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Elisa Ruohonen

Electrophysiological Brain Responses as Neural Markers of Depression and Aging

UNIVERSITY OF JYVÄSKYLÄ
FACULTY OF EDUCATION AND PSYCHOLOGY

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ABSTRACT

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Depression is one of the most common mental disorders. Currently, the diagnosis of depression is based on a clinical interview, and no reliable objective depression biomarkers have been recognized. Brain's event-related potentials (ERPs) could potentially be used as neural markers for diagnosing and planning treatment options for depression. ERPs could also potentially be used to differentiate depression-related alterations from aging-related alterations. In study I, ERPs to sound intensity changes were compared between first-episode and recurrent depression groups and non-depressed controls. Larger brain responses (N1 response) to rare sounds were found in the first-episode depression group, compared to the other groups. Sound intensity processing has been suggested to reflect monoaminergic neurotransmission and therefore the enlarged responses can reflect monoaminergic deficits. In study II, ERPs to sound intensity changes were compared between younger and older depressed adults and age-matched non-depressed adults. Augmented N1 responses were found in both older adults and depressed adults, indicating similar effects for aging and depression on intensity processing. The augmentation could index an inability to suppress activity in response to irrelevant stimuli (also called sensory gating). In study III, ERPs to emotional facial expressions were compared between depressed and non-depressed groups. In addition, changes in the brain responses were investigated by conducting follow-up measurements after 2 and 39 months. It was also investigated whether the baseline brain responses were associated with later response to a brief psychological intervention. Larger P1 responses to sad faces, compared to neutral faces, were found in the depressed group, indicating a negative bias in the automatic processing of facial expressions. The bias was corrected in the follow-up measurements after symptom reduction. Compared to the non-depressed control group, a larger negative bias was found in the group that did not recover after the intervention. However, the recovered and non-recovered groups did not differ in brain responses. The results of this thesis indicate that electrical brain responses related to early information processing can be used to study depression- and aging-related alterations in brain function and the brain responses can reflect illness state. Therefore, these responses have the potential to be further developed for clinical practice as neural markers for depression.

Keywords: aging, depression, event-related potentials, sensory processing

TIIVISTELMÄ (FINNISH ABSTRACT)

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Sähköfysiologiset aivovasteet masennuksen ja ikääntymisen hermostollisina merkkeinä
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Masennus on yksi yleisimmistä mielenterveyden häiriöistä. Sen diagnosointi perustuu kliiniseen haastatteluun, eikä luotettavia masennuksen biomarkkereita ole löydetty. Aivojen sähköisiä vasteita voidaan mahdollisesti hyödyntää masennuksen hermostollisina merkkeinä diagnostiikassa ja hoitojen suunnittelussa sekä masennuksen ja ikääntymisen aiheuttamien muutosten erottelussa. Väitöskirjan ensimmäisessä tutkimuksessa tutkin, miten aivojen kyky käsitellä äänen voimakkuuden muutoksia eroaa ei-masentuneiden henkilöiden sekä niiden masentuneiden välillä, joilla oli diagnosoitu joko yksittäinen masennustila tai toistuvan masennuksen masennusjakso. Yksittäisen masennustilan ryhmässä havaittiin muita ryhmiä suurempi N1-vaste harvoin esitettyihin ääniin. Äänen voimakkuuden käsittelyn on esitetty heijastavan monoamiinivälittäjäainejärjestelmän toimintaa, ja siten tulokset saattavat viitata välittäjäaineiden puutoksiin yksittäisen masennustilan ryhmässä. Toisessa tutkimuksessa verrattiin kuuloherätevasteita ikääntyneiden ja nuorempien masentuneiden ja ei-masentuneiden aikuisten välillä. N1-vasteet olivat suurentuneita sekä ikääntyneiden että masentuneiden ryhmissä, mikä saattaa viitata puutoksiin hermoston kyvyssä vaimentaa reagoivuutta epäolennaisiin aistiärsykkeisiin. Kolmannessa tutkimuksessa tarkasteltiin emotionaalisiin kasvokuviin syntyviä aivovasteita masentuneiden ja ei-masentuneiden henkilöiden välillä sekä niissä tapahtuvia muutoksia seurantamittauksissa. Lisäksi tutkittiin, heijastavatko ennen hoitoa mitatut aivovasteet hyötymistä psykologisesta hoidosta. Masennusryhmässä havaittiin negatiivinen vääristymä, joka ilmeni suurentuneina P1-vasteina surullisiin ilmeisiin. Vääristymän havaittiin korjaantuneen seurantamittauksissa masennusoireiden lievennyttyä. Suurempi negatiivinen vääristymä ei-masentuneisiin kontrolleihin verrattuna havaittiin niillä masentuneilla, jotka eivät hyötyneet hoidosta. Aivovasteet eivät kuitenkaan eronneet hoidosta hyötyneiden ja ei-hyötyneiden masentuneiden välillä. Tutkimusten tulokset osoittavat, että varhaisia aivovasteita voidaan mahdollisesti kehittää kliiniseen käyttöön, sillä ne erottelevat masennuksen alaryhmiä ja heijastavat sairauden vaihetta.

Avainsanat: aivojen herätevasteet, aistitiedon käsittely, ikääntyminen, masennus

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Taken into account the instructions and comments given by the co-authors, the author of this thesis contributed to the original publications as follows: In study I, the author participated to the data analysis and writing of the manuscript. In study II, the author participated to the planning of the research, data gathering, data analysis and writing of the manuscript. In study III, the author participated to the data gathering, data analysis and writing of the manuscript.

FIGURES

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1 INTRODUCTION

Depression is one of the most common mental health disorders and leading causes of disability in society (World Health Organization, 2017). The lifetime prevalence of depression has been estimated to be around 10% (Lim et al., 2018). Depression is highly recurrent, and estimates of people having one or more additional episodes after one episode vary between 30% and 70% (for a review, see Richards, 2011). The diagnosis of major depressive disorder, in accordance with the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10*), is determined by the presence of at least four depression symptoms, which include at least two of the primary symptoms of the disorder (World Health Organization, 2010). The primary symptoms are a depressed mood, loss of interest and fatigue and the secondary symptoms include, for example, exaggerated self-blame, disturbed sleep or appetite and suicidal thoughts. The symptoms are required to have continued for at least two weeks.

