) was applied to detect and correct the interference of eye-blinks.

The auditory intensity deviance data was segmented into 600 ms segments (100 ms before and 500 ms after stimulus onset) and the location deviance somatosensory data was segmented into

500 ms segments (100 ms prior to stimulus onset and 400 ms after stimulus onset). For both data, a time period of 100 ms before stimulus onset was determined as a baseline for a baseline correction. The EEG segments with a voltage difference exceeding 100 μV within a 100 ms period in any recording channel were omitted from the analysis. Segments with more than 50 μV difference between two consecutive time points (i.e., within 1 ms) and low activity periods (< 0.5 μV of change within a 100-ms range) were excluded as well. For aMMN and sMMR, as well as aP3a and sP3a, the time windows were chosen based on the study by Kangas et al., (2021). For the auditory intensity MMN, the time window applied was 140-180 ms following stimulus onset and for the location deviance sMMR, a time window of 150-190 ms post-onset was applied. A time window of 220-320 post-onset was chosen for aP3a and a time window of 200-300 ms post-onset was chosen for sP3a. For the auditory intensity experiment, aMMN amplitude values were extracted from channels 5, 6, 11, 12, and 16 (in the EGI 128-channel system, see Appendix 1) in the frontal channel cluster. For the somatosensory location deviance experiment, sMMR amplitude values from electrode channels 87, 104, 105, 110, and 11 (in the EGI 128-channel system, see Appendix 1) in the frontocentral channel cluster were extracted. For the aP3a and sP3a, amplitude values were extracted from channels 7, 31, 70, and 106 in the frontocentral channel cluster (in the EGI 128-channel system, see Appendix 1).

2.7 Statistical Analysis

The statistical analyses were carried out using IBM SPSS Statistics 28.0 (IBM Inc., Armonk, NY, USA). Because both the auditory and somatosensory experiments had two counterbalanced conditions, separate differential waveforms were calculated for both conditions. Repeated measures ANOVA was performed both for the auditory and the somatosensory data with group (depressed, non-depressed) as between-subject factor. In the auditory data, the within-subject factors were condition (increment: standard 60dB, deviant 80dB, decrement: standard 80dB, deviant 60dB) and stimulus type (standard, deviant) whereas in the somatosensory experiment, the within-subject factors were condition (condition 1: standard little finger, deviant forefinger, condition 2: standard forefinger, deviant little finger) and stimulus type (standard, deviant). Post hoc tests included separate repeated measures ANOVA for each counterbalanced condition in the case of three factor interactions and paired samples t-test in the case of two factor interactions.

To investigate links between depression severity and our chosen ERPs, Pearson's correlation

analyses were performed. For each of our chosen ERPs, we calculated the averaged difference between deviant and standard amplitudes across both counterbalances for this purpose.

3 RESULTS

3.1 Auditory modality

3.1.1 aMMN & aP3a

Table 2 presents the significant effects of the repeated measures ANOVA for aMMN and aP3a. Mean amplitude values for the two groups in aMMN and aP3a are presented in Figure 2. Topographical maps and grand-averaged waveforms for aMMN and aP3a responses in the depressed group and the non-depressed control group are presented in Figure 2.

Regarding aMMN, the repeated measures ANOVA revealed a significant three-way interaction of condition x stimulus type x group as well as a main effect for stimulus type (standard, deviant) (Table 2). To investigate this interaction further, we conducted two post hoc repeated measures ANOVAs, one for each condition separately (increment, decrement). The post hoc repeated measures ANOVAs revealed no group differences in neither the increment condition ($F = 3.756$, $p = .058$, $\eta^2p = 0.066$), nor the decrement condition ($F = 0.991$, $p = .324$, $\eta^2p = 0.018$). In both conditions (increment, decrement) a significant main effect for stimulus type was found (both ps = < .001) and the standard stimuli had a higher amplitude in comparison to the deviant stimuli. For the auditory P3a, repeated measures ANOVA revealed a significant main effect for stimulus type (standard, deviant), but no other significant main effects or interactions were found (Table 2).

Table 2. Results of the repeated measures ANOVA for Auditory MMN and aP3a responses with F-, p-, and η^2 p -values

Variable	Group	Condition	Stimulus Type	Condition x Stimulus Type	Condition x Group	Stimulus Type x Group	Condition x Stimulus Type x Group
Auditory intensity deviance							
MMN	F = 0,129 p = .721 η^2 p = 0.002	F(1, 54) = 0.844 p = .363 η^2 p = 0.016	**F(1, 54) = 99,999** **p = <.001** **η^2 p = .654**	F(1, 54) = 3,280 p = .076 η^2 p = 0.058	F(1, 54) = 1,893 p = .175 η^2 p = 0.034	F(1, 54) = 0.540 p = .466 η^2 p = 0.010	**F(1, 54) = 5.095** **p = .028** **η^2 p = 0.088**
P3a	F = 1.417 p = .239 η^2 p = 0.026	F(1, 54) = 1.297 p = .260 η^2 p = 0.024	**F(1, 54) = 63.149** **p = <.001** **η^2 p = 0.544**	F(1, 54) = 0.299 p = .587 η^2 p = 0.006	F(1, 54) = 0.329 p = .569 η^2 p = 0.006	F(1, 54) = 2,784 p = .101 η^2 p = 0.050	F(1, 54) = 3,890 p = .054 η^2 p = 0.068

Note. Significant differences in bold. Condition refers to the two counterbalanced conditions used (increment: deviant stimuli loud intensity; decrement: deviant stimuli silent intensity). Stimulus type refers to the two types of stimuli used (deviant, standard).

