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RESEARCH REPORT

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Intensity dependence of auditory evoked potentials distinguish participants with unmedicated depression from non-depressed controls

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Abstract

Depression is a heterogeneous syndrome that impacts an individual's emotional, social, cognitive and bodily functioning. Depression is associated with biases in emotional processing, but alterations in basic sensory processing have received less attention in depression research. Here, we measured event-related potentials (ERPs) in response to changes in the intensity of auditory stimuli and the location of somatosensory stimuli in participants with depression and in non-depressed control participants. We tested whether auditory mismatch negativity, P3a or N1 intensity dependence response or somatosensory mismatch response, P3a, P50 or N80 can dissociate depressed participants and non-depressed controls, and we also analysed the effects of depression medication and age in this sample. N1 intensity dependence response was increased in unmedicated depressed participants relative to non-depressed controls. When age was controlled for in the analysis, the effect of depression was only at a trend level. N1 intensity dependence response correlated with depression severity at the whole sample level. We did not observe any depression-related alterations in auditory mismatch negativity or P3a or somatosensory ERPs. Our results may reflect an association between the N1

Abbreviations: aMMN, auditory mismatch negativity; ANCOVA, analysis of covariance; ANOVA, analysis of variance; aP3a, auditory P3a; BDI-II Beck, Beck Depression Inventory-II; EEG, electroencephalography; ERPs, event-related potentials; ICD-10, International Classification of Diseases and Related Health Problems, 10th Revision; LDAEP, loudness dependence of auditory evoked potentials; MEG, magnetoencephalography; MMN, mismatch negativity; MMR, mismatch response; sMMR, somatosensory mismatch response; MRI, magnetic resonance imaging; SNRI, selective noradrenaline reuptake inhibitors/serotonin and noradrenaline reuptake inhibitors; SOA, Stimulus Onset Asynchrony; sP3a, somatosensory P3a; SPL, sound pressure level; SSRI, selective serotonin reuptake inhibitors.

intensity dependence response and altered neurotransmitter activity in depression, but this should be confirmed in future studies.

KEYWORDS
auditory, depression, event-related potentials, intensity dependence, somatosensory

1 | INTRODUCTION

Major depressive disorder is a very common mental disorder that affects roughly 4% of the global population (Institute of Health Metrics and Evaluation, 2019). The diagnosis criteria for major depressive disorder involve diverse affective, cognitive and vegetative symptoms, such as depressed mood, loss of interest or pleasure, feeling of worthless, decreased concentration, fatigue, weight loss/gain and insomnia/hypersomnia (American Psychiatric Association, 2013). Hence, depression is a heterogeneous syndrome that often comprehensively impacts an individual's emotional, social, cognitive and bodily functioning.

Information processing is also altered in depression (for reviews, see Nuno et al., 2021; Rock et al., 2014). Event-related potentials (ERPs) derived from electroencephalography (EEG) can be utilised to investigate the serial stages of information processing with a high temporal resolution (e.g., Sanei & Chambers, 2007). Especially, the processing of emotional information is shown to be disrupted; for instance, some depression-related alterations have been found in the processing of emotional face stimuli (e.g., Chang et al., 2010; Ruohonen, Alhainen, & Astikainen, 2020; Wu et al., 2016; Xu et al., 2018; Zhang et al., 2016; Zhao et al., 2015). Basic sensory processing has received less attention in research on depression compared to emotional processing. However, alterations in basic sensory information processing may also underlie some clinical symptoms and cognitive dysfunction in depressed patients. There are studies that have investigated the pre-attentive processing of basic auditory information in depression using ERPs (for a review, see Kangas, Vuoriainen, Lindeman, & Astikainen, 2022), but studies on the processing of basic somatosensory information in depressed patients are scarce. In the present study, pre-attentive auditory and somatosensory ERPs elicited in an ignore oddball paradigm were compared between a group of depressed participants and a non-depressed control group. More specifically, the focus of the investigation was on auditory and somatosensory ERPs that reflect sensory and cognitive functions and that are modulated by neurotransmitters involved in the pathophysiology of depression.

In previous studies, mismatch negativity (MMN) and P3a components have been used to investigate change detection (Kujala et al., 2007; Näätänen et al., 1978, 2007; Näätänen, Kujala, & Winkler, 2011) and pre-attentive information processing, which is a crucial aspect of perception and cognition (Näätänen et al., 2010) and the basis for later conscious processing stages. Auditory MMN (aMMN) typically occurs 150–250 ms after the onset of deviance in an ignore oddball condition, in which rare deviant stimuli are interspersed with repetitive standard stimuli (Näätänen et al., 1978, 2005, 2007). In the ignore condition, the participants are not attending to the stimuli. MMN is followed by P3a, which reflects an automatic re-orienting of attention towards the change (for reviews, see Escera et al., 2000; Friedman et al., 2001; Polich, 2007). It peaks approximately at 250–300 ms after the stimulus onset (e.g., Light et al., 2007; for a review, see Knight & Scabini, 1998).

MMN and P3a are associated with predictive coding theory, which states that the brain is constantly making predictions about future events based on previous sensory input (Friston, 2005). When the sensory input does not match the prediction, a prediction error occurs. The error signal is projected upward in the hierarchical neural network to update the predictive model, producing a new top-down prediction that then propagates downward to the lower areas (Friston, 2005). MMN and P3a have been suggested to reflect prediction errors (for reviews, see Carbajal & Malmierca, 2018; Denham & Winkler, 2020; Friston, 2005). Predictive coding, as a fundamental information processing mechanism, is theorised to be aberrant in depressive disorders (for reviews, see Kube et al., 2020; Smith et al., 2021). MMN is suggested to reflect the functioning of glutaminergic N-methyl-D-aspartate (NMDA) receptors (e.g., Javitt et al., 1996; Umbricht et al., 2000; Umbricht et al., 2002), and P3a is proposed to reflect the neuromodulatory effects of the dopaminergic system (for reviews, see Polich & Criado, 2006; Polich, 2007). Both glutaminergic NMDA receptor system (e.g., Adell, 2020; Inoshita et al., 2018; Sanacora et al., 2008) and dopaminergic regulation (for reviews, see Belujon & Grace, 2017; Malhi et al., 2005) have been suggested to be dysfunctional in depression. Given the MMN and P3a responses' association with glutaminergic and dopaminergic neurotransmitter systems and attentional and predictive coding functions, it can be assumed that MMN and/or P3a are altered in depressed patients.

An attenuated aMMN amplitude among depressed patients is, indeed, found in a few studies (Chen et al., 2015; Hirakawa et al., 2017; Naismith et al., 2012; Qiao et al., 2013; Qiao et al., 2015; Takei et al., 2009). In addition, an increased aMMN amplitude in patients with depression has been reported (Bissonnette et al., 2020; He et al., 2010; Kähkönen et al., 2007; Mu et al., 2016; Restuccia et al., 2016). However, some studies found no differences in the aMMN amplitude between depressed patients and controls (Kim et al., 2020; Lepistö et al., 2004; Ruohonen & Astikainen, 2017; Ruohonen, Kattainen, et al., 2020; Umbricht et al., 2003). Among depressed patients, aMMN has mostly been studied by applying duration deviance and frequency deviance oddball conditions (for a meta-analysis, see Tseng et al., 2021). Instead, research on intensity deviance aMMN in depression is scarce; Bissonnette et al. (2020) found an increased intensity deviance aMMN amplitude in depressed patients, while Mu et al. (2016), Ruohonen and Astikainen (2017) and Ruohonen, Kattainen, et al. (2020) did not find any differences in intensity deviance aMMN between depressed patients and non-depressed controls. Concerning the auditory P3a (aP3a) component in depression, previous studies using an ignore oddball condition with standard and deviant stimuli have reported attenuated aP3a amplitude in the depression group compared to controls (Chen et al., 2015; Xu et al., 2014) and increased aP3a amplitude in the group of depressed children compared to control children (Lepistö et al., 2004). In these previous aP3a studies, an intensity deviance oddball condition has not been applied. In the present study, an ignore intensity deviance oddball condition was employed to investigate alterations in aMMN and aP3a among depressed participants.

Auditory ERPs indirectly reflect the modulatory effects of serotonin on cortical functioning (Hegerl et al., 2001). High concentrations of serotonin have been detected in the primary auditory cortex in which serotonin behaves as a neuromodulator (Hegerl et al., 1998, 2001; Juckel et al., 1997). Especially, the processing of sound intensity is suggested to be associated with serotonergic functions (Hegerl et al., 2001), and serotonergic dysfunction is assumed to be one of the pathophysiological factors in depression (for reviews, see Kraus et al., 2017; Lin et al., 2014; Meltzer, 1990; Naughton et al., 2000; Nautiyal & Hen, 2017; Wang et al., 2016; for reviews showing no such results, see Liu et al., 2017; Moncrieff et al., 2023). Thus, investigating depression-related alterations in aMMN and aP3a applying an intensity deviance oddball condition is warranted. Regarding sound intensity processing, intensity dependence of auditory evoked potentials, also referred to as the loudness dependence of auditory evoked potentials (LDAEP), is a specific ERP index that can be used as a tool to assess serotonergic activity in the brain (Hegerl et al., 2001; Hegerl & Juckel, 1993). Intensity dependence response has been suggested to be useful in investigations of serotonergic dysregulation in patients with depression (e.g., Hegerl et al., 1998). However, it is important to notice that most of the evidence regarding the association between intensity dependence and serotonin comes from animal studies (e.g., Juckel et al., 1997; Juckel et al., 1999; Manjarrez et al., 2005; Wutzler et al., 2008). Instead, studies investigating humans have provided more inconsistent findings (e.g., Debener et al., 2002; Guille et al., 2008; Nathan et al., 2006; Simmons et al., 2011).

Intensity dependence of the auditory evoked potentials is a measure that assesses the amplitude increase of the obligatory auditory ERPs, initially as a difference between N1 and P2, in response to increasing loudness of auditory stimulation; a low intensity dependence response indicates high serotonergic activity, and vice versa (Hegerl et al., 2001; Hegerl & Juckel, 1993). However, there are also other ways to investigate intensity dependence; for instance, amplitude change in N1, P1, P2 and P1/N1 components in response to different auditory stimulus intensities have been studied (e.g., Jaworska et al., 2012; Linka et al., 2004; Linka et al., 2005; Linka, Sartory, Gastpar, et al., 2009; Linka, Sartory, Wiltfang, & Müller, 2009; Ruohonen, Kattainen, et al., 2020). Linka, Sartory, Gastpar, et al. (2009) have investigated associations between intensity dependence amplitude slopes and psychometric symptoms of depression; the association was found only for N1 but neither for the P1/N1 nor for the N1/P2 component. Also, an association between amplitude slope and selective serotonin reuptake inhibitors (SSRI) and selective noradrenaline reuptake inhibitors (SNRI) treatment outcome was found only for the N1 but neither for the P1/N1 nor for the N1/P2 component (Linka et al., 2004; Linka et al., 2005). Hence, Linka, Sartory, Gastpar, et al. (2009) suggest that N1 may be the most sensitive ERP component for investigating intensity dependence response regarding depression in their experimental setup in which N1/P2, P1/N1 and N1 components were investigated. In the present study, the N1 component was used to study intensity dependence response.

In line with the suggestion that a high intensity dependence response reflects low central serotonergic activity (Hegerl & Juckel, 1993), previous studies have shown that intensity dependence response predicts the treatment response of SSRIs in depressed patients; higher baseline intensity dependence response values predict a

favourable treatment response (for a meta-analysis, see Yoon et al., 2021). Instead, previous studies comparing patients with depressive disorder and non-depressed controls in intensity dependence response have yielded inconsistent findings. Increased intensity dependence response (Gopal et al., 2004; Ip et al., 2023; Medvedeva et al., 2023; difference only between depressed patients with diabetes and controls: Manjarrez-Gutierrez et al., 2009) and attenuated intensity dependence response (Fitzgerald et al., 2009; Gallinat et al., 2000; Jang et al., 2022; Jang et al., 2023; Kim et al., 2021; Ostermann et al., 2012; difference only between depressed patients with attention deficit hyperactivity disorder and controls: Kim et al., 2019) in depressed patients relative to non-depressed controls have been reported. Some studies have found no differences in intensity dependence response between depressed patients and controls (Graßnickel et al., 2015; Hwang et al., 2021; Jaworska et al., 2012; Linka, Sartory, Wiltfang, & Müller, 2009; Obermanns et al., 2022; Park et al., 2010; Ruohonen, Kattainen, et al., 2020; Uhl et al., 2011).