Depression is commonly treated with antidepressants, psychotherapy or a combination of these approaches. However, less than 50% of patients show remission after treatment with antidepressants or psychotherapy (Thase, Entsuah & Rudolph, 2001; for reviews, see Cuijpers et al., 2014; De Maat, Dekker, Schoevers, & De Jonghe, 2006). Several depression subtypes have been identified and associated with different underlying pathophysiologies (Lee & Kim, 2015; Musliner, Munk-Olsen, Eaton, & Zandi, 2016; Stewart, McGrath, Quitkin, & Klein, 2007). The heterogeneity of symptoms has led to the understanding that depression is not a unified disorder (e.g. Hasler, Drevets, Manji, & Charney, 2004). It has been suggested that patients with different subtypes of depression may benefit from different kinds of treatment (review see, Stewart et al., 2007). However, reliable predictors for guiding treatment choice based on clinical characteristics have not been found yet (Cuijpers et al., 2012, 2017).

Increasing interest has been shown for finding biomarkers that could be used to classify depression subtypes and predict responses to different kinds of treatments. Biomarkers are defined as objectively measured indicators of medical states (Strimbu & Tavel, 2010). Various biological markers have been identified in depression such as inflammatory, neurotransmitter, metabolic and brain response markers (for a review, see Strawbridge, Young, & Cleare, 2017). Electrical brain responses pose especially intriguing options because they are

cost-effective, and electroencephalography (EEG) equipment is widely available in hospitals, making it ideal for use in public health care.

The first aim of the present research was to identify possible neural markers of depression from electrical brain responses. Depressed participants' brain responses were compared to healthy participants' responses. Depressed participants with different illness histories (one or multiple episodes) were examined to determine if illness history is reflected differently in brain responses. Alterations related to the number of previous episodes were investigated because multiple episodes can produce progressive alterations in the brain (Moylan, Maes, Wray & Berk, 2013). A recurrent illness course has been associated with more serious cognitive impairments (see, for example, Fossati et al., 2004; Gałecki, Talarowska, Anderson, Berk, & Maes, 2015; Talarowska, Zajaczkowska, & Galecki, 2015) and structural changes in some brain regions compared to first-episode depression (for a review, see McKinnon, Yucel, Nazarov, & MacQueen, 2009).

The second aim was to examine if depression- and aging-related brain changes can be determined from a single measurement. Old age depression may be associated with distinct features compared to depression in younger people (Fiske, Wetherell, & Gatz, 2009). Furthermore, depression- and aging-related alterations can be difficult to differentiate because biological and social changes related to aging can result in psychological and somatic symptoms (Balsis & Cully, 2008), and similar changes in cognition are found in depression (Lee, Hermens, Porter, & Redoblado-Hodge, 2012) and aging (Harada, Natelson Love, & Triebel, 2013). Therefore, this research investigated whether brain responses can be used to study alterations related to normal aging and depression.

The third aim was to examine whether there is a negative bias in the automatic processing of facial expressions and whether it normalizes during remission that is, if the brain responses change according to symptom reduction. Furthermore, we investigated if the negative bias measured in acute depression differ between depressed adults who eventually recover or do not recover after a brief psychological intervention. If treatment responders and non-responders can be differentiated based on brain responses, brain response measures could be further developed to predict treatment response for future clinical practice.

1.1 Depression and aging

Although depression is less frequent in older adults than in younger adults, depression in old age can have serious consequences—as it has been associated with increased morbidity, the risk of suicide and decreased social and cognitive functioning (Blazer, 2003). The depression symptoms in old age depression can be somewhat distinct from those of younger groups. For example, somatic and cognitive symptoms are more frequently reported in older depressed patients than in younger patients (Fiske et al., 2009). Furthermore, old age depression has been associated with the risk of cognitive decline and dementia (Koenig, Bhalla,

& Butters, 2014). Old age depression includes both patients who have early-onset depression that continues or recurs in later life and patients who experience the first onset at old age (after 60 years of age) (Koenig et al., 2014).

Depression is sometimes difficult to differentiate from aging-related changes because both are associated with a similar decline in cognitive abilities (for reviews on depression, see Lee et al., 2012, and for aging, see Harada et al., 2013). In addition, deficits in monoaminergic neurotransmitter function—for example, deficits in serotonin (Meltzer et al., 1998; Rodríguez, Noristani, & Verkhratsky, 2012) and in dopamine neurotransmission (Barili, De Carolis, Zaccheo, & Amenta, 1998; Yadid & Friedman, 2008)—have been associated with both depression and aging. It is possible that a decline in serotonergic function in aging can predispose older adults to develop depression (Meltzer et al., 1998). However, depression itself can also affect aging, as recent research indicates that depression may accelerate biological processes related to aging (Han et al., 2018, for a review, see Wolkowitz, Epel, Reus, & Mellon, 2010). In addition to similarities between depression and normal aging, depression can also be confused with early-stage dementia, as it can first manifest as depression (Panza et al., 2010). It is a clinically relevant aim to search for biomarkers that could be used to differentiate cognitive alterations related to normal aging and depression.

1.2 Searching for biomarkers of depression and aging with electrophysiological brain responses

Electrical brain responses enable the investigation of early information processing stages, which provide the foundation for higher-order cognitive processing. Previous studies have attempted to identify depression-related biomarkers that could be used for diagnosing depression or predicting treatment response from electrophysiological recordings. In continuous EEG-measures, depressed participants have been found, for example, to have disturbances in sleep architecture, increases in EEG vigilance during rest (reflecting central nervous system arousal) and elevated alpha power during rest and increased theta activity in the frontal regions, compared to controls (Olbrich, van Dinteren, & Arns, 2015). Furthermore, sleep-related markers have been related to the recurrence of depression, and alpha and theta activity have been found to predict the response to antidepressant treatment (Olbrich et al., 2015).