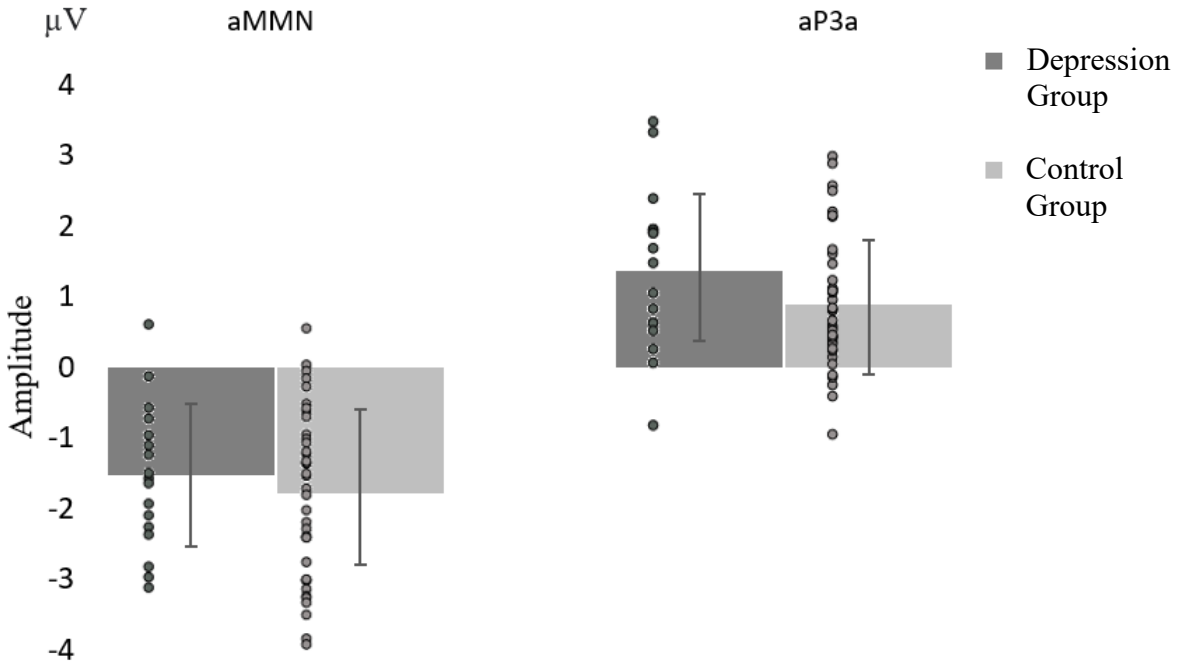

Figure 1. A bar chart comparison of the aMMN and aP3a amplitudes between the depression group and the control group showing mean amplitude values for each group in the two modalities. Error bars represent the standard deviation in each group and modality. Each boxplot dot represents an individual participant's value.