An important factor that may contribute to inconsistencies in prior research on intensity dependence response is the use of antidepressant medication by depressed participants, particularly SSRIs acting through the serotonergic system. Despite emerging evidence suggesting intensity dependence response as a predictor of SSRI treatment outcomes (for a meta-analysis, see Yoon et al., 2021), findings regarding the effects of SSRIs on intensity dependence response remain conflicting. Some studies have demonstrated no difference between pre-treatment and post-treatment intensity dependence response in depressed patients medicated with serotonergic antidepressants (Gallinat et al., 2000; Ip et al., 2023; Linka, Sartory, Wiltfang, & Müller, 2009). Furthermore, Gopal et al. (2004) and Min et al. (2012) found no difference in intensity dependence response between SSRI-medicated and unmedicated depressed patients, while Ostermann et al. (2012) observed no distinctions in intensity dependence response between patients treated with SSRIs and those treated with other antidepressants. Regarding healthy adults, neither an acute administration of SSRIs (Guille et al., 2008; Oliva et al., 2010; Uhl et al., 2006) nor an acute depletion of serotonin (Debener et al., 2002b; Dierks et al., 1999; Massey et al., 2004; Norra et al., 2008) appeared to affect intensity dependence response. However, a few investigations in healthy adults have reported decreased intensity dependence response following the administration of a single dose of the SSRI (Nathan et al., 2006; Segrave et al., 2006) and chronic SSRI administration (Simmons et al., 2011). Overall, the use of antidepressants targeting the serotonergic system may contribute to the varying results of previous intensity dependence response studies. Nevertheless, the contradictory findings concerning the impact of SSRIs on intensity dependence response add complexity and ambiguity to the issue.

In addition to auditory ERPs, we also investigated somatosensory processing. Depressive disorder is characterised not only by affective and cognitive symptoms but also by a variety of somatic symptoms. Furthermore, depression has been studied in the wider context of the interplay between the mind and body (e.g., Harshaw, 2015; Penninx et al., 2013). Vegetative symptoms, for instance, appetite changes and sleep disturbances, are a part of the diagnostic criteria for depressive disorder (American Psychiatric Association, 2013). Also, diverse other somatic symptoms, for instance, pain symptoms, are common among depressed patients (e.g., Bekhuis et al., 2015; Demyttenaere et al., 2006; Grover et al., 2012; Ohayon & Schatzberg, 2010; Simon et al., 1999, for reviews, see Bair et al., 2003; Lépine & Briley, 2004). The relationship between depression and pain is complex, each increasing the risk of the onset and gravity of the other (Lépine & Briley, 2004). It has also been shown that depression as a personality trait may moderate the way the pain is processed cortically (Vossen et al., 2006), and mood and emotional state have an impact on pain perception among both chronic and acute pain sufferers (for a review, see, Tracey & Mantyh, 2007). These issues suggest that there might be some alterations in the somatosensory processing regarding depression and depressed mood. However, there is a lack of somatosensory ERP research conducted on patients with depression. In a magnetoencephalography (MEG) study by Kurita et al. (2016), a prolonged P60 latency was found in depressed patients compared to non-depressed controls, while there were no between-group differences in the latency of N20, the amplitude of P60 or amplitude of N20 components. Dietl et al. (2001) found higher amplitudes of somatosensory P200 and P300 components in depressed patients relative to controls, while there were no differences between the groups in the amplitude of the P1 component. More research on somatosensory ERPs in depressed patients is needed to gain a better understanding of the underpinnings of somatic symptoms in depression.

Somatosensory P50 and N80 components generated in the primary somatosensory cortex reflect the encoding of physical stimulus properties (e.g., Forschack et al., 2020; Taylor-Clarke et al., 2002). Regarding psychiatric conditions, there are no depression-related EEG studies on somatosensory P50 and N80, but Arnfred and Chen (2004) found a reduced somatosensory P50 amplitude in schizophrenia patients compared to healthy

controls while there were no differences in the N80 amplitude or P50 or N80 latencies between schizophrenia group and control group. However, a magnetoencephalographic P60 may be a counterpart for P50 and N80, and the latency of the magnetoencephalographic P60 has been found to be prolonged in depressed patients compared to non-depressed controls (Kurita et al., 2016).

Somatosensory mismatch response (sMMR) and P3a (sP3a) have not been studied in depressed patients or other psychiatric patient groups. sMMR reflecting automatic change detection is a counterpart of auditory mismatch negativity (aMMN). It is often called a mismatch response due to its positive polarity in some of the studies (e.g., Akatsuka et al., 2005; Kangas, Vuoriainen, Li, et al., 2022; Shinozaki et al., 1998; Strömmer et al., 2017). sMMR is typically elicited at 100–200 ms after the stimulus onset to changes in spatial location, duration, vibratory frequency and a within-pair inter-stimulus interval of stimulus pairs (e.g., Akatsuka et al., 2005; Chen et al., 2014; Spackman et al., 2007; Strömmer et al., 2017). Similar to aMMN, sMMR has been associated with predictive coding theory (e.g., Naeije et al., 2018; Xu et al., 2021). Regarding clinical groups, sMMR has been studied in a few neurological conditions; sMMR was attenuated in cervical dystonia patients compared to healthy controls (Chen et al., 2018), and in the study investigating patients with unilateral cerebellar damage, sMMR was lacking when the affected hand (ipsilateral to the affected cerebellar hemisphere) was stimulated in the patient group while sMMR was elicited in the healthy control group (Restuccia et al., 2007). There are also a few studies on the P3a component elicited in the somatosensory modality (a counterpart of auditory P3a) in which healthy participants have been investigated (e.g., Kangas, Vuoriainen, Li, et al., 2022; Pesonen et al., 2023; Shen et al., 2018; Strömmer et al., 2017). In these P3a studies, a location deviance oddball condition (Kangas, Vuoriainen, Li, et al., 2022; Pesonen et al., 2023; Shen et al., 2018; Strömmer et al., 2017) and intensity deviance oddball condition (Kangas, Vuoriainen, Li, et al., 2022) have been applied.

Overall, the existing literature on auditory intensity deviance processing measured by MMN and P3a components in depressed patients is notably scarce. An intensity deviance oddball condition has been applied in only four of the aMMN studies (Bissonnette et al., 2020; Mu et al., 2016; Ruohonen & Astikainen, 2017; Ruohonen, Kattainen, et al., 2020), although intensity processing might be associated with serotonin levels in depression (e.g., Yoon et al., 2021). Furthermore, none of the previous studies compared depressed patients and non-depressed controls in intensity deviance aP3a amplitude. In this study, we aimed to address these research gaps by employing an intensity deviance oddball condition to examine aMMN and aP3a in a group of depressed participants and a group of non-depressed control participants. Additionally, we investigated auditory N1 intensity dependence response among depressed and non-depressed participants as a difference in N1 amplitude in response to low-intensity standard sounds and high-intensity standard sounds in an oddball condition. This approach allowed us to explore deviance detection ERPs (aMMN, aP3a) and N1 intensity dependence response within a single auditory experiment. Furthermore, there is a notable lack of research on somatosensory ERPs conducted among depressed participants. Our study seeks to contribute to this under-researched area by investigating somatosensory MMR, P3a, P50 and N80 components in a location deviance oddball condition, comparing a group of depressed participants with a group of non-depressed control participants. When we found a difference between depressed participants and non-depressed controls in these auditory and/or somatosensory ERP components, we investigated group differences also separately for medicated and non-medicated depression groups because antidepressant medication affects neurotransmitter functions. Careful consideration of medication is crucial, particularly when exploring intensity dependence response, which is associated with serotonergic functioning and commonly examined in relation to SSRI medication. Given that previous studies have indicated that auditory and somatosensory ERP responses are sensitive to ageing (e.g., Kiang et al., 2009; Näätänen et al., 2012; Näätänen, Kujala, Kreegipuu, et al., 2011; Pesonen et al., 2023; Ruohonen, Kattainen, et al., 2020; Strömmer et al., 2014; Strömmer et al., 2017), we also controlled for the effect of age in the analyses. Furthermore, whenever we found a difference between depressed participants and non-depressed controls, we investigated whether the amplitudes of the ERP responses correlated with the severity of depressive symptoms, as measured by the Beck Depression Inventory-II (BDI-II) (Beck et al., 1996).

Based on possible predictive coding impairments in depression (e.g., Kube et al., 2020) and on the idea of aMMN and aP3a as indicators of prediction errors (e.g., Friston, 2005), we expected that the amplitudes of aMMN and aP3a responses might be attenuated in depressed patients. In addition, aMMN and aP3a responses' association with glutaminergic and dopaminergic neurotransmitter systems (e.g., Javitt et al., 1996; Polich & Criado, 2006) relevant to depression (e.g., Adell, 2020; Belujon & Grace, 2017) suggests potential changes in these responses in depressed patients. Investigating aMMN and aP3a using an intensity deviance condition may further suggest potential depression-related modulations in these ERP components

since the processing of sound intensity has been linked to serotonergic functions (Hegerl et al., 2001), which are also proposed to be relevant to depression (e.g., Kraus et al., 2017).

N1 intensity dependence is suggested to reflect central serotonergic functions (Hegerl & Juckel, 1993), and since serotonin is assumed to be an important neurotransmitter in the pathophysiology of depression (e.g., Lin et al., 2014), we hypothesised that the N1 intensity dependence response might be altered in depressed patients. Because most antidepressant medications affect serotonergic neurotransmission, group differences may be best observed between unmedicated depressed and non-depressed control participants. However, the complexity of the issue regarding the intensity dependence response, serotonin and depression cannot be overlooked since there is no consensus on the significance of the brain's serotonergic functions in depressive disorders (for a review showing no such results, see Moncrieff et al., 2023) or on the relationship between N1 intensity dependence and serotonergic functions in human studies (for studies showing no such results, see Debener et al., 2002; Dierks et al., 1999; Guille et al., 2008; Massey et al., 2004; Norra et al., 2008; Oliva et al., 2010; Uhl et al., 2006). Our hypotheses are mostly two-sided due to the lack of a clear directional indication from both theory and previous research. Concerning previous investigations, studies focusing on auditory MMN have yielded contrasting results revealing both an attenuated amplitude (Chen et al., 2015; Hirakawa et al., 2017; Naismith et al., 2012; Qiao et al., 2013; Qiao et al., 2015; Takei et al., 2009) and an increased amplitude (Bissonnette et al., 2020; He et al., 2010; Kähkönen et al., 2007; Mu et al., 2016; Restuccia et al., 2016) among depressed participants compared to non-depressed controls. Similarly, when examining intensity dependence response, prior research has produced conflicting outcomes, with some studies reporting increased amplitude in depressed participants (Gopal et al., 2004; Ip et al., 2023; Manjarrez-Gutierrez et al., 2009; Medvedeva et al., 2023) and others observing attenuated amplitude (Fitzgerald et al., 2009; Gallinat et al., 2000; Jang et al., 2022; Jang et al., 2023; Kim et al., 2019; Kim et al., 2021; Ostermann et al., 2012).

Previous research on somatosensory MMR, P3a, P50 and N80 in relation to depression is limited and insufficient to form fully directional hypotheses. Since depression encompasses not only affective and cognitive symptoms but also a significant somatic component (e.g., Harshaw, 2015), disruptions in basic somatosensory processing may occur in depressed patients. It can be hypothesised that impaired early sensory encoding could lead to a reduced brain response in depression. On the other hand, impaired sensory gating has been observed in ageing, leading to increased P50/N80 responses in the somatosensory system (Pesonen et al., 2023; Strömmer et al., 2017). Similarly, in the auditory modality, deficits in sensory gating have been observed in depressed patients, manifesting as increased early brain responses (Ruohonen, Kattainen, et al., 2020). Both depression and ageing involve partly similar cognitive dysfunction (for reviews, see e.g., Hedden & Gabrieli, 2004; Rock et al., 2014), with early sensory processing serving as a foundational aspect. Also, if predictive coding functions are aberrant in depression (e.g., Kube et al., 2020), sMMR, which has been linked to predictive coding (e.g., Xu et al., 2021), may be altered in depressed patients. This alteration can be expected to be reflected in a reduction in prediction error responses (i.e., sMMR amplitude) in depressed participants compared to the control group.

2 | MATERIALS AND METHODS

2.1 | Participants

A sufficient sample size for the present study was estimated by conducting a priori power analysis in G*Power (Faul et al., 2007) (version 3.1.9.7). We selected a repeated-measures ANOVA to test the interaction between within-subject factors and a between-subject factor (depressed group, control group). For auditory MMN and P3a components, a repeated measures ANOVA with two within-subject factors (stimulus type and intensity), both with two levels, and one between-subject factor was selected as the statistical test, and for somatosensory MMR and P3a components, a repeated measures ANOVA with one within-subjects factor (stimulus type) with two levels, and one between-subjects factor was selected as the statistical test. For all the tests, the statistical power $(1 - \beta) = 0.80$, the significance level of alpha $= 0.05$ and the nonsphericity correction $= 1$. The effect size was set on the specification as in SPSS (IBM SPSS Statistics; IBM Corporation, NY, USA). The sample size in the present study was estimated based on a standard medium effect size ($\eta^2_p = 0.060$; Cohen, 1988). The calculations indicated that for the auditory MMN and P3a, 18 participants in each group (depressed, control) and for somatosensory MMR and P3a, 27 participants in each group (depressed, control) are required. The sample size for the correlation analysis was also estimated with a priori power analysis. To observe a weak association ($r = 0.3$) between the variables of interest, the calculation with the statistical power $(1 - \beta) = 0.80$, the significance level of alpha $= 0.05$ and a correlation ρ H0 $= 0$ showed that 84 participants are required.