Biomarkers have also been investigated with event-related potentials (ERPs) that are averaged from an EEG signal that is time-locked to a stimulus. Alterations in ERPs to various stimuli have been associated with both depression and aging. One of the most consistent findings related to depression in the ERP biomarker literature is that the early auditory potentials evoked by auditory intensity changes predict the treatment response to antidepressants (Gallinat et al., 2000; Jaworska et al., 2013; Juckel et al., 2007; Lee, Park, Lee, & Shim, 2015; Lee, Yu, Chen, & Tsai, 2005). There is also evidence that intensity processing

could be used as a marker for separating depression subtypes. For example, depressed participants with atypical and non-atypical depression (Lee, Park, Yoon, Kim, & Hahn, 2014) and depressed participants with melancholic and non-melancholic depression (Fitzgerald et al., 2009) have been found to differ in brain responses to intensity changes. However, more research is needed to compare the responses in various subtypes of depression.

One advantage of electrical brain responses is they can be used to study automatic processing that is not dependent on the motivation or the attentional capacity of the individual. Since a lack of motivation and concentration problems are common symptoms of depression (World Health Organization, 2010), measures that do not require the patient's attention could be useful for this group. A commonly used measure of automatic information processing is the change detection condition—that is, the oddball condition. This procedure can be used for investigating early obligatory responses that are elicited without attention (Näätänen & Picton, 1987) in auditory, visual and somatosensory modalities. In the oddball condition, a repeated "standard" stimulus is presented frequently, and it is rarely and randomly replaced by a "deviant" stimulus that differs in from the repeated stimulus in some feature. The deviant stimulus automatically elicits the mismatch negativity (MMN) response around 100–250 ms after stimulus onset, reflecting automatic change detection (Näätänen, Gaillard, & Mäntysalo, 1978; Näätänen, Paavilainen, Rinne, & Alho, 2007). The responses can be measured under an ignore condition—which means the participant is engaged in another task, —usually involving a different sensory modality than the stimuli under investigation. The response is elicited even in unconscious states, such as during sleep or in patients who are in a coma but have started to recover (for a review, see Näätänen et al., 2011). Abnormalities in MMN responses have been found in many neuropsychiatric disorders and in normal aging both in the auditory (Näätänen et al., 2011) and in the visual modality (Kremláček et al., 2016), and therefore, MMN could have potential as a biomarker. The oddball condition also enables the investigation of stimulus suppression—which could be a potential biomarker, as deficits in the suppression of early ERP responses to repeated stimuli (sensory gating) have been related to normal aging, neuropsychiatric disorders and depression (Baker et al., 1990; Boutros, Belger, Campbell, D'Souza, & Krystal, 1999; Boutros, Korzyukov, Jansen, Feingold, & Bell, 2004; Freedman et al., 1987; Friedman et al., 2011; Lijffijt et al., 2009).

Other potential biomarkers that could be used for predicting treatment response in depression are brain responses related to the so-called negative bias. Depression has been associated with a bias toward negative stimuli and away from positive stimuli, and the bias has been suggested to predispose patients to future depressive episodes (Beck, 2008). Negative bias as a marker of treatment response has been investigated in functional magnetic resonance imaging (fMRI) studies, but fewer ERP studies have been conducted. fMRI studies have shown that a negative bias in the processing of facial expressions (Costafreda, Khanna, Mourao-Miranda, & Fu, 2009; Fu et al., 2008), emotional pictures (Ritchey, Dolcos, Eddington, Strauman, & Cabeza, 2011) or emotional words (Siegle, Carter, &

Thase, 2006) predicts responses to cognitive behavioral therapy. One ERP study found that a negative bias in processing of aversive pictures predicted responses to cognitive behavioral therapy (Stange et al., 2017). Further investigations on biomarkers in ERP responses are warranted because EEG-equipment are low-cost and widely available in health care centers.

Next, the auditory responses investigated in the context of depression and aging are described in detail.

1.3 Markers of depression and aging in auditory brain responses

The modulation of auditory MMN responses has been found to be related to normal aging and many neuropsychiatric disorders and suggested to index cognitive decline (Näätänen et al., 2011). While MMN amplitude has been found to be attenuated in older adults (Alain & Woods, 1999; Čeponienė, Westerfield, Torki & Townsend, 2008; Cooper, Todd, McGill, & Mitchie, 2006; Czigler, Csibram & Csontos, 1992; Gaeta et al., 1998; Schroeder, Ritter, & Vaughan, 1995), findings on depression have been more mixed. Some studies have found enlarged MMN responses in depressed participants compared to controls (He et al., 2010; Kähkönen et al., 2007; Restuccia et al., 2016), while others have found smaller MMN responses in depressed participants (Chen et al., 2015; Naismith et al., 2012; Qiao et al., 2013; Takei et al., 2009) and one study found no MMN modulation related to depression (Umbricht et al., 2003). The differences could be related to differences in the applied stimuli. For example, studies that found enhanced MMN applied stimuli with a relatively high intensity (He et al., 2010; Kähkönen et al., 2007; Restuccia et al., 2015). Since a greater increase in brain responses for sound intensity increments has been associated with a serotonergic deficit (Hegerl et al., 2001; Hegerl & Juckel, 1993), it may be feasible to investigate how sound intensity change detection is affected in depression. Previous studies on depression have applied experiments where the change occurs in sound frequency or duration, but intensity processing has not been studied in depression in the oddball condition. An intensity change detection procedure could possible aid in distinguishing depression- and aging-related alterations if the MMN modulation related to aging and depression are in different directions (attenuation in aging and enhancement in depression).

Auditory intensity processing has been one of the targets of biomarker search in depression because of its connection to neurotransmitter functions. Originally, Buchsbaum and Silverman (1968) found that there are considerable individual differences in augmenting or reducing brain responses to increases in stimulus intensity. Later, this augmenting / reducing behavior in auditory responses was associated with neurotransmitter function. Hegerl and Juckel (1993) suggested a steeper increase in brain responses to an increase in stimulus intensity—that is, the intensity dependence of auditory evoked potentials—reflects low serotonergic neurotransmission, while a shallower rise in brain responses to intensity increments reflects high serotonergic innervation. Since

deficits of serotonin function have been implicated in the pathophysiology of depression (Coppen, 1967; Hasler, 2010; Meltzer, 1990) and brain responses to auditory intensity changes have been suggested to reflect serotonin neurotransmission (Hegerl et al., 2001; Hegerl & Juckel, 1993), intensity dependence may prove to be a useful biomarker for depression.