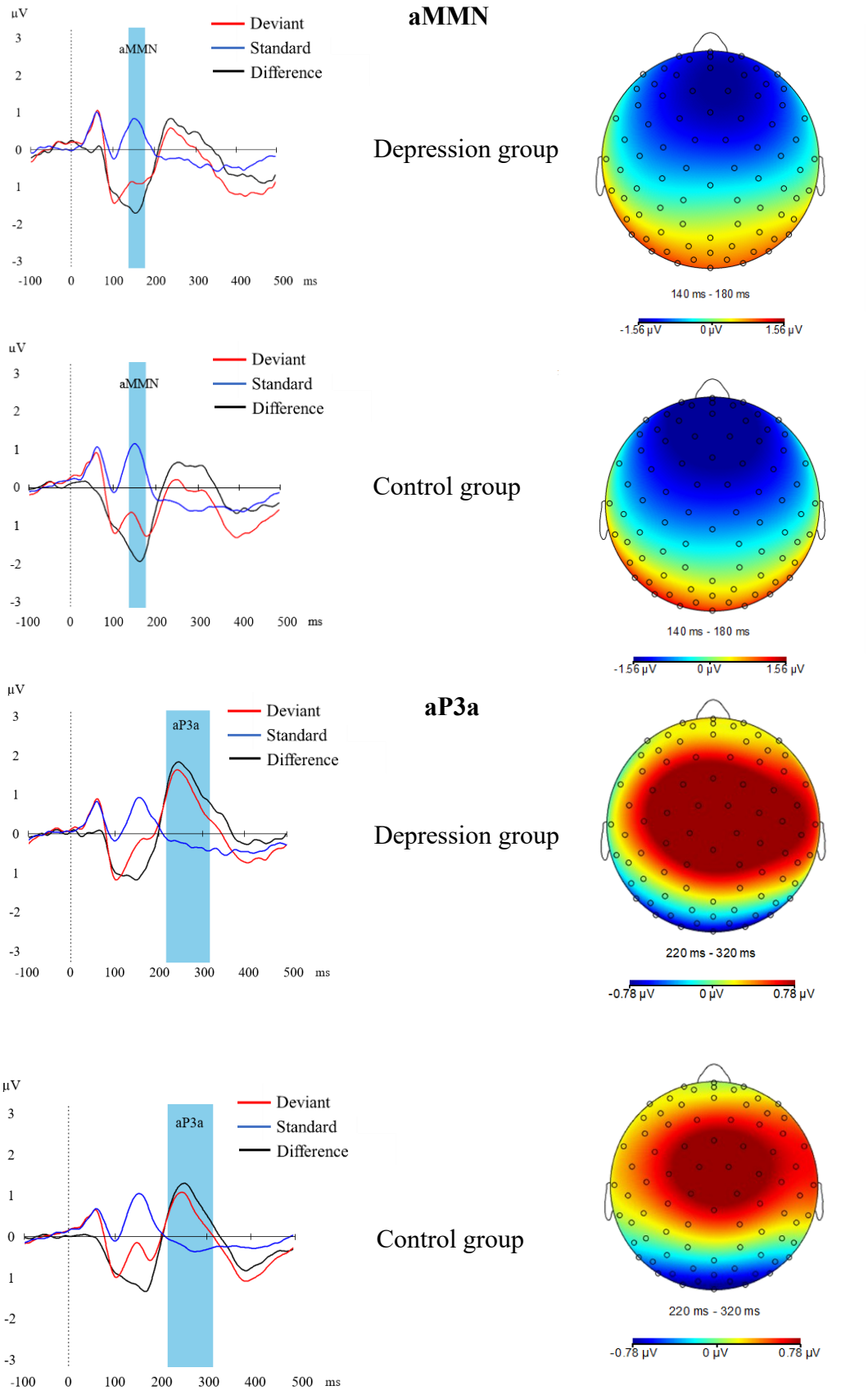

Figure 2. Differential responses of the aMMN and aP3a (deviant minus standard stimuli) and topographical maps of the responses for both groups.

3.1.2 Correlations

Pearson's correlation analysis revealed no significant correlations between aMMN or aP3a amplitudes and the BDI-II total score, BDI-II somatic index score, or the BDI-II cognitive-affective index score (see Table 3).

Table 3. Correlations for auditory modality in the depressed group

Variable (sig)	1	2	3	4	5
1. BDI-II	1				
2. BDI-II (Somatic)	.832	1			
3. BDI-II (Cognitive-affective)	.949**	.616**	1		
4. aMMN	.164	.215	.110	1	
5. aP3a	-.040	-.135	.019	.247	1

**. Correlation is significant at the 0.01 level (2-tailed).

3.2 Somatosensory Modality

3.2.1 sMMR and sP3a

Table 4 presents the significant effects of the repeated measures ANOVA for sMMR and sP3a. Mean amplitudes for the two groups in sMMR and sP3a are presented in Figure 3. Topographical maps and grand-averaged waveforms for aMMN and aP3a responses in the depressed group and the non-depressed control group are presented in Figure 4.

For sMMR, repeated measures ANOVA revealed only one significant main effect (stimulus type: standard, deviant) and no interaction effects (Table 4). For sP3a, repeated measures ANOVA revealed a significant main effect of condition (standard: little finger, deviant: forefinger; standard:

forefinger, deviant: little finger) and stimulus type (standard, deviant). A significant interaction between condition and stimulus type was also found but no significant three-way interactions involving the factor group (Condition x Stimulus Type x Group) were found. To explore the Condition x Stimulus Type interaction further, a post hoc paired samples t-test was conducted. The paired samples t-test revealed a significant main effect of stimulus type in only one of the conditions (standard: forefinger, deviant: little finger), $t(51) = 4.246$, $p = <.001$. The mean amplitude difference was 0.74 μV, SD = 1.26, 95 % CI [0.39, 1.09]. In the other condition (standard: little finger, deviant: forefinger) no significant main effect of stimulus type was observed, $t(51) = 1.887$, $p = .065$. Mean amplitude difference was 0.27 μV, SD = 1.04, 95 % [-0.02, 0.56].

Table 4. Results of the repeated-measures ANOVA for somatosensory MMR and sP3a responses with F-, p- and η^2 p -values.

Variable	Group	Condition	Stimulus Type	Condition x Stimulus type	Condition x Group	Stimulus Type x Group	Condition x Stimulus type x Group
Somatosensory location deviance							
MMR	F = 0.946 p = .335 η^2 p = .019	F(1, 51) = 0.072 p = .789 η^2 p = 0.001	**F(1, 51) = 5.888** **p = <.019** **η^2 p = 0.105**	F(1, 51) = 0.661 p = .420 η^2 p = 0.013	F(1, 51) = 0.007 p = .935 η^2 p = 0.000	F(1, 51) = 0.881 p = .352 η^2 p = 0.017	F(1, 51) = 0.462 p = .500 η^2 p = 0.009
sP3a	F = 0.005 p = .941 η^2 p = 0.000	**F(1, 51) = 4.874** **p = 0.032** **η^2 p = 0.089**	**F(1, 51) = 10.738** **p = .002** **η^2 p = 0.177**	**F(1, 51) = 8.305** **p = .006** **η^2 p = 0.142**	F(1, 51) = 0.257 p = .614 η^2 p = 0.005	F(1, 51) = 0.684 p = .412 η^2 p = 0.013	F(1, 51) = 2.047 p = .159 η^2 p = 0.039

Note. Significant differences in bold. Condition refers to the two counterbalanced conditions used (deviant: little finger; deviant: forefinger). Stimulus type refers to the two types of stimuli used (deviant, standard).