The data for this study have been compiled from three separate research projects in which ageing- and depression-related modulations in auditory and somatosensory ERPs have been investigated. Depressed and non-depressed volunteers were recruited via notice board advertisements, email lists of the University of Jyväskylä, the University of the Third Age in Jyväskylä, the Society of the Retired and newspaper advertisements. The eligibility for the investigation was assessed for each person who responded to the recruitment announcement and volunteered for the study. The experiments were conducted in accordance with the Declaration of Helsinki. Ethical approval for the study was obtained from the ethical committee of the Central Finland Health Care District (18 U/2018, 14 U/2015 and 5E/2015). Written informed consent was obtained from all the participants prior to their participation.

Participants were, in part, recruited separately for somatosensory and auditory experiments. Thus, auditory experiments and somatosensory experiments were conducted with partly different participants, and therefore, the background information of the participants is presented separately for auditory and somatosensory experiments.

2.1.1 | Participants in the auditory experiment

In the auditory experiment, all participants were aged between 18 and 80 years, right-handed, and had no history of neurological conditions (except migraine that was not recently active, fibromyalgia or learning disabilities) or alcoholic or narcotic addictions. Participants had normal or corrected-to-normal vision and normal hearing. Participants' hearing thresholds were measured using a SA-51 audiometer (Mediroll Medico-Technical Limited). The ears were measured individually. An exclusion criterion was a hearing threshold above 20 dB for 1000 Hz sounds. Nine participants were excluded because the hearing threshold was too high. All of them were over 61 years old. Hearing threshold measurement was not conducted for eight depressed participants (aged between 18 and 40 years), and in their case, normal hearing was based on the self-report.

The inclusion criterion for the depressed group was current depressive symptoms measured with the Beck Depression Inventory-II (BDI-II; Beck et al., 1996). The BDI-II scores of depressive symptoms had to be over 13, which is the limit for mild depression (Beck et al., 1996). The exclusion criteria for the depressed group were a self-reported diagnosis of bipolar disorder or schizophrenia. The exclusion criteria for the non-depressed group were a self-reported current or previous diagnosis of depressive disorders, any other psychiatric diagnosis, current use of medication that can affect the central nervous system, and a BDI-II score over nine. The information related to the inclusion and exclusion criteria was collected through a phone interview and a questionnaire.

Hereafter, 'participants with depression' and 'depressed participants' refer to participants with BDI-II > 13, and 'participants without depression' and 'non-depressed participants' to participants with BDI-II < 10.

The auditory data were collected from 63 participants with depression (11 males, 51 females, 1 other) and 82 control participants without depression (14 males, 68 females) (Table 1). The data of 33 of the participants in the depression group and the data of 37 of the participants in the non-depressed control group have also been reported in the study by Ruohonen, Kattainen, et al. (2020) in which age- and depression-related modulations in auditory ERP components were investigated. The mean age of the depressed participants was 41.9 ($SD = 18.3$) years, ranging between 18 and 76 years. The mean age for the controls was 38.3 ($SD = 18.4$) years, ranging between 19 and 80 years. There was no statistically significant difference in age between the depressed group and the non-depressed control group, U ($N_{\text{depressed}} = 63$, $N_{\text{controls}} = 82$) = 2226.50, $z = -1.423$, $P = .155$ (two-sided). Regarding gender, there was no significant difference in male and female genders between

TABLE 1 Auditory data-related demographic and clinical characteristics of non-depressed controls and depressed participants.

	Non-depressed controls ($n = 82$)	**Depressed participants ($n = 63$)**
Age $M \pm SD$ (range)	38.3 ± 18.4 (19–80)	41.9 ± 18.3 (18–76)
Gender (male/female/other)	14/68/0	11/51/1
Depressive disorder diagnosis (yes/no)	Na	49/14
Medication (medicated/unmedicated)	Na	29/34
BDI-II $M \pm SD$ (range)	2.13 ± 2.37 (0–9)	27.46 ± 7.41 (15–42)
Depressive symptom severity (mild/moderate/severe)	Na	9/26/28

the depressed and non-depressed groups, $\chi^2(1) = 0.01$, $P = .916$ (two-sided), but in the depressed group, there was also one participant in the gender category "other". In the group of participants with depression, the mean score of the BDI-II was 27.46 ($SD = 7.41$, range 15–42). In the non-depressed control group, the mean score in the BDI-II was 2.13 ($SD = 2.37$, range 0–9).

In the group of participants with depression, 49 participants had been diagnosed as having a depressive disorder in accordance with the International Classification of Diseases and Related Health Problems, 10th Revision, ICD-10. They had a depressive episode (F32), recurrent depressive disorder (F33) or dysthymic disorder (F34.1). Fourteen depressed participants did not have any depressive disorder diagnosis, but they currently had an elevated number of depressive symptoms (score 15–38 in BDI-II). There was no significant difference between a group of depressed participants with a diagnosis and a group of depressed participants without a diagnosis in the BDI-II score, $t(61) = -0.38$, $P = .703$ (two-sided). Regarding comorbid psychiatric disorders aside from depressive disorder, 11 participants with depressive disorder diagnoses reported anxiety disorders and two reported personality disorders. Depressed participants without a clinical diagnosis of depressive disorder had no other psychiatric diagnoses.

In the group of depressed participants, 34 participants were unmedicated (5 males, 28 females, 1 other) and 29 participants were on antidepressant medication (6 males, 23 females). In the group of medicated participants, 9 participants had SSRI medication, 5 had SNRI (serotonin and noradrenaline reuptake inhibitors) medication, 3 had serotonin modulator medication (vortioxetine), 3 had atypical antidepressants (agomelatine, bupropion) and 9 had a combination of two or three antidepressants of different classes or a combination of antidepressants and quetiapine or benzodiazepines. There were no significant differences in BDI-II scores, $t(61) = 0.53$, $P = .597$ (two-sided), in age, U ($N_{\text{unmedicated}} = 34$, $N_{\text{medicated}} = 29$) = 383.50, $z = -1.511$, $P = .131$ (two-sided) or in the number of male and female participants, $\chi^2(1) = 0.32$, $P = .569$ (two-sided) (in the unmedicated group, there was also one participant in the gender category "other"), between a group of medicated depressed participants and a group of unmedicated depressed participants. When comparing a group of medicated depressed participants, a group of unmedicated depressed participants and a group of non-depressed control participants, there were no significant differences in age, $H(2) = 3.77$, $P = .152$ or in the number of male and female participants $H(2) = 0.34$, $P = .844$ (in the unmedicated group, there was also one participant in the gender category "other").

2.1.2 | Participants in the somatosensory experiment

In the somatosensory experiment, all participants were aged between 19 and 83 years, right-handed, and had no history of neurological conditions (except migraine that was not recently active, fibromyalgia or learning disabilities) or alcoholic or narcotic addictions.

The inclusion criterion for the depressed group was current depressive symptoms measured with BDI-II. The BDI-II scores of depressive symptoms had to be over 13. The exclusion criteria for the depressed groups were a self-reported diagnosis of schizophrenia or bipolar disorder. The exclusion criteria for the non-depressed group were a self-reported current or previous diagnosis of any psychiatric disorders, current use of medication that can affect the central nervous system and a BDI-II score over nine. The information related to the inclusion and exclusion criteria was collected through a phone interview and a questionnaire.

The somatosensory data were collected from 38 participants with depression (4 males, 33 females, 1 other) and 84 control participants without depression (11 males, 73 females) (Table 2). The participants were partly the same as in the auditory experiment. The data of 48 of the participants in the non-depressed control group have also been reported in the study by Strömmer et al. (2017), in which age-related modulations in somatosensory ERP components were investigated. The mean age of the depressed participants was 54.2 ($SD = 18.8$) years, ranging between 20 and 83 years. The mean age for the controls was 52.4 ($SD = 20.4$) years, ranging between 19 and 83 years. There was no statistically significant difference in age between the depressed group and the non-depressed control group, U ($N_{\text{depressed}} = 38$, $N_{\text{controls}} = 84$) = 1588.00, $z = -0.044$, $P = .965$ (two-sided). Regarding gender, there was no significant difference in male and female genders between the depressed and non-depressed groups $\chi^2(1) = 0.12$, $P = .725$ (two-sided). In the depressed group, there was also one participant in the gender category "other". In the group of participants with depression, the mean score of the BDI-II self-report questionnaire was 27.42 ($SD = 7.24$, range 14–40). In the control group, the mean score in the BDI-II was 3.35 ($SD = 2.91$, range 0–9).

In the group of depressed participants, 30 participants had been diagnosed as having a depressive disorder in accordance with the International Classification of Diseases and Related Health Problems, 10th Revision, ICD-10. They had a depressive episode (F32), recurrent depressive disorder (F33) or dysthymic disorder (F34.1). Eight participants did not have any depressive disorder diagnosis, but they had an elevated number of depressive

TABLE 2 Somatosensory data-related demographic and clinical characteristics of non-depressed controls and depressed participants.

	Non-depressed controls ($n = 84$)	Depressed participants ($n = 38$)
Age $M \pm SD$ (range)	52.4 ± 20.4 (19–83)	54.2 ± 18.8 (20–83)
Gender (male/female/other)	11/73/0	4/33/1
Depressive disorder diagnosis (yes/no)	Na	30/8
Medication (medicated/unmedicated)	Na	17/21
BDI-II $M \pm SD$ (range)	3.35 ± 2.91 (0–9)	27.46 ± 7.24 (14–40)
Depressive symptom severity (mild/moderate/severe)	Na	5/17/16

symptoms (score 16–34 in BDI-II). There was no significant difference between a group of depressed participants with a diagnosis and a group of depressed participants without a diagnosis in the BDI-II score, $t(36) = -0.18$, $P = .856$ (two-sided). Regarding comorbid psychiatric disorders aside from depressive disorder, 6 participants with depressive disorder diagnoses reported anxiety disorders, and one reported a personality disorder. Depressed participants without a clinical diagnosis of depressive disorder had no other psychiatric diagnoses.

In the group of participants with depression, 21 participants were unmedicated (1 male, 19 females, 1 other), and 17 participants were on antidepressant medication (3 males, 14 females). In the group of medicated participants, two participants had SSRI medication, four had SNRI (serotonin and noradrenaline reuptake inhibitors) medication, two had serotonin modulator medication, one had an atypical antidepressant, and eight had a combination of two or three antidepressants of different classes or a combination of antidepressants and quetiapine or benzodiazepines. There were no significant differences between a group of medicated depressed participants and a group of unmedicated depressed participants in BDI-II scores, $t(36) = -0.80$, $P = .429$ (two-sided), or in the number of male and female participants, $\chi^2(1) = 1.52$, $P = .217$ (two-sided) (in the unmedicated group, there was also one participant in the gender category "other"). The mean age was higher in the group of unmedicated depressed participants compared to medicated depressed participants, U ($N_{\text{unmedicated}} = 21$, $N_{\text{medicated}} = 17$) $= 90.00$, $z = -2.602$, $P = .009$ (two-sided).

2.2 | Procedure

This study included two types of measurements: EEG recording and questionnaires (BDI-II and background information questionnaire). During the EEG recording, the participants sat in a chair in an electrically shielded, soundproof, dimly lit room. The experimenter monitored them via a video camera. The participants were instructed to avoid body and head movements and facial expressions. They were also instructed to concentrate on watching a silent movie on the screen and to ignore the auditory and somatosensory stimuli.

2.3 | Stimulus presentation

EEG was measured for changes in auditory and somatosensory stimuli. During the auditory measurement, the sinusoidal sounds of 1000 Hz in frequency and 100 ms in duration (with a 10-ms onset and offset time) were presented from a loudspeaker located approximately one meter above the participant. The intensity of the sounds varied at either 80 dB or 60 dB (sound pressure level, SPL). SPLs were measured with a sound level meter (type 2235, Brüel and Kjaer, Naerum, Denmark) with A-weighting.

The somatosensory stimulation was generated with a constant current stimulator (Digitimer Ltd, model DS7A, Welwyn Garden City, UK). Each stimulus duration was 200 μs. The electrical stimuli were delivered through flexible metal ring electrodes that were moistened with conductive jelly to reduce impedance. To prevent conductivity between the two electrodes on the same finger, a piece of gauze was placed on the finger between the electrodes. The stimuli were delivered to the left forefinger and little finger by stimulating the cathode around the proximal phalanx and the anode around the distal phalanx. The subjective somatosensory thresholds were determined before the EEG recording, and the somatosensory stimulus intensities were adjusted for each participant independently for the left forefinger and little finger. An individually adjusted stimulation was applied because it is difficult to find a fixed somatosensory stimulus intensity that is not noxious for someone and is still discernible for all participants. The intensity of the stimulus was either 1.5 or 2.0 times the individual somatosensory threshold. We used a higher factor in the sub-studies with older adults than in the sub-studies with only young

adults. However, in the whole data set of the present study, roughly the same proportion of subjects in the depressed and control groups received the stimulus at the same factor: In the depressed group, 57.9% of the participants, and in the control group, 57.1% of the participants were given stimuli in which the intensity was set at twice the threshold.

In the auditory and somatosensory measurements, the stimuli were presented in an oddball condition in which a repeated standard stimulus was occasionally replaced by a deviant stimulus. The order of the stimuli was pseudorandomised: at least two standard stimuli were presented between consecutive deviant stimuli. In the auditory experiment, there were standard and deviant sounds of different intensities (60 dB, 80 dB). In the auditory increment condition, the standard stimulus was 60 dB (SPL), and the deviant stimulus was 80 dB (SPL). In the decrement condition, these intensities were reversed. In the somatosensory experiment, the stimuli were presented in a location deviance condition in which, in one block, the standard stimulus was delivered to the forefinger and the deviant stimulus to the little finger. In the other block, the assignment to the standard and the deviant stimulus was reversed.