The intensity dependence of auditory responses is usually measured with N1 or P2 responses in ERPs. N1 is a negative polarity response elicited in the frontocentral scalp regions around 100 ms after stimulus onset (Näätänen & Picton, 1987), whereas P2 is a positive polarity deflection elicited around 150–250 ms after stimulus onset (Crowley & Colrain, 2004). Intensity dependence is commonly measured in experiments where various intensities of the same stimuli are presented in equal numbers and in a random order. Intensity dependence is calculated as the slope of the linear regression between brain responses and stimulus intensities—that is, the steepness of the increase in brain response as a function of increase in stimulus intensity. Most of the support for the connection between intensity dependence and serotonin function comes from animal studies (Juckel, Hegerl, Molnár, Csépe, & Karmos, 1999; Juckel, Molnár, Hegerl, Csépe, & Karmos, 1997). In humans, one of the most robust findings is that a steeper intensity dependence (reflecting low serotonin function) predicts treatment response to selective serotonin reuptake inhibitors in depressed patients (Gallinat et al., 2000; Jaworska et al, 2013; Juckel et al., 2007; Lee et al., 2015; Lee et al., 2005). Sometimes, the specificity of the intensity dependence as a marker of serotonin function has been questioned because it has also been associated with other monoaminergic neurotransmitters, such as dopamine (Lee et al., 2011; Pogarell et al., 2004). However, both altered dopamine and serotonin system functions have been associated with depression (Meltzer, 1990; Yadid & Friedman, 2008), making intensity dependence a relevant candidate marker related to depression and its treatment.

Most of the previous studies did not find differences in intensity dependence between depressed and control participants (Jaworska, Blier, Fusee, & Knott, 2012a; Linka, Sartory, Bender, Gastpar, & Müller, 2007; Park, Lee, Kim, & Bae, 2010; for opposite results, see Gopal, Bishop, & Carney, 2004). However, greater intensity dependence has been associated with some subtypes of depression, such as atypical depression (Lee et al., 2014) or non-melancholic depression (Fitzgerald et al., 2009). Therefore, it is feasible to investigate intensity processing in subgroups of depressed participants.

Older depressed participants could be expected to be especially affected by altered neurotransmitters because serotonin and dopamine alterations have been related to both aging and depression (for depression, see Meltzer, 1990; Yadid & Friedman, 2008; for aging, see Barili et al., 1998; Rodríguez et al., 2012). Therefore, intensity dependence could be a potential marker related to depression in older adults. Previous studies on intensity dependence in older age groups have been scarce.

In addition to intensity dependence, early auditory brain responses can be used to investigate cortical inhibition, also referred to as sensory gating

(Freedman et al., 1987). A deficit in the inhibition of task-irrelevant information (i.e., sensory gating) is a common finding in older adults (Friedman, 2011) and could therefore potentially be used to differentiate between depression and aging effects. Filtering out irrelevant information is important for efficient information processing and to protect the brain against unnecessary distractions. Sensory gating can be measured in the oddball condition—where it is reflected by a decrease in early brain responses, such as N1, to a repeated stimulus (Friedman, 2011). In younger adult participants, the repetition of stimuli results in the suppression of the N1 responses, but in older adult participants, this suppression is less evident or absent (Alain & Woods, 1999; Amenedo & Díaz, 1998; Anderer, Semlitsch, & Saletu, 1996; Fabiani, Low, Wee, Sable, & Gratton, 2006; Stothart & Kazanina, 2016; Strömmer et al., 2017; for a review, see Friedman, 2011). In addition to normal aging, sensory gating deficits have been commonly found in schizophrenia and bipolar disorder (Baker et al., 1990; Boutros et al., 1999, 2004; Lijffijt et al., 2009), but depression has been less studied (see, however, Baker et al., 1990).

1.4 Markers in facial expression processing

Depression has been suggested to be associated with bias in the processing of emotional environmental stimuli. This bias was originally suggested by Beck (1967) in his cognitive theory of depression, and cognitive behavioral therapy was developed based on the theory. Beck (1967, 1976, 1987) postulated that persistent negative thought patterns, also referred to as schemas, are at the core of depression. Beck proposed a cognitive triad where depressed people have negative thoughts about themselves, their environment and the future. These schemas were thought to be automatically activated in response to environmental stressors and can maintain and predispose people to depressive episodes (Beck, 2008). It is suggested that the negative thought patterns guide memory and attention to negative aspects in the environment and away from positive stimuli. Behavioral studies have shown, for example, that depressed individuals have enhanced recall for negative material, difficulty in disengaging from negative stimuli and a tendency to interpret ambiguous material as negative (for a review, see Gotlib & Joormann, 2010). Bias in the processing of facial expressions has been widely studied in relation to depression and can be related to the problems of social interaction that are commonly found in depression (for a review, see Delle-Vigne, Wang, Kornreich, Verbanck, & Campanella, 2014).