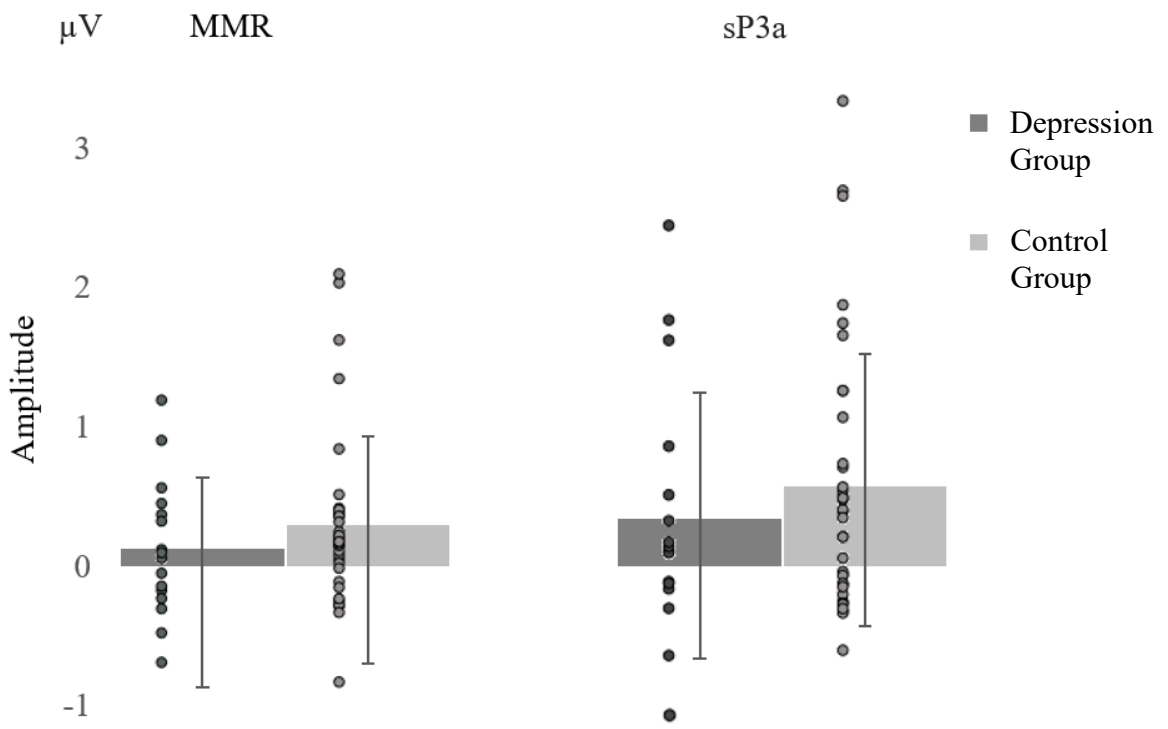

Figure 3. A bar chart comparison of the MMR and sP3a amplitudes between the depression group and the control group showing mean amplitude values for each group in the two modalities. Error bars represent the standard deviation in each group and modality. Each boxplot dot represents an individual participant's value.