Hence, in the somatosensory experiment, both locations and in the auditory experiment, both intensities were applied as standard and deviant stimuli for all participants in a randomised order across participants. In the auditory experiment, for 145 participants, there were 2000 stimuli in total, and for 8 participants (all depressed), there were 1000 stimuli in total. The deviant stimulus probability was 10%, as in our previous studies (Kangas, Vuoriainen, Li, et al., 2022; Ruohonen & Astikainen, 2017; Ruohonen, Kattainen, et al., 2020). In the somatosensory experiments, there were 1680 stimuli in total for 52 participants (16 depressed participants, 36 controls), 1430 stimuli for 39 participants (22 depressed participants, 17 controls) and 1000 stimuli for 31 participants (all controls). The deviant stimulus probability was 14%, as in our previous studies (Kangas, Vuoriainen, Li, et al., 2022; Strömmer et al., 2017).

In the auditory experiment, the Stimulus Onset Asynchrony (SOA) in the stimulus presentation was randomly set at either 530 ms, 580 ms or 630 ms for 56 participants, and at either 500, 550 or 600 ms for 89 participants. In the somatosensory experiments, the SOA was randomly set at either 406, 456 or 506 ms for 52 participants, at either 400, 450 or 500 ms for 31 participants, and at either 450, 500 or 550 ms for 39 participants. The stimulus presentation was controlled using E-Prime 2.0 software (Psychology Software Tools Inc., Sharpsburg, MD, USA).

2.4 | EEG acquisition and EEG data processing

The EEG was recorded using a high-impedance amplifier (either NeurOne Bittium Biosignals, Ltd. and Net Amps 200 or Electrical Geodesic Inc., Eugene, OR, USA) and a 128-channel Sensor Net (Electrical Geodesics Inc., HydroCel GSN 128, 1.0). The sampling rate was 1000 Hz, and data were filtered online from 0.1 to 250 Hz. During the recording, the data were referenced to a vertex electrode (Cz).

The EEG data were analysed with Brain Vision Analyzer 2.2. software (Brain Products GmbH, Munich, Germany). An average of all the channels was calculated and applied as a new reference. The data were filtered with a low cut-off at 0.1 Hz and a high cut-off at 30 Hz, a roll-off of 24 dB/octave and a notch filter of 50 Hz. The Gratton and Coles method (Gratton et al., 1983) was applied to detect and correct the interference of eye blinks. Channel 8, which is above the midpoint of the right eye, was chosen as the vertical electro-oculogram (VEOG) channel. Channels with excessive noise were interpolated with a spherical spline model.

The auditory data were segmented into 600 ms segments from 100 ms prior to stimulus onset to 500 ms after stimulus onset, and somatosensory data were segmented into 500 ms segments from 100 ms prior to stimulus onset to 400 ms after stimulus onset. For auditory and somatosensory data, a pre-stimulus onset time of 100 ms was determined as a baseline for a baseline correction. The EEG segments with a signal amplitude difference larger than 150 μV within a 200-ms period in any recording channel were omitted from the analysis. Segments with a difference of more than 50 μV 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 also excluded.

In auditory data, averages were calculated separately for three different stimulus types: responses to deviants, responses to standards immediately preceding the deviants (pre-deviant standard) and responses to standards immediately after deviants (post-deviant standard). In somatosensory data, averages were calculated separately for two different stimulus types: responses to deviants and responses to standard stimuli immediately preceding the deviant stimuli (pre-deviant standard).

The channels and time windows were defined based on previous literature (auditory: Kangas, Vuoriainen, Li, et al., 2022; Ruohonen, Alhainen, & Astikainen, 2020; somatosensory: Kangas, Vuoriainen, Li, et al., 2022; Strömmer et al., 2017) and visual observations of the grand averaged waveforms and topographies of the

activity calculated across the depressed group and non-depressed control group. Regarding auditory ERP components, for aMMN, the mean deviant and pre-deviant standard response amplitude values were calculated for the latency of 140–180 ms after stimulus onset over a frontal channel cluster of five electrodes (channels 5, 6, 11, 12 and 16 in the EGI 128-channel system). For aP3a, the applied time window was 220–320 ms after stimulus onset, and the amplitude values for deviants and pre-deviant standards were extracted from a frontocentral channel cluster of four electrodes (channels 7, 31, 80 and 106). For N1, the applied time window was 80–130 ms after stimulus onset, and the amplitude values for post-deviant standards were extracted from a frontocentral channel cluster of eight electrodes (channels 5, 6, 7, 11, 12, 13, 106 and 112).

Regarding somatosensory ERP components, for sMMR, the mean deviant and pre-deviant standard response amplitude values were calculated for the latency of 150–190 ms after stimulus onset over a central channel cluster of four electrodes (channels 55, 79, 87, 80). For aP3a, the applied time window was 200–300 ms after stimulus onset, and the amplitude values for deviants and pre-deviant standards were extracted from a frontocentral channel cluster of four electrodes (channels 7, 31, 80 and 106). For P50 and N80 components, the maximum peak amplitude value for deviants and pre-deviant standards at the 104 (C4) electrode and its latency was extracted from time windows of 30–80 ms (P50) and 40–110 ms (N80) after stimulus onset.

2.5 | Statistical analysis

The data were analysed using IBM SPSS Statistics 28.0 (IBM Inc., Armonk, NY, USA).

A repeated measures analysis of variance (ANOVA) with stimulus type (standard, deviant) and intensity (high, low) as within-subject factors and group (depressed, control) as a between-subject factor was conducted separately for auditory intensity deviance MMN and P3a. The intensity was included in the model because previous studies suggest that auditory intensity processing may be altered in depression (for a review, see Kangas, Vuoriainen, Lindeman, & Astikainen, 2022). When a significant interaction effect was found, follow-up tests were performed using the paired samples *t*-test (two-tailed, bootstrap statistics with 1000 iterations) for within-group comparisons and independent samples *t*-tests (two-tailed, bootstrap statistics with 1000 iterations) for between-group comparisons.

Auditory N1 intensity dependence was calculated as the difference between N1 amplitudes in response to low- and high-intensity standard sounds (as in Ruohonen, Kattainen, et al., 2020). Only responses to post-deviant standard sounds were included in this analysis because this procedure reduces the effect of repetition on the responses. This procedure is also more comparable to those intensity dependence studies in which sounds are presented with equal probability and without repetition in consecutive stimuli (Ruohonen, Kattainen, et al., 2020). The differential response (N1 elicited by high-intensity stimuli minus N1 elicited by low-intensity stimuli) reflects the change in responses as a function of an increase in intensity, and according to Ruohonen, Kattainen, et al. (2020), it, therefore, resembles a regression slope that is often used to study the intensity dependence of auditory responses (Hegerl et al., 1994). Independent samples *t*-test (two-tailed, bootstrap statistics with 1000 iterations) was performed to compare N1 intensity dependence responses between a depressed group and a control group.

N1 intensity dependence response was also studied in three groups: a group of medicated depressed participants, a group of unmedicated depressed participants and non-depressed controls. A one-way ANOVA was used to compare these three groups, and follow-up pairwise comparisons were performed using a Bonferroni post hoc test.

A repeated measures ANOVA with stimulus type (standard, deviant) as a within-subject factor and group (depressed, control) as a between-subject factor was conducted separately for somatosensory location deviance MMR and P3a. When a significant interaction effect was found, follow-up tests were performed using the independent samples *t*-tests (two-tailed, bootstrap statistics with 1000 iterations) for between-group comparisons.

One-sample *t*-test was used to determine whether the means of the peak amplitude values of somatosensory P50 and N80 in response to standard and deviant stimuli differed statistically significantly from zero, i.e., whether these components were robustly elicited. To compare differences in the peak amplitude and latency of somatosensory P50 and N80 between the depressed group and control group separately for deviant and standard stimuli, an independent samples *t*-test (two-tailed, bootstrap statistics with 1000 iterations) was applied. Multiple comparisons between the groups were controlled by applying a false discovery rate (FDR) (Benjamini & Hochberg, 1995). FDR-adjusted *P*-values are reported.

Since previous studies have shown that ERP responses are affected by ageing (e.g., Kiang et al., 2009; Näätänen et al., 2012; Näätänen, Kujala, Kreegipuu, et al., 2011; Pesonen et al., 2023; Ruohonen, Alhainen, & Astikainen, 2020; Strömmer et al., 2014; Strömmer et al., 2017), separate analyses were conducted using age

as a covariate. Repeated measures analyses of covariance (ANCOVAs) were conducted separately for aMMN, aP3a, sMMR and sP3a using age as a covariate to control for its potential influence on the effect of stimulus type (standard vs. deviant) and the interaction effect between stimulus type and group (depressed vs. control) because these components are typically defined as differential responses (Näätänen, 1992). Univariate ANCOVAs with age as a covariate were applied to compare N1 intensity dependence responses between the groups. For somatosensory P50 and N80 responses, univariate ANCOVAs were applied to control for the effect of age on the peak amplitude and latency whenever a group difference was found.

To examine the evidence for the null statistical results in post hoc tests (auditory MMN and N1 intensity dependence responses) and independent samples t-tests (P50 and N80 responses), Bayes factor analyses (Bayesian t-tests) were conducted using JASP software 0.16.4 (JASP Team, Amsterdam, The Netherlands). If BF_{10} is less than 1, there is more evidence in favour of the null hypothesis compared to the alternative hypothesis. Effect size estimates are described as partial eta squared (η^2_p) scores for ANOVAs and Cohen's *d* for *t*-tests.

Since a statistically significant difference between depressed participants and non-depressed controls was found only in N1 intensity dependence response, correlations between auditory N1 intensity dependence response and BDI-II score, as well as between auditory N1 intensity dependence response and age, were calculated using the Spearman rank-order correlation coefficient. Correlations were calculated both across the whole sample and separately in the depression group and non-depressed control group. Multiple correlations were controlled by applying a false discovery rate (FDR) (Benjamini & Hochberg, 1995). FDR-adjusted *P*-values are reported. *P*-values smaller than 0.05 were considered significant for all tests.

3 | RESULTS

3.1 | Auditory ERPs

3.1.1 | Auditory MMN

For the auditory MMN, a repeated measures ANOVA with within-subject variables stimulus type (standard vs. deviant) and intensity (high vs. low) and a between-subject variable group (depressed vs. control) showed a main effect of stimulus type (F[1,143] = 271.87, $P < .001$, $\eta^2_p = 0.655$) (Table 3). The main effect was modulated by an interaction effect of stimulus type × intensity (F[1,143] = 7.33, $P = .008$, $\eta^2_p = 0.049$). The interaction effect of stimulus type × intensity was further investigated with paired samples *t*-tests (Figure 1). For the high-intensity stimuli, responses were larger for the deviant stimuli ($M = -0.86$ μV, $SD = 1.64$) compared to the standard stimuli ($M = 0.77$ μV, $SD = 0.95$), ($t(144) = -14.07$,

TABLE 3 Results of the repeated-measures ANOVA for auditory and somatosensory mismatch (MMN/MMR) and P3a responses. *F*- and *P*-values and partial eta squared (η^2_p) for effect size estimates. Significant effects in bold.