Early ERP responses P1 and N170 have been used to study the processing of facial expressions. P1 is a positive polarity deflection peaking around 80–140 ms after stimulus onset (Di Russo, Martínez, Sereno, Pitzalis, & Hillyard, 2002). P1 is suggested to reflect low-level feature encoding and the holistic processing of faces (Itier & Taylor, 2002; Taylor, 2002). N170 is a face-sensitive response elicited around 200 ms after stimulus onset at the occipito-temporal areas and reflects the structural encoding of faces (Bentin, Allison, Puce, Perez, & McCarthy,

1996; Eimer & McCarthy, 1999). Both P1 and N170 have been shown to be modulated by facial expression (Batty & Taylor, 2003). Enlarged P1 and N170 responses for sad faces, compared to neutral or happy faces, have been found in depressed participants, whereas controls have shown enlarged responses to happy faces, compared to neutral / sad faces, when evaluating faces (Dai & Feng, 2012; Zhao et al., 2015). Enlarged P1 and N170 responses have also been found to subliminally presented sad faces in depressed participants (Zhang, He, Chen, & Wei, 2016), suggesting that the bias is related to the pre-conscious processing phase. The change detection condition has been employed in some studies to investigate whether there is an automatic processing bias in depression. Chang, Xu, Shi, Zhang, and Zhao (2010) found evidence of an attenuated visual MMN response to sad and happy faces presented among neutral faces, but no evidence of a specific negative bias. Xu et al. (2018) found in a magnetoencephalography study that rarely presented sad faces elicited a larger M300 response, compared to repeated happy faces, in depressed participants, indicating a negative bias in task-irrelevant face processing. Although previous studies have indicated an automatic processing bias in depression, the persistence of this bias related to remission has not been studied. In other words, it is not clear if the ERP modulations related to depression reflect trait or state.

1.5 Negative bias: A marker for illness state and treatment response?

Negative bias in depression has been suggested to be a latent trait that can predispose a patient to recurring depressive episodes and persist even in remission (Beck, 2008). Behavioral studies have, for example, shown bias in the categorization of emotional faces (LeMoult, Joormann, Sherdell, Wright, & Gotlib, 2009; Leppänen, Milders, Bell, Terriere, & Hietanen, 2004) and selective attention to sad faces (Joormann & Gotlib, 2007) in formerly depressed participants. In addition, studies on sub-clinically depressed participants have shown a negative bias in the evaluation of sad faces, suggesting that it is a latent trait of depression (Dai & Feng, 2012; Dai, Wei, Shu, & Feng, 2016). Bouhuys, Geerts, Mersch and Jenner (1996) found in a follow-up study that the evaluation of the emotions of ambiguous faces stayed stable over time, although depression symptoms decreased. However, follow-up studies investigating ERP responses to facial expressions have not been previously conducted. However, some fMRI studies have shown that facial expression processing can normalize after symptom reduction (Fu et al., 2008; Victor, Furey, Fromm, Ohman, & Drevets, 2010). In addition, some studies have given indirect support for the state dependency of the negative bias measured with ERPs. For example, Wu et al. (2016) found a positive correlation between the number of depression symptoms and N170 amplitude to sad faces, indicating that the bias may vary according to symptom severity. Chen et al. (2014) found enhanced N170 responses to sad faces only in

recurrent depressed participants but not in first-episode depressed participants, suggesting that the bias may be related to illness progression.

Negative bias has also been used to predict treatment response to antidepressants or psychotherapy. Bouhuys et al. (1996) found that participants who initially perceived less sadness in the face evaluation task were less likely to show remission after antidepressant treatment. ERP studies on treatment response prediction are scarce. One study found that a larger initial negative bias, reflected by the late positive potential response to aversive pictures, predicted a better treatment response to treatment with cognitive behavioral therapy (Stange et al., 2017). However, there are no ERP studies investigating if bias in processing facial emotions can predict response to psychological treatments. Some fMRI studies have been conducted to predict response to cognitive behavioral therapy. Costafreda et al. (2009) showed that initial brain activity patterns as a response to sad faces dissociated patients who remitted from those who did not after treatment. Fu et al. (2008) found that a smaller negative bias, indicated by similar fMRI activity patterns relative to the non-depressed controls in sad face processing, predicted a better treatment response.

1.6 Aims of the research

The purpose of this thesis was to identify neural markers of depression, which potentially can be useful in the future in diagnosing depression more accurately and individually optimizing treatments. The neural markers were investigated from ERPs to auditory (sound intensity changes) and visual (facial expression changes) stimuli. Previous studies have shown support for auditory intensity responses in separating specific depression subtypes (for atypical vs. non-atypical depression, see Lee et al., 2014; for melancholic vs. non-melancholic depression, see Fitzgerald et al., 2009), but they have not been studied in relation to episode history or in old age depression. A negative bias in facial expression processing has been found in depression in many studies, but the stableness of the bias has not been thoroughly investigated. In addition, more attention could be directed to finding EEG-based markers that can predict response to psychological treatment. Because different subgroups of depressed participants can be expected to have different underlying pathophysiologies (Lee & Kim, 2015; Musliner et al., 2016; Stewart et al., 2007), one focus was comparing subgroups of depression. Three studies were conducted. All the studies utilized an ignore change detection condition, and ERPs reflecting the early stage of information processing were investigated.

Study I aimed to investigate whether brain responses in first-episode depression and / or recurrent depression differ from the brain responses of non-depressed controls. An intensity change detection condition was applied to investigate the intensity dependence that has been related to altered monoaminergic neurotransmitter function in depression (Hegerl et al., 2001; Hegerl & Juckel, 1993; Lee et al., 2011; Pogarell et al., 2004). To the best of my

knowledge, this was the first study to investigate brain responses in an intensity change detection condition (i.e., in an oddball condition) in depression, although the change detection responses related to frequency and duration changes have been found to be abnormal in depression (He et al., 2010; Kähkönen et al., 2007; Restuccia, Vollono, Scaloni, Buccelletti, & Camardese, 2016). Larger N1 and MMN responses were expected in the depressed groups because of monoaminergic dysfunction, but it could not be predetermined whether the brain responses would differ between the first-episode and recurrent groups.

Study II investigated, with the same experimental condition as Study I, the effects of depression and aging on the brain responses. Depressed and non-depressed participants from younger and older adult groups were compared. The study attempted to find depression- and aging-related alterations by investigating the intensity dependence of auditory responses, sensory gating and change detection. Enlarged N1 responses to repeated sounds were expected in both non-depressed and depressed older adult groups because of an aging-related deficit in sensory gating (Alain & Woods, 1999; Amenedo & Díaz, 1998; Anderer et al., 1996; Fabiani et al., 2006; Stothart & Kazanina, 2016; Strömmer et al., 2017; Tusch, Alperin, Holcomb, & Daffner, 2016). Depression-related effects were expected for the intensity dependence, especially in the older depressed adult group, because this group could be expected to have serotonergic deficits either because of aging (Rodríguez et al., 2012) or depression (Meltzer, 1990). The effects of depression and aging on serotonergic function could also be cumulative. It was considered that depression-related effects might not be found in the younger depressed group because intensity dependence alterations have not been found consistently in younger samples (Jaworska, et al., 2012a; Linka, et al., 2007, Park, et al., 2010). Aging effects were expected to be demonstrated as attenuated MMN (Näätänen et al., 2011), but it was not clear, based on the previous studies, whether the effect could be expected for depression.