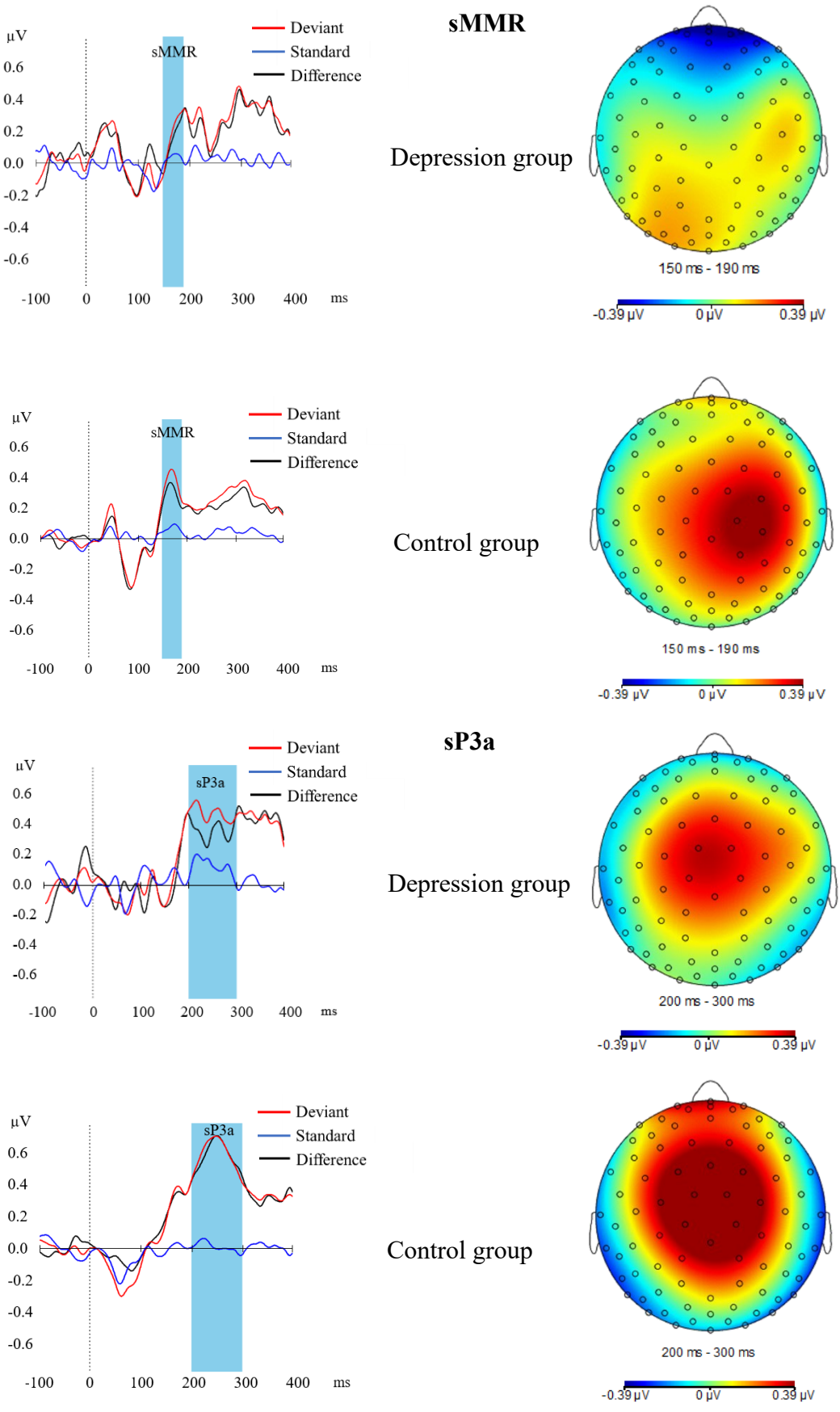

Figure 4. Differential responses of the aMMN and aP3a (deviant minus standard stimuli) and topographical maps of the responses for both groups.

3.2.2 Correlations

Pearson's correlation analysis revealed no significant correlations between sMMR and sP3a amplitudes and the BDI-II total score, BDI-II somatic index score, or the BDI-II cognitive-affective index score (see Table 5).

Table 5. Correlations for somatosensory modality in the depressed group

Variable	1	2	3	4	5
1. BDI-II	1				
2. BDI-II (Somatic)	.877**	1			
3. BDI-II (Cognitive-affective)	.970**	.733**	1		
4. sMMR	-.211	-.150	-.222	1	
5. sP3a	.142	-.071	.236	.145	1

**. Correlation is significant at the 0.01 level (2-tailed)

4 DISCUSSION

The aim of this study was to investigate whether depressed patients display abnormalities in the brain's early automatic change detection system as opposed to non-depressed controls. More precisely, we investigated via a passive oddball paradigm whether early automatic electrical brain responses elicited in the auditory and the somatosensory modality are sensitive enough to differentiate between depressed patients and non-depressed controls, and thus whether they show promise as biomarkers for depression. We focused on aMMN, aP3a, sMMR and sP3a amplitudes of the ERP. aMMN and aP3a were elicited via sound intensity change and sMMR and sP3a via finger location change. Furthermore, we explored whether any of the ERPs correlate with depression severity, depression-related somatic symptom severity and/or depression-related cognitive-affective symptom severity as measured by the BDI-II questionnaire (Psykologian Kustannus Oy, 2004; Thombs et al., 2010).

Our findings show that depressed patients do not differ from non-depressed controls in terms of any of the ERPs. Thus, our findings do not support the theoretical assumption that depression is associated with suboptimal functioning of the predictive coding apparatus (Barrett et al., 2016; Sumner et al., 2020). The findings indicate normal levels of early automatic processing of changes in sound intensity and somatosensory location amongst depressed patients. In addition, our chosen ERPs did not correlate with overall depression severity nor with somatic or cognitive-affective symptom severity.

However, all the ERPs were elicited in the study (as was displayed by a significant main effect of stimulus type across all of the performed repeated measures ANOVA tests). In the case of sP3a, a significant main effect of stimulus type was noted in only one of the conditions (standard: forefinger, deviant: little finger). aMMN has also previously been elicited via sound intensity change (e.g., Ruohonen & Astikainen, 2017; Bissonette et al., 2020; Ruohonen et al., 2020) and sMMR and sP3a via finger location change of electrical stimuli (Strömmer et al., 2014, 2017; Kangas et al., 2021) in a passive oddball setting similar to ours. The fact that all the chosen ERPs were elicited in our study provides further support for the notion that aMMN and aP3a can concurrently be obtained via sound intensity deviants, and that sMMR and sP3a can concurrently be elicited via finger location deviants in a passive oddball setting.

Below, we will first discuss our findings pertaining to the auditory and the somatosensory ERPs and how they align with existing literature. From there on we will proceed to mirror our findings from the correlative analyses to existing literature. Finally, we will discuss the limitations regarding

our study and draw some final conclusions, practical implications, and suggestions for future research.

4.1 MMN and P3a to auditory intensity change do not demonstrate depression-related effects

In terms of aMMN, our findings are in line with the findings of Ruohonen & Astikainen, (2017) and Ruohonen et al., (2020) who similarly did not find depression-related effects on aMMN amplitude, whilst utilising a study design similar to ours. On the other hand, our results are contradictory to Bissonette et al., (2020), who found an increased aMMN amplitude in depressed patients compared to non-depressed controls in an experimental setting similar to ours. Sound intensity processing could be expected to reflect depression-related alterations due to the association between serotonergic function and sound intensity processing as well as depression (Hegerl & Juckel, 1993; Hegerl et al., 2001). Despite this, the scientific evidence thus far seems to indicate that duration and frequency deviants (particularly duration deviants), might be more sensitive than intensity deviants in discerning differences between depressed patients and non-depressed controls.