Variable	Group	Stimulus type	Stimulus type x Group	Intensity	Intensity x Group	Stimulus type x Intensity	Stimulus type x Intensity x Group
Auditory MMN	$F(1, 143) = 1.537$	$\mathbf{F(1, 143) = 271.873}$	$F(1, 143) = 0.018$	$F(1, 143) = 0.008$	$F(1, 143) = 0.035$	$\mathbf{F(1, 143) = 7.329}$	$F(1, 143) = 0.647$
	$P = .210$	$\mathbf{P < .001}$	$P = .892$	$P = .930$	$P = .852$	$\mathbf{P = .008}$	$P = .422$
	$\eta^2_p = 0.011$	$\mathbf{\eta^2_p = 0.655}$	$\eta^2_p < 0.001$	$\eta^2_p < 0.001$	$\eta^2_p < 0.001$	$\mathbf{\eta^2_p = 0.049}$	$\eta^2_p = 0.005$
Auditory P3a	$F(1, 143) = 0.156$	$\mathbf{F(1, 143) = 96.755}$	$F(1, 143) = 0.333$	$F(1, 143) = 0.396$	$F(1, 143) = 1.620$	$F(1, 143) = 0.043$	$F(1, 143) = 3.167$
	$P = .693$	$\mathbf{P < .001}$	$P = .565$	$P = .530$	$P = .201$	$P = .855$	$P = .077$
	$\eta^2_p = 0.001$	$\mathbf{\eta^2_p = 0.404}$	$\eta^2_p = 0.002$	$\eta^2_p = 0.003$	$\eta^2_p = 0.011$	$\eta^2_p < 0.001$	$\eta^2_p = 0.022$
Somatosensory MMR	$F(1, 120) = 0.077$	$\mathbf{F(1, 120) = 31.488}$	$F(1, 120) = 0.687$				
	$P = .782$	$\mathbf{P < .001}$	$P = .409$				
	$\eta^2_p = 0.001$	$\mathbf{\eta^2_p = 0.208}$	$\eta^2_p = 0.006$				
Somatosensory P3a	$F(1, 120) = 2.228$	$\mathbf{F(1, 120) = 38.094}$	$F(1, 120) = 0.556$				
	$P = .130$	$\mathbf{P < .001}$	$P = .457$				
	$\eta^2_p = 0.019$	$\mathbf{\eta^2_p = 0.241}$	$\eta^2_p = 0.005$				

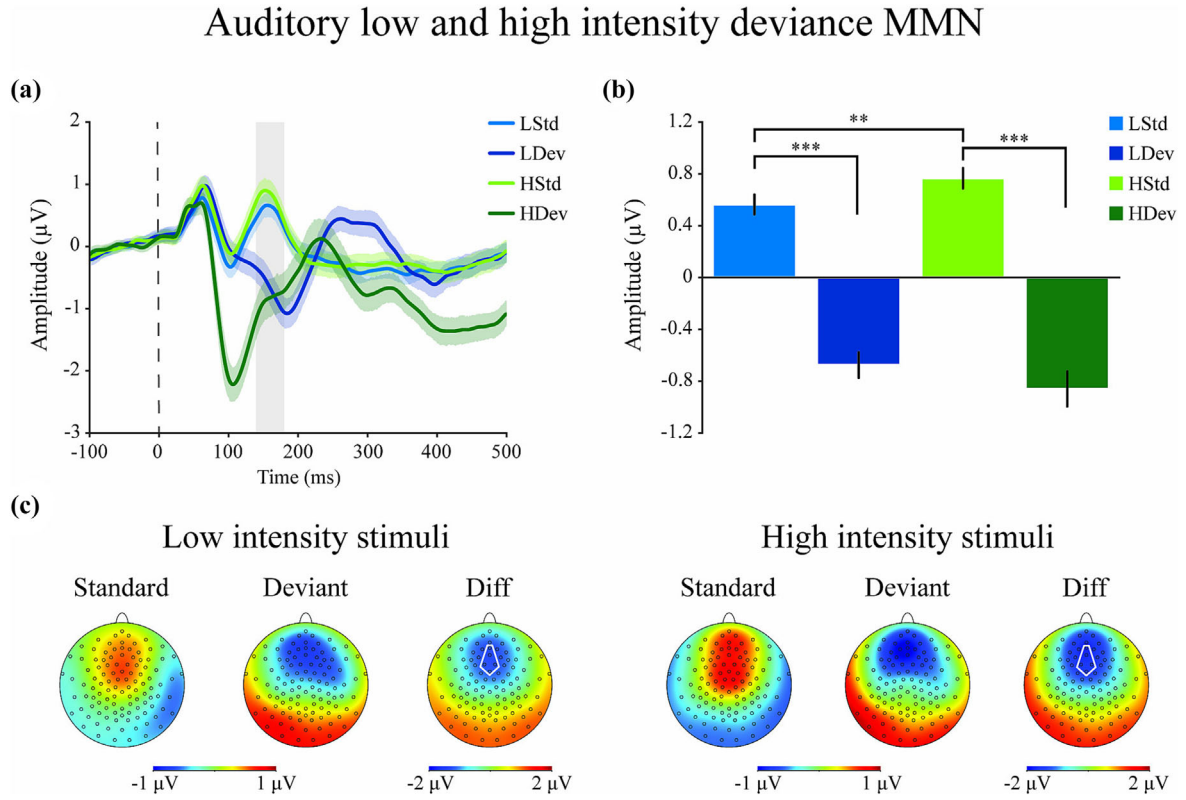

FIGURE 1 Auditory low and high-intensity deviance MMN averaged over the depressed group and non-depressed control group. (a) Grand-averaged waveforms to low-intensity deviant (LDev) and standard (LStd) stimuli and high-intensity deviant (Hdev) and standard (HStd) stimuli. Waveforms represent averages of the electrode pools applied in the analyses. The grey rectangle shows the analysis window for aMMN (140–180 ms). (b) Bar chart represents mean amplitudes for responses to low-intensity standard and deviant stimuli and high-intensity standard and deviant stimuli (averaged over the electrodes applied in the analysis). Error bars represent the standard error of the mean. ***$P < .001$, **$P < .01$. The *P*-values reflect post hoc *t*-test results. (c) The topographical maps of grand averaged responses to low-intensity standard and deviant stimuli and low-intensity differential response (deviant minus standard; Diff) and high-intensity standard and deviant stimuli and high-intensity differential response (deviant minus standard; Diff). The electrodes applied in the analysis are marked in the white frame in the topographical maps of differential response.

$P < .001$ (one-sided), $d = 1.392$). The mean amplitude difference was −1.63 μV, $SD = 1.39$, 95% *CI* [−1.85, −1.40]. Also, for the low-intensity stimuli, responses were larger for the deviant stimuli ($M = -0.68$ μV, $SD = 1.20$) compared to the standard stimuli ($M = 0.56$ μV, $SD = 0.93$), ($t(144) = -11.23$, $P < .001$ (one-sided), $d = 1.330$). The mean amplitude difference was −1.24 μV, $SD = 1.33$, 95% *CI* [−1.46, −1.02]. Regarding a difference in the intensities within a stimulus type, the responses were larger for the high-intensity standard stimuli ($M = 0.77$ μV, $SD = 0.95$) compared to the low-intensity standard stimuli ($M = 0.56$ μV, $SD = 0.93$), ($t(144) = 2.65$, $P = .009$ (two-sided), $d = 0.215$). The mean amplitude difference was 0.20 μV, $SD = 0.92$, 95% *CI* [0.05, 0.35]. Instead, there was no statistically significant difference between responses to the high-intensity deviant stimuli ($M = -0.86$ μV, $SD = 1.64$) and low-intensity deviant stimuli ($M = -0.68$ μV, $SD = 1.20$), ($t(144) = -1.37$, $P = .173$ (two-sided), $d = 0.114$, $BF_{10} = 0.230$). There were no other main or interaction effects (Table 3).

When controlling for age, the main effect of stimulus type (standard vs. deviant) remained significant ($F[1,142] = 64.22$, $P < .001$, $\eta^2_p = 0.311$) while the interaction effect of stimulus type × intensity was non-significant ($F(1,142) = 0.74$, $P = .392$, $\eta^2_p = 0.005$).

3.1.2 | Auditory P3a

For the auditory P3a, a repeated measures ANOVA with within-subject variables stimulus type (standard vs. deviant) and intensity (high vs. low) and a between-subjects variable group (depressed vs. control) showed a main effect of stimulus type ($F[1,143] = 96.76$, $P < .001$, $\eta^2_p = 0.404$). The responses were larger for the deviant stimuli ($M = 0.46$ μV, $SD = 0.89$) compared to the

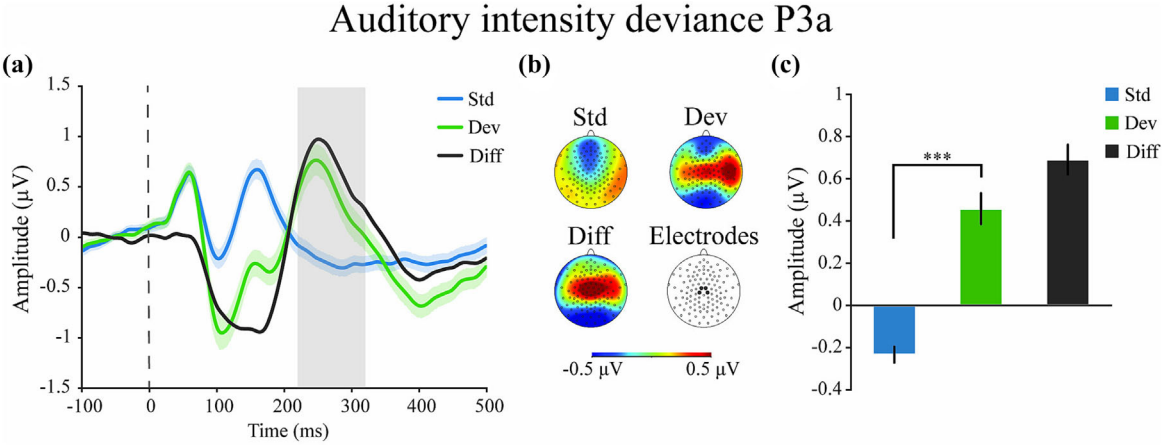

FIGURE 2 Auditory intensity deviance P3a averaged over the depressed and control groups. (a) Grand-averaged waveforms to deviant (Dev) and standard (Std) stimuli (averaged over the intensities) and a differential waveform (deviant minus standard; Diff). Waveforms represent averages of the electrode pools applied in the analyses. The grey rectangle shows the analysis window for aP3a (220–320 ms). (b) The topographical maps of grand averaged responses to standard and deviant stimuli and differential response. The electrodes applied in the analysis are marked in the figure (electrodes). (c) Bar chart represents mean amplitudes for responses to standard and deviant stimuli and differential response (averaged over the intensities and electrodes applied in the analysis). Error bars represent the standard error of the mean. ***$P < .001$. The P-values reflect the post hoc t-test results.

standard stimuli ($M = -0.23$ μV, $SD = 0.46$). The mean amplitude difference was 0.69 μV, $SD = 0.84$, 95% CI [0.55, 0.83]. No other main or interaction effects were observed (Table 3). A repeated measures ANCOVA showed that the main effect of stimulus type remained significant when controlling for age ($F(1,142) = 28.73$, $P < .001$, $\eta^2_p = 0.168$). The results of the auditory P3a are illustrated in Figure 2.

3.1.3 | Auditory N1 intensity dependence responses

An independent samples t-test showed that auditory N1 intensity dependence responses were larger in the depressed group ($M = -0.37$ μV, $SD = 1.08$) than in the control group ($M = 0.0003$ μV, $SD = 1.03$) ($t(143) = 2.09$, $P = 0.037$ (two-sided), $d = 0.352$). The mean amplitude difference was −0.37 μV, $SD = 0.18$, 95% CI [−0.72, −0.02]. When age was controlled, a univariate ANCOVA showed that the effect of the group (depressed vs. control) was non-significant ($F(1,142) = 3.25$, $P = .074$, $\eta^2_p = 0.022$).

When comparing a group of medicated depressed participants, a group of unmedicated depressed participants, and a control group in N1 intensity dependence response, a one-way ANOVA showed a significant group effect ($F[2,142] = 3.833$, $P = .024$, $\eta^2_p = 0.051$). Follow-up pairwise comparisons (Bonferroni test) showed that the unmedicated depressed group had larger N1 intensity dependence responses ($M = -0.59$ μV, $SD = 0.86$) compared to the control group ($M = 0.0003$ μV, $SD = 1.03$), $P = .020$. No differences in N1 intensity dependence responses were found between the medicated depressed group ($M = -0.12$ μV, $SD = 1.23$) and the control group ($P = 1.000$, $BF_{10} = 0.250$) or between the medicated depressed group and the unmedicated depressed group ($P = .229$, $BF_{10} = 0.931$). The mean amplitude difference in N1 intensity dependence response between the unmedicated depressed group and the control group was −0.59 μV, 95% CI [−1.11, −0.07]. The results are shown in Figure 3. When age was controlled, a univariate ANCOVA showed that the effect of group (medicated depressed participants vs. unmedicated depressed participants vs. controls) was non-significant ($F[2,141] = 2.44$, $P = .091$, $\eta^2_p = 0.033$).