Study III examined the stableness of early-stage facial expression processing reflected by ERPs and the association of these responses with treatment response. P1 and N170 responses to sad, neutral and happy faces were compared between depressed participants and controls. The stability of possible negative bias was investigated by conducting follow-ups at 2 months and 39 months after the first measure at the acute depression phase. Larger ERPs to sad faces, compared to neutral and happy faces, were expected in the depressed group (Dai & Feng, 2012; Zhang et al., 2016; Zhao et al., 2015), reflecting a negative bias in early automatic processing. The negative bias was expected to be corrected in the follow-up studies when depression symptoms had been reduced (Fu et al., 2008; Victor et al., 2010). A larger initial negative bias was expected in the group that showed no clinical recovery after cognitive psychotherapy treatment compared, to treatment responders (Fu et al., 2008).

2 METHODS

2.1 Participants

Three samples were used: for **Study I,** a total of 65 depressed female and male adults and non-depressed control participants; for **Study II,** 76 older and younger female adults with and without depression symptoms, and for **Study III,** 68 depressed and non-depressed female and male controls were recruited. **Study I** and **Study III** had a partly overlapping sample. All the participants were right-handed, had normal hearing and vision (or were corrected to normal vision) and reported no history of head trauma and no current substance abuse. The depressed participants in all the studies were recruited as a part of larger intervention studies investigating the effects of psychological interventions.

For **Studies I** and **III**, the inclusion criterion for both depressed and control groups was an age of 18–65 years and the exclusion criteria were neurological disorders or psychiatric disorders (except depression in the depression groups). For the depression group, the inclusion criterion was clinical depression confirmed by a physician and the exclusion criteria were depression with psychotic features, other psychiatric disorders, a serious risk for suicide that had come up during the interview and ongoing psychological treatment (because of the intervention study). However, in the depression group, there were a few participants with a history of other psychiatric diagnosis, except depression, included in the sample (see below for details).

For **Study II**, participants were recruited for four groups: depressed and non-depressed participants for younger adult groups (age of 18–40 years) and for older adult groups (age over 61 years). Only female participants were recruited. The exclusion criteria were any report of neurological disorders (except migraine that was not currently active, learning disabilities and fibromyalgia) and a hearing threshold over 20 dB (for 1000 Hz) measured with an audiometer. For the depressed groups, the inclusion criterion was a self-reported current depression, that is, at least 14 points on Beck's depression inventory II (BDI; Beck, Steer, & Brown, 1996). The exclusion criteria for depression groups were a self-reported psychiatric diagnosis other than depression or an anxiety disorder or a history of electroconvulsive therapy treatment. However, three participants with

previous other psychiatric disorders were included in the sample: one with an eating disorder, one with anankastic personality disorder and one with emotionally unstable personality disorder. For the non-depressed groups, the exclusion criteria were a self-report of any psychiatric diagnosis or current medication that can affect the central nervous system and BDI-II scores over 9 points.

For **Study I**, 43 participants (15 male) with depression and 22 non-depressed controls (8 male) were recruited with local newspaper announcements and from the email lists of the University of Jyväskylä. After excluding participants with excessive artifacts in the EEG data, there remained 41 depressed and 21 non-depressed participants. The mean age of the depressed participants was 42.8 years (SD 11.2) and the mean age of the controls was 39.0 years (SD 11.9). The depression diagnosis was confirmed with a clinical interview conducted by a physician independent of the study and to separate the depressed participants into first-episode and recurrent depression groups. Of the depressed participants, 16 had first-episode depression and 25 had recurrent depression. There was one participant who reported having an undefined anxiety disorder, one who reported a previous diagnosis of anorexia nervosa and one with an unclear other diagnosis.

For **Study II**, the participants were recruited with newspaper advertisements, notice board advertisements, the email lists of the University of Jyväskylä and from the University of Third Age in Jyväskylä. After excluding data with excessive artifacts, there remained 20 participants (one excluded) in the younger adult group (YOUNG), 16 participants in the younger depressed adult group (YOUNG-D), 17 participants (one excluded) in the older adult group (OLD) and 19 participants (two excluded) in the older depressed adult group (OLD-D). The mean ages were 27.5 years (SD = 6.6) for YOUNG, 27.9 years (SD = 6.9) for YOUNG-D, 67.5 years (SD = 4.0) for OLD and 68.0 years (SD = 4.3) for OLD-D. The age range in the younger group was 18–40 years and 62–80 for the older groups.

For **Study III**, 37 depressed and 31 non-depressed control participants were recruited with an advertisement in the local newspaper and via email lists at the University of Jyväskylä. When data with excessive artifacts were excluded, there remained 27 (four male) participants for the depressed group and 27 (three male) participants for the control group. The mean age of the depressed participants was 48.4 years (SD = 13.6) and the mean age of the control participants was 45.4 years (SD = 15.7). Two of the depressed participants reported having previous or current comorbid anxiety disorder and one reported having previously had another psychiatric diagnosis (unclear diagnosis). The depressed participants also attended two follow-up measurements. All the depressed participants attended the two-month follow-up (2-m) measurement and 17 participants attended the 39-month follow-up (39-m) measurement. After excluding data with excessive artifacts, there remained data on 25 participants (one male) and 17 (one male) for the 39-m measurement. The mean age of the participants included

for the 2-m analyses was 50.0 years (SD = 12.7) and the mean age of the participants included for the 39-m analyses was 47.8 years (SD = 13.4)[1].

All the participants gave a written informed consent before participating. The experiments were undertaken in accordance with the Declaration of Helsinki. The ethical committee of the University of Jyväskylä approved the research protocols.