Studies utilising duration deviants in an oddball setting have reported more streamlined depression-related aMMN amplitude abnormality than their counterparts utilising other deviants. Most studies utilising duration deviants have reported reduced aMMN amplitudes in depressed patients compared to non-depressed controls (Takei et al., 2009; Naismith et al., 2012; Qiao, Yu, et al., 2013; Qiao, Yang, et al., 2015; Chen et al., 2015). Some have reported a lack of depression-related effects on duration aMMN amplitude (Umbricht et al., 2003; Bissonnette et al., 2020), whereas to the best of our knowledge there are no reports of depression-related increase of duration aMMN amplitudes. In terms of frequency deviants, the findings are more mixed with reports of increased (Kähkönen et al., 2007; He et al., 2010; Restuccia et al., 2016), unaffected (Umbricht et al., 2003; Bissonnette et al., 2020), and reduced (Takei et al., 2009; Hirakawa et al., 2017) aMMN amplitudes in depressed patients compared to non-depressed controls. Studies utilising intensity deviants have thus far produced more consistent findings than studies utilising frequency deviants, but contrary to studies utilising duration deviants, a majority of them have found that aMMN does not differentiate depressed patients from non-depressed controls.

Due to more consistent findings in distinguishing depressed patients from non-depressed controls via duration deviants than other forms of deviants, duration aMMN seems to show more potential as a biomarker than frequency or intensity aMMN, when it comes to identifying acute stages

of depression. However, it is noteworthy that intensity aMMN has been studied to a lesser degree than duration and frequency aMMN. The overall scarceness of research addressing depression-related effects on aMMN and the inconsistency in the findings create uncertainty regarding the potential utility of aMMN as a biomarker of depression. It seems too early to say with a sufficient level of certainty whether depressed patients display aMMN abnormality via any of the deviant types, and whether the potential abnormality is more evident in duration aMMN, than in aMMN elicited via other deviants.

As noted by Ruohonen and Astikainen (2017), it might be expected that different types of sound deviants activate different neural sources in the brain, which might account for some of the discrepancies in results from depression studies that have utilised different deviant types. However, as mentioned above, there is a lack of consistency in the aMMN findings within the deviant categories (intensity, frequency, duration). The inconsistent results from depression-related aMMN studies might be due to numerous factors, such as various differences in study design (e.g., passive vs. active oddball design and subtle differences in applied stimuli), and differences in sample size and sample characteristics (e.g., the depressed group being unequal in terms of demographic and clinical variables such as gender and age distribution, illness history, illness stage, illness severity, medication status, and other treatments at the time of measurement that might affect aMMN). As an example, most of the existing studies that have found reduced aMMN amplitudes in depressed patients have included a uniformly, or for the most part medicated depressed sample (Takei et al., 2009; Naismith et al., 2012; Qiao, Yu, et al., 2013; Qiao, Yang, et al., 2015; Chen et al., 2015; Hirakawa et al., 2017), whereas most existing studies that have found increased aMMN amplitudes in depressed patients, have included a uniformly or to the most part non-medicated (at least 3 days of abstinence prior to measurements) depressed sample (Kähkönen et al., 2007; He et al., 2010; Restuccia et al., 2016). This is in line with the findings of Oranje et al., (2008), who found antidepressant medication to decrease aMMN amplitude.

In terms of aP3a, our findings are in line with those of Kähkönen et al., (2007) who did not find depression-related effects on frequency aP3a, and Chen et al., (2015) who found aP3a amplitude not to differentiate patients with first major depression from non-depressed controls in an oddball setting. On the other hand, Chen et al., (2015) noted lower aP3a amplitudes in patients with recurrent depression compared to patients with first major depression and non-depressed controls. In our study, as well as in the study by Kähkönen et al., (2007), the recurrence of depression was not controlled for, which might partially explain the observed results. More consistent findings of depression-related deficiency (reduction) in aP3a amplitude have been noted in studies utilising a three stimuli novelty oddball setting that encompasses a standard sound, a deviant sound and e.g., an animal or environment

sound as novelty (e.g., Bruder et al., 2009; Lv et al., 2010; Tenke et al., 2010). As noted by Bruder et al., (2009), the aP3a elicited via a novelty oddball setting is more prominent than the aP3a elicited via two-stimulus oddball setting (Polich & Criado, 2006), which indicates that a novelty oddball setting might be more sensitive in discerning depression-related effects on aP3a.

4.2 MMR and P3a to somatosensory location change do not demonstrate depression-related effects

Contrary to our expectations, no differences between depressed patients and non-depressed controls were found in somatosensory location change MMR and P3a. One might have expected to find differences, since there is evidence of interoceptive and somatosensory processing partly activating the same brain areas (Herman et al., 2021), and evidence of depression-related abnormalities in interoception (e.g., Harshaw, 2015). Depression has also been linked to alterations in the structural, metabolic, and functional connectivity of the somatosensory cortex (Kropf et al., 2018; Kang et al., 2018), which might influence sMMR and sP3a amplitudes. We are unaware of any previous studies investigating sMMR in relation to depression. However, there are findings of sMMR amplitude attenuation in older adults when compared to younger adults (Strömmer et al., 2014, Strömmer et al., 2017). Considering that both depression and ageing are associated with a somewhat similar decline in cognitive ability (depression: Lee et al., 2012, ageing: Harada et al., 2013), it seems plausible that sMMR also differentiates depressed patients from non-depressed controls.