In the whole sample, there was a significant negative correlation between N1 intensity dependence response and BDI-II score ($rs = -0.204$, $P = .028$, $n = 145$). When correlations were calculated separately for the depression group and non-depressed control group, there were no significant correlations between N1 intensity dependence response and BDI-II score in either the depression group ($rs = -0.037$, $P = .774$, $n = 63$) or control group ($rs = -0.091$, $P = .498$, $n = 82$). In the whole sample, a significant negative correlation was found between N1 intensity dependence response and age ($rs = -0.294$, $P = .002$ $n = 145$). When correlations were calculated separately for the depression group and non-depressed control group, a significant negative correlation between N1 intensity dependence response and age was found only in the non-depressed control group ($rs = -0.353$,

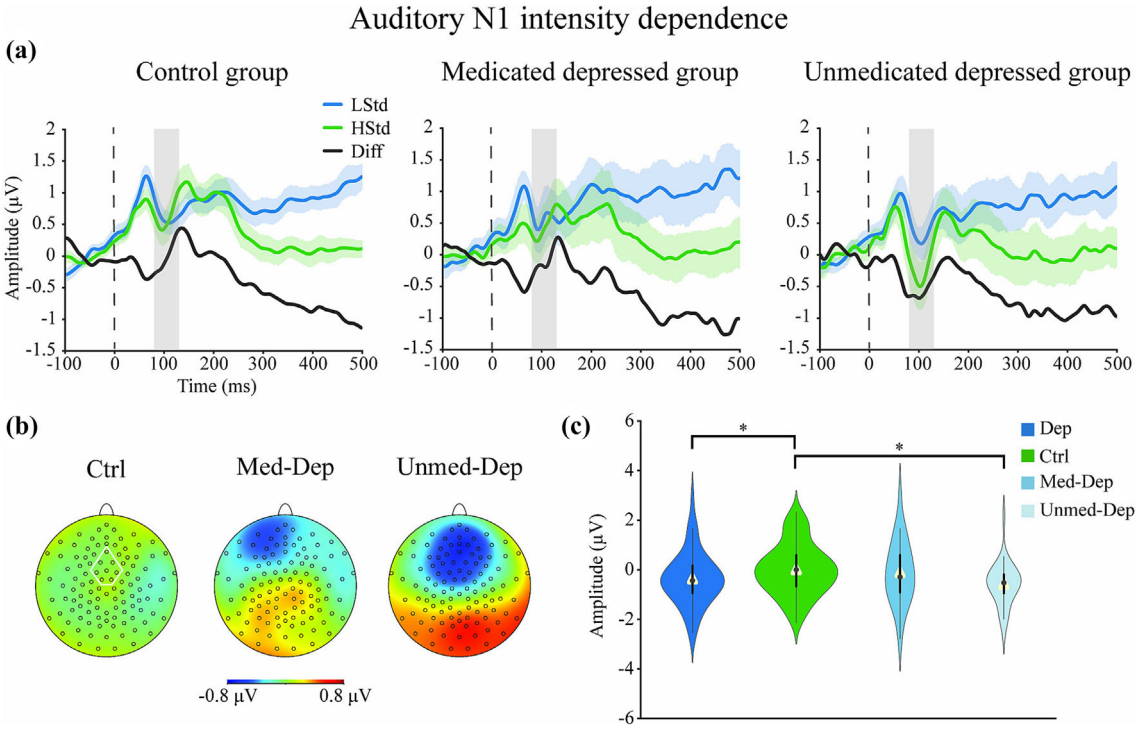

FIGURE 3 Auditory N1 intensity dependence response in the group of medicated depressed participants (Med-Dep), unmedicated depressed participants (Unmed-Dep) and non-depressed controls (Ctrl). (a) Grand-averaged waveforms to low-intensity standard (LStd), high-intensity standard (HStd) and a differential waveform (high-intensity standard minus low-intensity standard, Diff). Waveforms represent averages of the electrode pools applied in the analyses. The grey rectangle shows the analysis window for N1 (80–130 ms). (b) The topographical maps that represent the intensity dependence response (differential response) are shown as average voltages over the analysis time window for N1. (c) Violin plot for the N1 intensity dependence response amplitude showing the statistical results of independent sample *t*-test (Dep vs. Ctrl) and one-way ANOVA (Ctrl vs. Med-Dep vs. Unmed-Dep). The outline of the violin illustrates the distribution of N1 intensity dependence response estimates using kernel density curves. The bandwidth for the kernel density is determined according to Scott's rules. The size of the violin shape depends on the number of participants. Within the interior of the violin, boxplots are displayed in black. Grey dots on the boxplots represent the median of the response, and yellow triangles indicate the mean of the responses. The lower and upper adjacent values of the boxplots are calculated as 1.5 times the interquartile range. $^*P < .05$.

$P = .003$, $n = 82$), while there was no statistically significant correlation in depression group ($rs = -0.197$, $P = .182$, $n = 63$). The results of the correlations are shown in Figure 4.

3.2 | Somatosensory ERPs

3.2.1 | Somatosensory MMR

For the somatosensory MMR (Figure 5), a repeated measures ANOVA with a within-subject variable stimulus type (standard vs. deviant) and a between-subject variable group (depressed vs. control) showed a main effect of stimulus type ($F[1,120] = 31.49$, $P < .001$, $\eta^2_p = 0.208$). The responses were larger for the deviant stimuli ($M = 0.47$ μV, $SD = 0.67$) compared to the standard stimuli ($M = 0.11$ μV, $SD = 0.33$). The mean amplitude difference was 0.36 μV, $SD = 0.62$, 95% *CI* [0.25, 0.47]. There were no other main or interaction effects (Table 3). A repeated measures ANCOVA showed that the main effect of stimulus type remained significant when controlling for age ($F[1,119] = 4.38$, $P = .038$, $\eta^2_p = 0.035$).

3.2.2 | Somatosensory P3a

For the somatosensory P3a (Figure 5), a repeated measures ANOVA with a within-subject variable stimulus type (standard, deviant) and a between-subjects variable group (depressed, control) showed a main effect of stimulus type ($F[1,120] = 38.09$, $P < .001$, $\eta^2_p = 0.241$). The responses were larger for the deviant stimuli ($M = 0.49$ μV, $SD = 0.71$) compared to the standard stimuli ($M = 0.06$ μV, $SD = 0.36$). The mean amplitude difference was 0.43 μV, $SD = 0.74$, 95% *CI* [0.29, 0.56]. No other main effects or interaction effects were found (Table 3). A repeated measures ANCOVA showed that

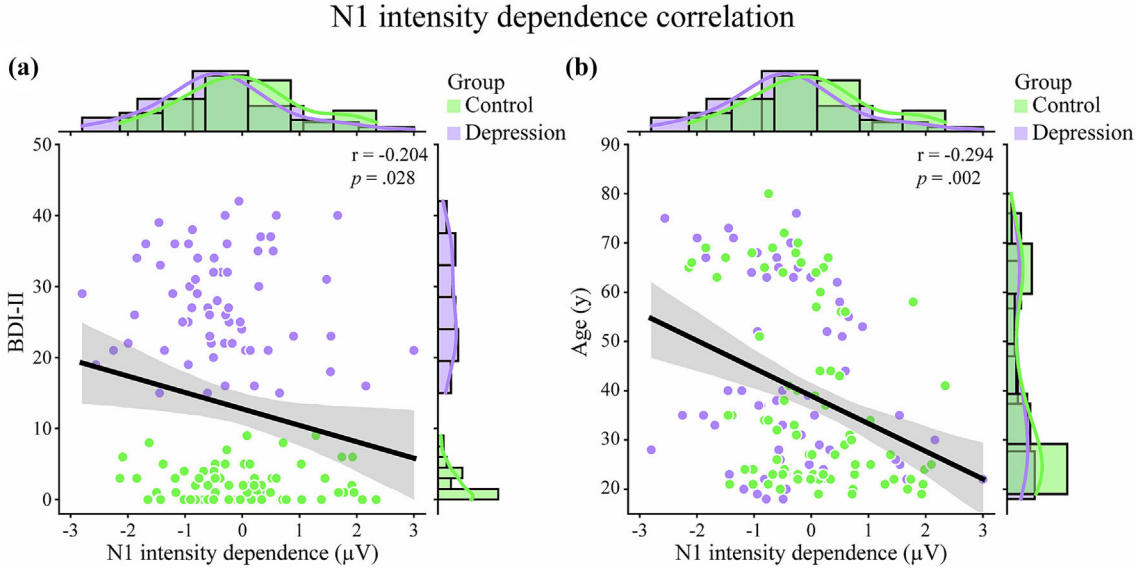

FIGURE 4 Scatterplots with marginal histograms showing (a) correlation (Spearman's rho) between auditory N1 intensity dependence response and BDI-II score and (b) correlation between auditory N1 intensity dependence response and age. Linear regression fits are depicted as lines over the scatterplots, with grey shadows indicating a 95% confidence interval used to estimate the central tendency for discrete values of N1 intensity dependence. Curves on the marginal histograms represent the kernel density estimate of the distribution.

the main effect of stimulus type remained significant when controlling for age ($F[1,119] = 19.05$, $P < .001$, $\eta^2_p = 0.138$).

3.2.3 | Somatosensory P50 and N80

When somatosensory P50 and N80 amplitudes and latencies in response to standard and deviant stimuli were compared by an independent samples *t*-test between the group of depressed participants and the non-depressed control group, no between-group differences in P50 or N80 amplitudes or latencies were found (all $P \geq .216$, all $BF_{10} \leq .998$). The results are shown in Figure 6.

Both components were robustly elicited for standard and deviant stimuli. This was investigated by one-sample *t*-tests (one-sided) showing that the peak amplitude values differed from zero: P50 to standard stimuli ($M = 0.74$ μV, $SD = 0.64$; $t[121] = 12.78$, $P < .001$, $d = 0.637$); P50 to deviant stimuli ($M = 0.98$ μV, $SD = 0.82$; $t[121] = 13.23$, $P < .001$, $d = 0.816$); N80 to standard stimuli ($M = -0.46$ μV, $SD = 0.37$; $t[121] = -13.71$, $P < .001$, $d = 0.372$), and N80 to deviant stimuli ($M = -0.66$ μV, $SD = 0.65$; $t[121] = -11.26$, $P < .001$, $d = 0.645$).

4 | DISCUSSION

This study investigated whether there are differences in the amplitudes of auditory MMN, P3a and N1 intensity dependence ERP components as well as in the amplitudes of somatosensory MMR and P3a components, and the amplitudes and latencies of somatosensory P50 and N80 components between a group of participants with depression and a non-depressed control group. In addition, a relationship between the amplitude of N1 intensity dependence response and depression severity was explored. We found that the N1 intensity dependence response was heightened in unmedicated depressed participants compared to non-depressed controls. Additionally, the N1 intensity dependence response was correlated with depression severity across the entire sample. Next, we discuss the results in detail.

4.1 | Auditory N1 intensity dependence response

Consistent with our hypothesis, we found an increased N1 intensity dependence response amplitude in the depressed group compared to non-depressed controls, suggesting an altered function of the serotonergic neurotransmission in depression (e.g., Hegerl & Juckel, 1993). However, age had an impact on this result; when age was controlled, the depression effect was only at a trend level. This may be, at least partly, due to the relatively small sample size. Additionally, we found a correlation between the N1 intensity dependence response and the severity of depressive symptoms, as measured by the BDI-II score, across the whole sample: a larger N1

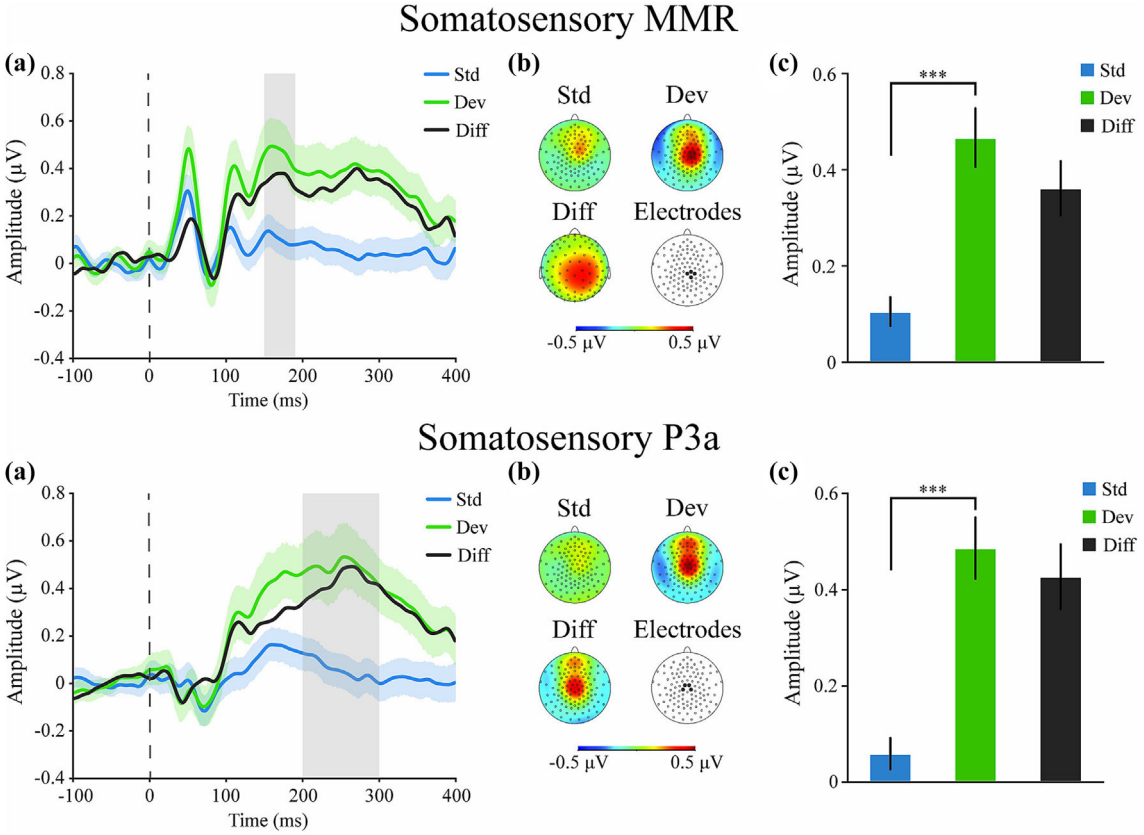

FIGURE 5 Somatosensory location deviance MMR and P3a averaged over the depressed and control groups. (a) Grand-averaged waveforms to deviant (Dev) and standard (Std) stimuli (averaged over the locations) and a differential waveform (deviant minus standard; Diff). Waveforms represent averages of the electrode pools applied in the analyses. The grey rectangle shows the analysis window for sMMR (150–190 ms) and sP3a (200–300 ms). (b) The topographical maps of grand averaged responses to standard and deviant stimuli and differential response. The electrodes applied in the analysis are marked in the figure (electrodes). (c) Bar chart represents mean amplitudes for responses to standard and deviant stimuli and differential responses (averaged over the locations and electrodes applied in the analysis). Error bars represent the standard error of the mean. ***$P < .001$. The P-values reflect the post hoc t-test results.

intensity dependence response was associated with greater severity of depressive symptoms.