2.2 Stimuli and procedure

In all of the experiments, the participants were seated in an electrically sealed, soundproofed and dimly lit room and they were monitored through a video camera placed on top of a screen. In **Studies I** and **II**, auditory stimuli were played through a loudspeaker situated on top of the participants. The participants were asked to watch a silent movie and ignore the sounds. In **Study III**, facial expressions were played on a screen situated approximately 1 meter in front of the participant. The participant was told to fixate their gaze in the middle of the screen, but to ignore the visual stimuli and to focus on a story played from the loudspeakers situated above the participant. The participant was asked questions about the story during breaks to ensure that they focused on the story.

In **Study II**, the participants attended another session on a separate day for the measurement of their performance on cognitive tests. The cognitive tests were administered by students majoring in psychology who received training on the measurements. Various cognitive tests measuring memory and attentional functions were applied.

In **Study III**, the experiment was conducted at the baseline when all the depressed participants had a recently confirmed depression diagnosis. The same experiments were repeated for the depressed participants approximately two months (2-m measurement) and 39 months (39-month measurement) later. After the baseline measurement, the depressed participants were randomly assigned either to a treatment group that received a psychological therapy intervention immediately or to a wait-list control group that received the same intervention after the treatment group. The intervention was conducted by master-level psychology students and lasted approximately two months. The 2-m measurement was conducted for both groups after the treatment group's intervention. The depression symptoms and anxiety symptoms were evaluated with questionnaires for all the depressed participants at the baseline, at the 2-m measurement and at the 39-m measurement and in addition, for the wait-list group after their treatment (approximately 4 months from the baseline).

In **studies I** and **II**, the stimuli were sinusoidal sounds (1000 Hz). The stimuli were presented in an oddball paradigm where deviant stimuli were presented infrequently among repeated frequently presented standard stimuli.

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[1] The age at the baseline measurement for the participants included in the 2-m and the 39-m analyses

The stimulus onset to onset asynchrony (SOA) was randomly set to be 400, 450 or 500 ms for **Study I** and 500, 550 or 600 ms for **Study II**. Two stimulus intensities, 60 dB or 80 dB (sound pressure level, SPL), were presented in two stimulus conditions. In the increment condition, the standard stimuli were 60 dB and the deviant stimuli were 80 dB, and in the decrement condition the stimuli were reversed. The conditions were presented in a randomized order. The stimuli were presented in a pseudorandom order wherein at least two standards were presented between the deviants. The presentation probability for the standards was 90% and the presentation probability for the deviants was 10%. In **Study I**, 50 deviant sounds and 450 standard sounds were presented. In **Study II**, 100 deviant sounds and 900 standard sounds were presented.

In **Study III**, the stimuli were pictures of neutral, happy and sad facial expressions derived from Ekman's and Friesen's Pictures of Facial Affect (1976). The stimuli were presented with E-Prime software (version 2.0.8.90, Psychology Software Tools, Inc, Sharsburg, MD, USA) via a 23'' monitor (Asus VG236 series H; refresh rate = 120 Hz; display resolution = 1920 × 1080) in a 11˚ × 16˚ visual angle. The stimuli were presented in pseudorandomized order (with a restriction that at least two standard stimuli were presented between the deviant stimuli) in an oddball paradigm, where infrequent deviant faces (sad or happy) were presented among frequent standard (neutral) faces. The sad and happy faces were presented in separate conditions: Sad and Happy condition. The stimulus duration was 200 ms and the presentation probability of the standard faces was 86%, while the presentation probability of the deviant faces was 14%. The identity of the faces was different for consecutive stimuli. For each condition, 480 standard and 80 deviant stimuli were presented. The stimulus onset asynchrony (SOA) was randomly set to be either 400, 450 or 500 ms.

2.3 Electrophysiological recordings and preprocessing of the data

In all the experiments, the electroencephalography (EEG) data was recorded with a high-impedance Net Amps 200 amplifier (Electrical Geodesics Inc.) using a 128-channel sensor net. The Net Station version 4.2.1 software was applied for the recordings. The sampling rate was 1000 Hz and the data was filtered with a bandpass filter 0.1-400 Hz and referenced to the vertex electrode (Cz).

The BrainVision Analyzer 2.1 was used for the preprocessing of the data (Brain Products GmbH, Munich, Germany). The data was offline re-referenced to an average calculated over all the channels. The data was filtered with 0.1 Hz low cut-off and 30 high cut-off filters (24 dB/octave roll-off) and a 50 Hz notch filter was applied. In **Studies I** and **II**, an independent component analysis (ICA), as implemented in the Brain Vision Analyzer, was applied to correct for the eye movements. The best representations of horizontal and vertical eye movements were selected manually based on visual inspection from the ICA components proposed by the ICA algorithm. In **Study III**, the method suggested by Gratton, Coles and Donchin (1983) was used for correction of the eye movements.

Channels with excessive electrical noise were interpolated with a spherical spline model.

In **Studies I** and **II**, the data were segmented from -100 ms to 500 ms relative to the stimulus onset and baseline corrected against the mean activity from -100 to 0 ms. Segments containing excessively large amplitude values (beyond -150/150 μV) within a 200 ms time period or a 50 μV difference between two consecutive time points were omitted from further analysis. In **Study III**, segments of -200 ms to 600 ms relative to the stimulus onset were extracted and corrected against the baseline averaged from -200 to 0 ms. Segments containing amplitude values beyond -200/200 μV within a 200-ms time period were excluded from further analyses.

In **Study I**, the mean values were calculated from a frontocentral channel pool (channels 3, 10, 11, 15, 16, 18, 23, 24, 27, 123, and 124 in the EGI 128-channel system) from two time windows: 90–140 ms (corresponding to N1) and 150–200 ms (corresponding to MMN). The time windows and channel selections were based on previous literature (Näätänen, 1990) and visual inspection of the data.