As in the case of sMMR, our results indicate that sP3a does not differentiate depressed patients from non-depressed controls. As far as we know, no previous studies have investigated depression in relation to sP3a. That said, for example Dietl et al., (2001) found increased amplitudes of late ERP components (P200 and P300) in depressed patients compared to non-depressed controls in a somatosensory, non-oddball paradigm. Considering that P3a is a subcomponent of the P300 complex, our findings are not quite in line with the findings of Dietl et al., (2001). This discrepancy could at least partly be explained by differences in study design (oddball vs. non-oddball paradigm).

The fact that we did not find any significant differences between the groups could be explained by multiple factors, one being the relatively weak sMMR and sP3a amplitudes themselves observed in both groups (see Figure 4). One might assume that ERPs characterised by higher amplitudes (allowing for more variation) are more suitable in discerning between-group differences, suggesting that the somatosensory domain might not be optimal for this purpose. In addition, the signal-to-noise ratio of sMMR and sP3a amplitudes for the depressed group was not as good as for the non-depressed

control group (see Figure 4), which could be related to the relatively small sample size. It is possible that due to the small sample size, trials without interference did not stand out enough.

4.3 Auditory intensity change and somatosensory location change processing do not differ based on depression severity, somatic symptom severity, or cognitive-affective symptom severity

The assumption that the more severe the depression, the more functional deficiency in the predictive coding apparatus, was not supported by our data. Our findings indicate that neither depression severity, somatic symptom severity, nor cognitive-affective symptom severity correlates with intensity aMMN or aP3a, nor with location sMMR or sP3a. Previous studies investigating the potential link between depression severity and change detection ERPs have focused mainly on the auditory domain, especially on aMMN (with aP3a receiving minimal attention and the somatosensory domain virtually no attention) and the results have been somewhat mixed. In terms of the relationship between depression severity and aMMN, non-correlative findings (e.g., Chen et al., 2015; Mu et al., 2016) clearly outnumber the correlative findings (e.g., Bissonette et al., 2020: depression severity and location aMMN). There are reports of no correlation between depression severity and frequency aMMN (e.g., Takei et al., 2009; He et al., 2010; Bissonette et al., 2020), duration aMMN (e.g., Qiao et al., 2013; Chen et al., 2015; Bissonette et al., 2020), and location aMMN (e.g., Mu et al., 2016). Our results align with those of Bissonette et al., (2020) and Mu et al., (2016), in showing no link between depression severity and intensity aMMN.

In terms of aP3a, our findings align with e.g., Bruder et al., (2009) who did not find a correlation between depression severity and frequency aP3a. On the other hand, our findings are contradictory to the ones reported by Chen et al., (2015), who found that higher depression severity correlated with decrease in aP3a amplitude in both the first major depression- and recurrent major depression group. Thus, Chen et al., (2015) suggest that aP3a might be a useful index of disease severity. However, our findings do not support this notion.

The fact that most studies have not found a link between depression severity and MMN/MMR or P3a might be due to several reasons, one of which being that there is no actual link to be found. Other possible explanations are the inherent difficulties of depression research in gaining a large enough depressed sample, making it more challenging to obtain statistically significant results. One might also expect that patients with high depression severity receive more intense treatment, medical and other, which might affect the MMN/MMR and P3a amplitudes. Furthermore, the depressed group

in both the auditory and the somatosensory experiment was quite homogenous in terms of the BDI-II scores, with roughly half of the participants in each experiment suffering from severe depression (BDI-II score > 29). The homogeneity of the depressed sample might have masked the effects of depression severity on MMN/MMR and P3a. It is also possible that some specific depression features and symptoms are more closely related to change detection ERPs than broader measures of depression severity.

4.4 Limitations

Several noteworthy limitations pertaining to this study need to be noted. First, some effects might have been masked due to the small sample size of depressed participants in both the auditory and the somatosensory experiments. Acquiring a large enough and representative depressed sample poses a common challenge for depression studies. Another limitation of our study was the disproportionate group sizes (depressed vs. non-depressed) in both experiments. The decision to include all possible participants in our analysis was done in order to gain the advantage of more data, while still recognizing that disproportionate group sizes are not ideal for between-group comparisons. A major challenge in depression studies, ours included, is how to approach the challenges associated with the heterogeneity of the depressed population (Hasler, 2010). There is large variability within the depressed population and naturally also in the samples obtained from it in several respects, such as pathophysiologies, treatment history and medication status, recurrence, severity, comorbidity, and so forth that might be relevant in terms of the ERPs under investigation. In addition, individual differences in skull thickness and cortical folding can thwart the ERP findings (Luck et al., 2011). Furthermore, there are findings indicating that demographic variables such as age (Näätänen et al., 2011b; Strömmer et al., 2014) and gender (Barrett & Fulfs, 1998; Qiao et al., 2015) affect the auditory ERPs, partly explaining the mixed results observed in the literature.

We addressed the impact of depression severity on the ERPs, but recurrence of the disease was not taken into account. Furthermore, we tried to minimise the impact of comorbidity and medication use via strict inclusion and exclusion criteria. Despite this, we cannot completely rule out the possibility of these factors confounding the results. Most depressed participants in our study were medicated but a few were not, and the precise prescription medication used by participants also varied. Considering the potential effects of antidepressants on aMMN and aP3a (e.g., Oranje et al., 2008), it is uncertain to what extent our results can be generalised, especially to unmedicated depressed patients, but also to medicated patients. There was also a gender imbalance in the studies,

as most of the participants in our study were women. Therefore, it is not known how well the findings generalise to men.