Our result aligns with a few previous studies in which an increased auditory intensity dependence response has been found in depressed patients (Gopal et al., 2004; Ip et al., 2023; Medvedeva et al., 2023; difference only between depressed patients with diabetes and controls: Manjarrez-Gutierrez et al., 2009). However, it is important to note that previous studies have yielded inconsistent results regarding differences in auditory intensity dependence response between depressed and non-depressed groups; also, attenuated intensity dependence response amplitude in the depressed group has been observed (Fitzgerald et al., 2009; Gallinat et al., 2000; Jang et al., 2022; Jang et al., 2023; Kim et al., 2019; Kim et al., 2021; Ostermann et al., 2012) and in some studies, no differences in intensity dependence response between depressed patients and controls have been reported (Graßnickel et al., 2015; Hwang et al., 2021; Jaworska et al., 2012; Linka, Sartory, Wiltfang, & Müller, 2009; Obermanns et al., 2022; Park et al., 2010; Ruohonen, Kattainen, et al., 2020; Uhl et al., 2011).

The discrepancy between the findings of auditory intensity dependence response studies may partly be because the inclusion criteria for depressed participants varied regarding the factors that could potentially influence intensity dependence response. These factors include antidepressant medication (e.g., Gopal et al., 2004), suicidality (e.g., Chen et al., 2005; Cho et al., 2023; Hwang et al., 2021; Kim & Park, 2013; Uhl et al., 2012; for a review, see Park, 2015), depression severity (e.g., Kim et al., 2019; Obermanns et al., 2022) and comorbid disorders (e.g., Kim et al., 2019; Manjarrez-Gutierrez et al., 2009) as well as demographic factors such as gender (e.g., Jaworska et al., 2012; Oliva et al., 2011) and age (e.g., Jang et al., 2022; Ruohonen, Kattainen, et al., 2020). Also, in our study, age affected N1 intensity dependence response results. The variability of the previous findings may also reflect the heterogeneity of depression with multiple subtypes and underlying

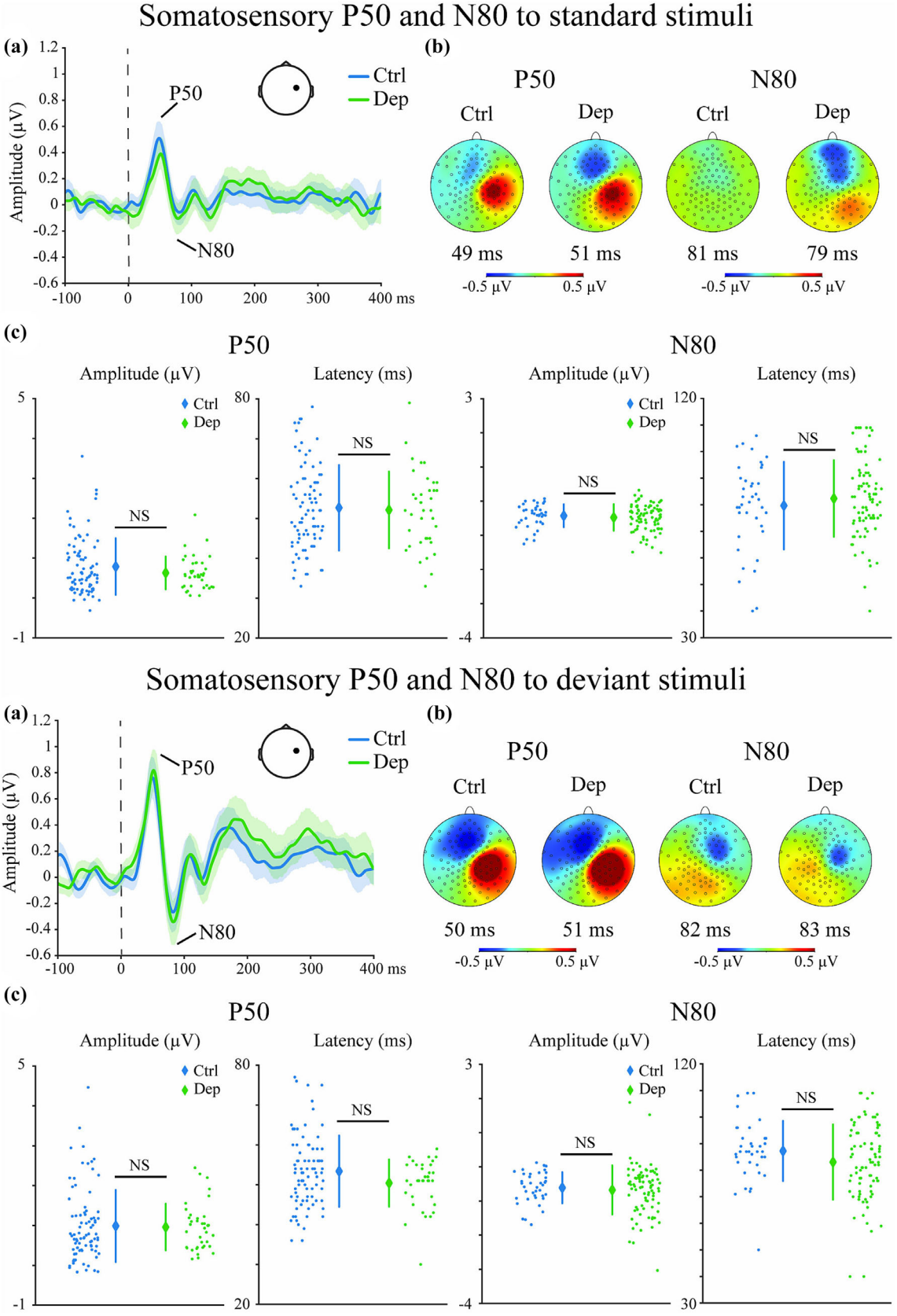

FIGURE 6 Legend on next page.

FIGURE 6 Somatosensory P50 and N80 responses to standard and deviant stimuli in the group of depressed participants (Dep) and non-depressed control group (Ctrl). The group differences were non-significant, and the groups are shown separately for illustrative purposes only. (a) Grand-averaged waveforms to standard/deviant stimuli (averaged over the locations) for the depressed and control groups. The electrode applied in the analysis is marked in the figure above the waveforms. (b) Topographical maps show grand averaged P50 and N80 peaks in depressed and control groups. The time shows the peak latency of the grand averaged responses. (c) Strip plots show individuals' values for P50 and N80 amplitudes and latencies. Next to the strip plot, the diamond point shows the mean values and the error bar indicates the standard deviation.

neural mechanisms. For instance, melancholic depression and atypical depression seem to have opposite characteristics in terms of the strength of intensity dependence response (Fitzgerald et al., 2009; Lee et al., 2014). It is obvious that in addition to serotonin, which is suggested to be reflected by intensity dependence response, other neurotransmitters, not only other monoamines (noradrenaline and dopamine) but also glutamate and gamma-aminobutyric acid, contribute to the development and maintenance of depressive disorders (for reviews, see Belujon & Grace, 2017; Duman et al., 2019; Malhi et al., 2005; Moret & Briley, 2011). Various subtypes of depression and depressive symptoms may differ in terms of neurotransmitter functions (Malhi et al., 2005). Inconsistencies in previous findings may also be due to methodological heterogeneity in prior research. The methods used to measure the auditory intensity dependence response varied in terms of which ERP components were used and whether the intensity dependence response was derived from scalp electrodes or from source estimation. For instance, akin to our study, Gopal et al. (2004) and Medvedeva et al. (2023) identified an increased intensity dependence response through scalp electrodes. Instead, Ip et al. (2023) explored both scalp and source-derived responses, observing an increased intensity dependence response only when the response was derived from source estimation. Similarly, Manjarrez-Gutierrez et al. (2009) found an increased source-derived intensity dependence response.

In our investigation, we examined the N1 intensity dependence response using an oddball condition as a difference in N1 amplitude in response to low-intensity standard sounds and high-intensity standard sounds. Similarly, Gopal et al. (2004) calculated intensity dependence by comparing the responses elicited by sound stimuli of the highest and lowest levels of intensity. Their study demonstrated a significantly higher amplitude growth in N1/P2 component and brainstem response peak V among unmedicated depressed participants compared to controls, while there were no differences between medicated depressed participants and controls. Consistent with Gopal et al.'s (2004) findings, our study only detected a significant difference between the group of unmedicated depressed participants and the group of non-depressed controls, which is in line with our hypothesis. However, as mentioned before, in our study, age impacted this result; when we controlled for age, the group effect was only at a trend level. Furthermore, in the studies by Medvedeva et al. (2023) and Ip et al. (2023), in which an increased auditory intensity dependence response was identified in depressed patients, the participants were unmedicated. Hence, the intensity dependence response may, indeed, reflect neurotransmitter activity in depression. This is supported by the fact that medication tends to normalise neurotransmitter levels in medicated patients with depression, and we found no group difference between depressed participants with medication and control participants in the intensity dependence response.

It is worth noting that our results cannot be directly compared to those of Gopal et al. (2004) due to variations in medication profiles. In Gopal et al.'s (2004) study, all medicated depressed participants were on SSRI medication. In contrast, our study encompassed medicated participants who had antidepressants of different classes as well as combinations of different antidepressants and quetiapine and benzodiazepines. Therefore, it is crucial to notice that the medications in our study were not restricted solely to antidepressants modulating serotonergic neurotransmission. Nonetheless, a majority of the medicated participants in our study were taking medication that affects serotonergic functioning, even if they also had medications acting through other neurotransmitter systems. Our findings suggest that medication may normalise the N1 intensity dependence response in depressed patients. In line with this suggestion, a few studies conducted with healthy adults have demonstrated a decrease in intensity dependence response following the administration of a single dose of an SSRI (Nathan et al., 2006; Segrave et al., 2006), as well as chronic SSRI administration (Simmons et al., 2011). However, conflicting findings exist, as neither acute SSRI administration (Guille et al., 2008; Oliva et al., 2010; Uhl et al., 2006) nor acute serotonin depletion (Debener et al., 2002; Dierks et al., 1999; Massey et al., 2004; Norra et al., 2008) had an impact on intensity dependence response in healthy adults. Regarding depressed patients, several studies have shown no difference between pre-treatment and

post-treatment intensity dependence response in depressed patients medicated with SSRIs (Gallinat et al., 2000; Ip et al., 2023; Linka, Sartory, Wiltfang, & Müller, 2009) or SNRIs (selective serotonin noradrenaline reuptake inhibitor: Ip et al., 2023). Furthermore, the intensity dependence response of depressed patients taking SSRIs did not differ from that of depressed patients not taking any antidepressants (Min et al., 2012). Consequently, while our findings regarding N1 intensity dependence response and antidepressant medication in depressed patients align with the theory of intensity dependence as an ERP component reflecting central serotonergic activity, previous empirical evidence on the impact of antidepressants on intensity dependence response indicates an intricate relationship, rather than a straightforward and unambiguous conclusion.

In our study, N1 intensity dependence response correlated with depression severity across the whole sample: the larger the response, the more severe the depressive symptoms. Based on the assumption that a larger N1 intensity dependence response implicates a lower central serotonergic functioning (Hegerl & Juckel, 1993), the correlation results may indicate that the downregulation of serotonin neurotransmission could induce an increase in the severity of depressive symptoms. However, the correlation between depression scores and N1 intensity in the whole sample should be treated with caution, as participants were recruited into two groups based on their depression scores. When the depression group and control group were investigated separately, no significant correlations between N1 intensity dependence response and depression severity were observed in either group. One potential explanation for the absence of correlations in separate group analyses could be attributed to the relatively small sample size. In previous studies, correlations between intensity dependence response and depression severity have typically been examined only within the group of depressed participants. The findings have been inconsistent. In accordance with our findings, no correlation between intensity dependence response and depression severity has been found in a group of depressed patients in several studies (Fitzgerald et al., 2009; Gallinat et al., 2000; Jang et al., 2022; Juckel et al., 2007; Park et al., 2010). A few previous studies have demonstrated a positive relationship between intensity dependence response and the severity of depression in depressed participants (Kim et al., 2019; Obermanns et al., 2022; Ostermann et al., 2012), which is congruent with our finding regarding the correlation within the sample comprising both depressed and non-depressed participants. Also, in some studies, a negative correlation has been reported in depressed patients (Jaworska et al., 2012; Park & Lee, 2013). Our correlation results cannot be directly compared to those of previous studies because, in our study, the investigation of intensity dependence was based on N1 response, whereas in the previous studies in which correlations have been explored, intensity dependence investigations were based on N1/P2 component. Moreover, measures to investigate depression severity varied across the studies. Overall, due to the different methodological choices and incongruent results of previous studies, conclusions on whether intensity dependence response is more likely a state or a trait marker of depression cannot be drawn. To address this issue and gain a better understanding, future research should consider longitudinal studies with multiple assessments.

As background information, we investigated the correlation between N1 intensity dependence response and age within the whole sample as well as separately in the depression group and non-depressed control group. This investigation was motivated by previous studies that have indicated an age-related decrease in serotonergic functioning in older adults with depression (e.g., Meltzer et al., 1998). Furthermore, a study by Ruohonen, Kattainen, et al. (2020) reported a larger N1 intensity dependence response in a group of older adults compared to a group of younger adults (both groups included depressed and non-depressed participants). In line with the results by Meltzer et al. (1998) and Ruohonen, Kattainen, et al. (2020), we found a correlation between age and the N1 intensity dependence response across the whole sample, indicating that the response becomes larger with increasing age. However, when the depression group and control group were investigated separately, a significant correlation was found only in the non-depressed control group, while in the depression group, no significant correlation was observed. Our result regarding depression group aligns with studies by Gallinat et al. (2000), Juckel et al. (2007), Linka et al. (2007) and Linka, Sartory, Gastpar, et al. (2009) in which no relationship between intensity dependence response and age has been found in a group of participants with depression. In contrast, Jang et al. (2022) found a positive correlation between age and intensity dependence response in a group of depressed participants, but in their study, no such correlation was found among non-depressed control participants. Additionally, Min et al. (2012) found gender-specific associations, where higher age was linked to weaker intensity dependence response in female participants with depression and stronger intensity dependence response in male participants.

Taken together, our results indicate increased N1 intensity dependence response in the depressed group compared to non-depressed controls. More specifically, this increased response was observed only in the subgroup of depressed participants who were not taking

antidepressants relative to the non-depressed controls. Furthermore, N1 intensity dependence response correlated with depression severity across the whole sample. A larger N1 intensity dependence response was associated with greater severity of depressive symptoms. These findings support our initial hypothesis that the N1 intensity dependence response may be altered in depressed patients, as this response is suggested to reflect central serotonergic functions (Hegerl & Juckel, 1993), and serotonin is considered an important neurotransmitter in the pathophysiology of depression (e.g., Lin et al., 2014). However, it is important to interpret these results cautiously. Some studies suggest that serotonin may not be a significant neurotransmitter in depression (for a review, see Moncrieff et al., 2023). Moreover, when it comes to the association between intensity dependence and serotonin, most of the evidence comes from animal studies (e.g., Juckel et al., 1997; Juckel et al., 1999; Manjarrez et al., 2005; Wutzler et al., 2008), while findings in human studies have been more inconsistent (e.g., Debener et al., 2002; Dierks et al., 1999; Guille et al., 2008; Kähkönen et al., 2002; Massey et al., 2004; Nathan et al., 2006; Norra et al., 2008; Oliva et al., 2010; Segrave et al., 2006; Simmons et al., 2011; Uhl et al., 2006). Additionally, the intensity dependence response may be modulated by multiple neurotransmitter systems beyond the serotonergic system (e.g., glutamatergic system: O'Neill et al., 2007; Teichert, 2017; dopaminergic system: Juckel et al., 2008; Lee et al., 2011). To draw more conclusive conclusions about the relationship between the intensity dependence response and depression, further research is needed. Future research should investigate the connection between intensity dependence and various neurotransmitter systems, as well as explore the central serotonergic functioning in depressed patients. Only through a comprehensive understanding of these factors might it be possible to elucidate the link between intensity dependence and depression.

4.2 | Auditory MMN and P3a

Contrary to our hypothesis, no depression-related modulations were observed in the MMN response. However, MMN was elicited for both high- and low-intensity stimuli similarly, as could be expected (e.g., Näätänen et al., 2007). Sound intensity as a physical property of the stimulus did not affect the amplitude of the deviant response, indicating that responses to deviant stimuli reflect deviance detection per se. Our finding of no group difference in MMN is in line with some previous studies investigating intensity deviance MMN, where no differences between depressed and non-depressed groups were found (Mu et al., 2016; Ruohonen & Astikainen, 2017; Ruohonen et al., 2020b). However, this finding is contrasted by a study by Bissonnette et al. (2020) in which an increased intensity deviance MMN amplitude in depressed patients compared to non-depressed controls was observed. It is important to note that the stimulus conditions in these intensity deviance MMN studies varied. In the present study, as well as in the studies by Ruohonen and Astikainen (2017) and Ruohonen, Kattainen et al. (2020), an ignore oddball condition with sinusoidal sounds of two different intensities was applied. Conversely, Mu et al. (2016) and Bissonnette et al. (2020) utilised an ignore multi-feature paradigm with multiple deviant tone types. Also, in the study by Mu et al. (2016), MMN was measured to musical sound features instead of simple auditory stimuli. Thus, due to these methodological differences, direct comparisons between the findings of these intensity deviance MMN studies cannot be made.

Contrary to our expectations, we did not observe any depression-related effects on the auditory P3a component. This finding aligns with the results of the study by Kähkönen et al. (2007) but contrasts with previous studies that have found an attenuated aP3a amplitude in the group of depressed adults compared to controls (Chen et al., 2015; Xu et al., 2014). However, it is worth noting that stimulus conditions differed between our study and previous studies. In our study, we applied an intensity deviance oddball condition, whereas Kähkönen et al. (2007) employed an oddball condition with frequency deviance and with novel stimuli, Chen et al. (2015) used a duration deviance oddball condition and Xu et al. (2014) applied an oddball condition with 60 dB deviant stimuli and 0 dB (no sound, i.e., stimulus omission) standard stimuli.

In sum, we expected that an intensity deviance oddball condition might be suitable for revealing depression-related alterations in aMMN and aP3a as prior research has associated the processing of sound intensity with serotonergic functioning (Hegerl et al., 2001), which may be pertinent to depression (e.g., Kraus et al., 2017). Furthermore, drawing from predictive coding impairments in depression (e.g., Kube et al., 2020) and the idea of aMMN and aP3a as indicators of prediction errors in predictive coding theory (e.g., Friston, 2005), we hypothesised that the amplitudes of these responses might be altered in depressed participants. Contrary to our assumption, our results do not suggest that auditory intensity deviance MMN and P3a are suitable tools for investigating deficits in predictive coding functions in participants with depression.

4.3 | Somatosensory ERPs

We hypothesised that somatosensory MMR, P3a, P50 and N80 components might be altered in depression since depression contains a variety of somatic symptoms, including pain symptoms (for reviews, see Bair et al., 2003; Lépine & Briley, 2004). These somatic symptoms suggest that some disruptions in somatosensory processing may occur in depressed patients. However, contrary to our expectations, we did not observe any depression-related modulations in these somatosensory ERPs. These findings align with the findings of a MEG study in which no between-group differences were found in P60 or N20 components (Kurita et al., 2016) as well as an EEG study in which no between-group differences were found in the P1 component (Dietl et al., 2001). On the other hand, our results contrast with the results by Dietl et al. (2001) concerning the amplitudes of somatosensory P200 and P300 which were found to be higher in depressed patients compared to controls. However, there were differences in stimulus conditions and the specific ERP components investigated across these somatosensory ERP studies. In addition, in the present study, the mean age of the participants was relatively high (depressed participants 54.2 years, controls 52.4 years), which may have had an impact, especially on the sMMR results since previous research has identified attenuated sMMR in older adults compared to younger adults (Strömmer et al., 2017).

4.4 | Limitations and future directions

This study has some limitations that should be considered when interpreting the results. First, the sample size was relatively small, which may have impacted the statistical power of certain analyses, such as univariate ANCOVAs and correlation analyses.

Secondly, in the present study, all the depressed participants did not have a formal diagnosis of depressive disorder. Regarding auditory data, 49 out of 63 depressed participants reported a diagnosis of a depressive disorder, while for the somatosensory data, 30 out of 38 depressed participants reported a diagnosis of a depressive disorder. The inclusion criterion for the depressed participants was current depressive symptoms, as measured with a self-report questionnaire BDI-II. However, the BDI-II scores did not differ significantly between participants with a depressive disorder diagnosis and participants without the diagnosis in either the auditory or somatosensory experiments. Importantly, we did not consider the heterogeneity of depressive disorder; our sample may have included depressed participants with different subtypes of depression. Previous studies on aMMN, aP3a and auditory intensity dependence response have found a difference between depressed and non-depressed participants when specific subtypes of depression were investigated (e.g., first-episode depression: Chen et al., 2015; Qiao et al., 2013, 2015; treatment-resistant depression: He et al., 2010; Xu et al., 2014; melancholic depression: Chen et al., 2015; Fitzgerald et al., 2009; depression with suicidality: Kim et al., 2021). Hence, it is possible that depression-related modulations also in aMMN and aP3a components might have been observed if our study had a more homogeneous sample consisting solely of participants with a specific subtype of depression.

Regarding somatosensory ERPs, in the present study, the degree of pain symptoms or other somatic symptoms in depressed participants was not investigated. Consequently, conclusions could not be drawn on whether the pain symptoms or other somatic symptoms in depressed patients are related to somatosensory ERP amplitudes. Future studies are needed to address this issue.

Also, there was an uneven gender distribution, with the significant majority of the participants being female in both depressed and non-depressed groups within the auditory and somatosensory experiments. Therefore, our results cannot unconditionally be generalised to both genders. However, there were no significant differences between the depression group and the non-depressed control group in terms of gender distribution.

Thirdly, our sample had both medicated and unmedicated depressed participants (auditory data: 29 medicated, 34 unmedicated, somatosensory data: 17 medicated, 21 unmedicated). The participants had diverse antidepressant medications as well as combinations of antidepressants, benzodiazepines and quetiapine. It is important to note that we did not control for the effect of antidepressants on the results of auditory MMN and P3a. Previous studies investigating the serotonergic modulation of MMN amplitude have provided inconsistent findings (e.g., Ahveninen et al., 2002; Kähkönen et al., 2005; Kuang et al., 2016; Leung et al., 2010; Oranje et al., 2008; Pan et al., 2020; Wienberg et al., 2010). Studies on the effect of serotonin on P3a are scarce (e.g., Ahveninen et al., 2002; Heitland et al., 2013). The use of antidepressants may be a confounding factor when investigating MMN and P3a in patients with depression. Therefore, in future studies, it is crucial to endeavour to distinguish the effects of antidepressants from the effects of depression itself on MMN and P3a. Furthermore, regarding N1 intensity dependence response, the use of antidepressants, especially SSRIs, is an essential potential confounder because intensity dependence response is suggested to reflect central serotonergic functions

(e.g., Hegerl et al., 2001). It would be better to either include only medication-free participants or investigate whether the use of SSRIs has an impact on N1 intensity dependence response. In the present study, a limitation was that medication was not restricted to antidepressants that specifically affect serotonergic neurotransmission. In future studies focusing on N1 intensity dependence, it would also be essential to compare non-depressed control participants, unmedicated depressed participants and depressed participants who use antidepressants that selectively target the serotonergic system.

Last, our analysis focused mainly on the amplitude (and latency) of the ERP components. We did not have magnetic resonance imaging (MRI) images of the brain structure of the participants, so we could not examine group differences in the sources of brain activity. Given the wide age range of the participants, the same head models would not have been suitable for all participants.

5 | CONCLUSION

In conclusion, our results indicated increased N1 intensity dependence response in the depressed group compared to controls. More specifically, N1 intensity dependence response was increased only in the group of depressed participants who were unmedicated relative to non-depressed controls. Our results indicate a potential association between the N1 intensity dependence response and neurotransmitter activity in depression, although it is important to note that serotonin may not be the sole contributing factor. Furthermore, N1 intensity dependence response correlated with depression severity across the whole sample consisting of depressed participants and non-depressed controls.

Contrary to our assumption, we did not observe any depression-related alterations in MMN/MMR or P3a. Thus, our results suggest that auditory intensity deviance MMN and P3a, as well as somatosensory location deviance MMR, may not be suitable tools for the investigations of deficits in predictive coding functions in depressed patients. Regarding somatosensory ERPs, our results did not reveal any depression-related alterations. Heterogeneous symptom profiles and the use of medication among depressed participants may be one reason for the absence of depression-related effects in auditory MMN, P3a and somatosensory responses.

AUTHOR CONTRIBUTIONS

Elina S. Kangas: Conceptualisation; methodology; validation; formal analysis; investigation; data curation; writing-original draft; writing-review & editing; project administration; funding acquisition. Xueqiao Li: Conceptualisation; methodology; formal analysis; software; investigation; writing-review & editing; visualisation. Elisa Vuoriainen: Conceptualisation; methodology; investigation; writing-review & editing; funding acquisition. Sari Lindeman: Writing-review & editing; project administration; funding acquisition. Piia Astikainen: Conceptualisation; methodology; investigation; writing-review & editing; supervision; project administration; funding acquisition.

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ETHICAL STATEMENT

The experiments were conducted in accordance with the Declaration of Helsinki. Ethical approval for the study was obtained from the ethical committee of the Central Finland Health Care District. Written informed consent was obtained from all of the participants prior to their participation.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/ejn.16569.

DATA AVAILABILITY STATEMENT

The raw data are not publicly available due to legal restrictions. The data that support the findings of this study are available upon reasonable request from Piia Astikainen (piia.astikainen@jyu.fi).

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