4.5 Conclusions, practical implications, and suggestions for future research

In conclusion, the findings from our study indicate no difference between depressed patients and non-depressed controls in terms of our chosen ERPs, nor a correlation between depression severity and the ERPs among those suffering from depression. However due to the limitations discussed above, our results should be considered preliminary, and care should be taken when drawing generalisations based on them.

Future studies should strive for innovative ways of obtaining larger and more representative depressed samples, which in turn would enable more meaningful statistical analysis and reliable findings. The heterogeneity of depression poses several challenges when the depressed group is approached as a unified whole. To reduce heterogeneity, future studies could apply a more rigorous control of various factors potentially affecting change detection ERPs, such as demographic variables, depression subtypes, and treatment. Most previous studies have included a mixed gender sample characterised by gender imbalance, with the majority of participants being female. In the future, studies should consider reducing heterogeneity by including solely male or female participants. In particular, there seems to be a need for studies focusing on the depressed male population. The medication status might also be worth controlling in future studies in order to increase homogeneity. Future studies should confirm our findings with non-medicated participants who have no previous medication history and perhaps, if possible, also pursue a path where all the depressed participants are under the same antidepressant medication. In addition, more ERP studies utilising multiple deviant types in a given modality are needed to explore whether some deviant types are more sensitive than others in discerning differences between depressed patients and non-depressed controls.

Although depression-related change-detection ERP research has thus far provided mixed results, the inherent benefits of the change detection paradigm (e.g., cost efficiency, speed, and availability) encourage further investigations into its diagnostic utility.

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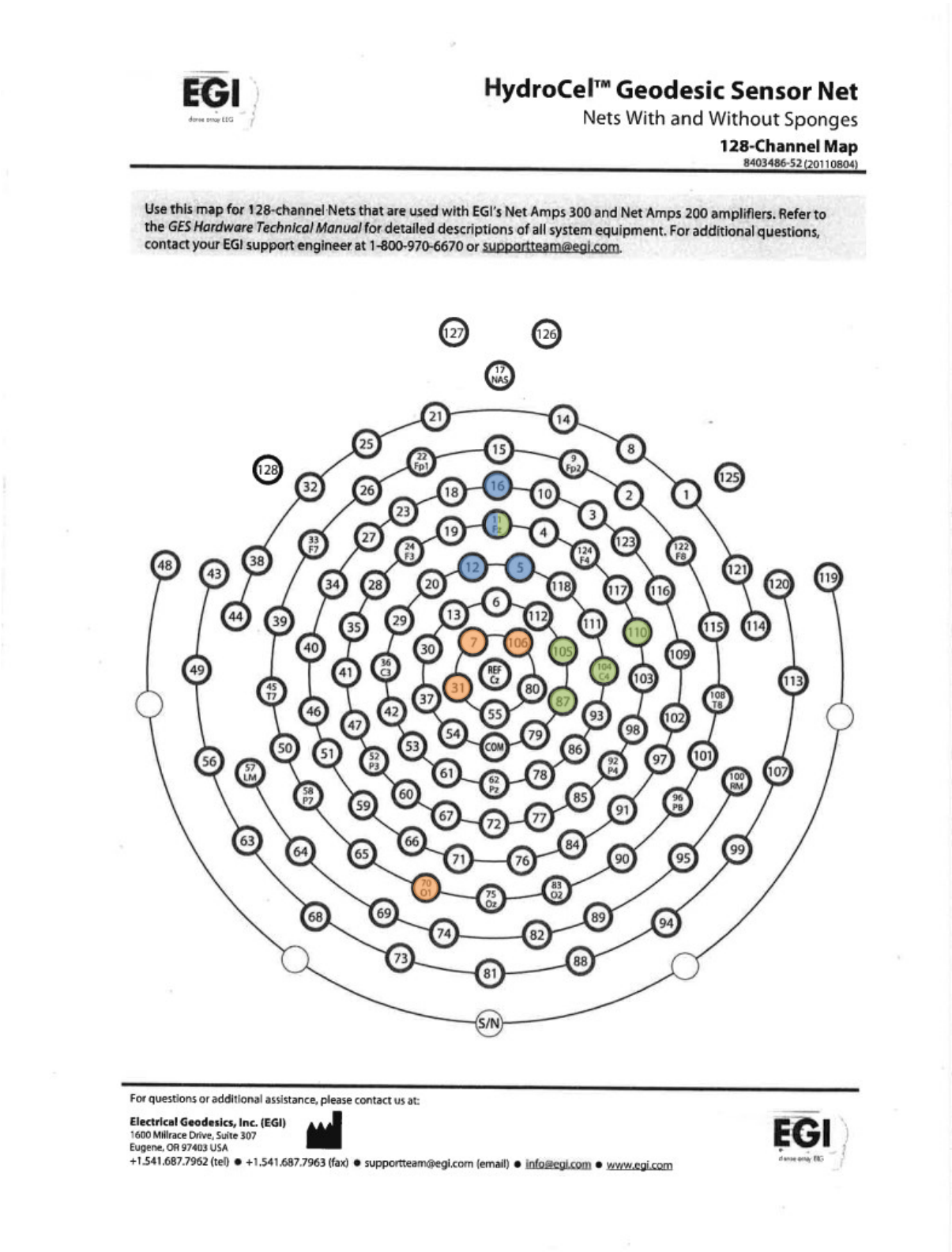
APPENDIX 1



Appendix 1. Electrode map displaying the electrodes used. Channels used to extract aMMN values are displayed as blue and the channels used to extract sMMR values are displayed in green. Channels used to extract aP3a and sP3a are displayed as orange.