In **Study II**, mean amplitude values were extracted from two frontocentral channel pools (separate for N1 and MMN) from 80–130 ms after stimulus onset (corresponding to N1) and from 140–180 ms after stimulus onset (corresponding to MMN). The channels for N1 were 5, 6, 7, 11, 12, 13, 106 and 112 and the channels for MMN were 5, 6, 11, 12 and 16 in the EGI 128-channel system. The time window and channel choices were based on visual inspection and previous literature (Gudlowski et al., 2009; Näätänen, 1990; Näätänen & Picton, 1987; Park et al., 2010). The visual inspection was based on an average calculated over the groups.

In **Study III**, the maximum peak amplitude values were obtained for P1 from 80–150 ms at the occipital channels (channels 65, 69, 70 and 74) and for the N170 from 130–210 ms at the parieto-occipital channels (channels 58, 64, 65, 69, 70 and 74). An average of the peak values was calculated over the channels separately for the left and right sites.

2.4 Statistical analyses

The statistical analyses were carried out with IBM SPSS version 24.0 (IBM Inc, Armonk, NY). In **Study I**, the N1 and MMN amplitudes were analyzed with repeated measures of multivariate analysis of variance (MANOVA) comparing the responses between the non-depressed controls (Ctrl), first-episode depressed (FE-dep) and recurrent depressed (REC-dep). Separate MANOVAs were conducted for N1 and MMN responses. The within-subject variables were stimulus type (deviant vs. standard) and condition (increment vs. decrement) and the between-subject variable was the group (Ctrl vs. FE-dep vs. REC-dep). For the post-hoc tests, a one-way analysis of variance (ANOVA) with Bonferroni correction was applied for the between-subjects comparisons and paired sample t-tests (two-tailed with bootstrap statistics based on 1000 iterations) were utilized

for within-subjects comparisons. To control for the effects of antidepressant medication, a covariate analysis was applied with medication status (medicated vs. non-medicated) as a covariate for the MANOVA /ANOVA whenever group main or interaction effects were found. In addition, a separate analysis was conducted by excluding the participants using antidepressants. The correlations between the brain responses and BDI-II were examined with a two-tailed Pearson correlation.

In **Study II**, the N1 and MMN amplitudes were analyzed. For the N1 responses, separate analyses were conducted for the sensory gating and intensity dependence analyses. For the sensory gating analysis, the N1 amplitude values were entered as dependent variables in repeated measures of MANOVA comparing the age group (older vs. younger) and depression group (depressed vs. non-depressed) with the within-subject variables stimulus type (deviant vs. standard) and condition (increment vs. decrement). In addition to the deviant responses, the responses to standards immediately preceding the deviant sounds were analyzed to produce a similar signal-to-noise ratio with the deviant responses and to ensure enough repetition of the stimulus for the study of habituation. The intensity dependence was operationalized as the difference between responses to high- and low-intensity standard sounds. For this analysis, only the standard sounds immediately following the deviant sounds were applied. This way the effect of stimulus repetition was reduced. The differential response corresponds to the regression slope that is typically used in the intensity dependence studies (see, for example, Hegerl, Gallinat, & Mrowinski, 1994). An ANOVA was conducted comparing the age group (younger vs. older) and depression group (depressed vs. non-depressed) in the differential response. The MMN was examined by calculating a differential response (deviant minus standard) separately for the increment and decrement conditions. A repeated measures of MANOVA was conducted comparing the age group (older vs. younger) and depression group (depressed vs. non-depressed) in the increment and decrement MMN. For all the analyses, separate analyses of covariance (ANCOVA/MANCOVA) were applied controlling for the hearing threshold, because the older age groups had higher hearing thresholds compared to the younger groups. The effect of medication was examined, by controlling for medication status (medicated vs. non-medicated).

In Study III, separate averages of the peak amplitudes were calculated for the responses to the sad deviants, happy deviants and neutral standards immediately preceding the deviants. The responses to the neutral standards were averaged over the conditions (sad and happy collapsed). For the baseline measurement comparing depressed and controls, a repeated measures of MANOVA was applied between the groups (Ctrl vs. Dep) with the within-subject variables: stimulus type (happy vs. sad vs. neutral), hemisphere (left vs. right) and component (P1 vs. N170). Significant group main or interaction effects were followed with separate MANOVAs for the components and / or groups. Post-hoc tests for between-group comparisons were examined with two-tailed independent-samples t-tests and within groups with paired samples t-tests.

Separate analyses were conducted within the depression group to investigate change in the negative bias that was found in the depression group at the baseline. The negative bias was operationalized as the difference between the P1 responses to sad and neutral faces. A differential response was calculated by subtracting the responses to neutral standard faces (immediately preceding the sad deviant faces) from the responses to sad deviant faces. For the two-time-point and the three-time-point comparisons, a repeated measures of MANOVA was conducted with the within-subject variable time point (baseline vs. 2-m and baseline vs. 2-m vs. 39-m, respectively). For the three-time-point comparison, paired sample t-tests were conducted comparing differential responses between the time points, whenever MANOVA indicated a main effect of time.

In **Study III**, the difference in the brain responses was also examined between recovered (n = 16) and non-recovered (n = 8) depressed and controls (n = 27). The depressed group was divided into recovered and non-recovered groups, based on changes in the BDI-II-scores from the baseline to post intervention. A method suggested by Jacobson and Truax (1991) was applied to assess the clinical significance of the BDI-II change. A reliable change index was calculated to assess the clinical significance of the change. A cut-off value was also calculated based on normative values for a non-clinical population derived from a previous study (Kjaergaard, Wang, Waterloo, & Jorde, 2014) and the values for the clinical population based on the **Study III** sample. This cut-off estimates the weighted midpoint between the mean BDI-II values of the clinical and the non-clinical population. To be included in the recovered group, the participants' BDI-II change had to be clinically significant (reliable change index equal or lower than -1.96) and the post-intervention BDI-II values had to be below the cut-off value (14.2). The negative bias was examined by applying a differential response calculated by subtracting responses to sad faces from responses to neutral faces. Only the P1 responses were compared, because the baseline analysis indicated negative bias in the depression group at baseline only for the P1 responses. The difference in negative bias was assessed between the groups by applying a one-way ANOVA with within-subject variable P1 differential response (sad minus neutral) and between subjects variable group (recovered vs. non-recovered vs. Ctrl).

For **Study I**, p-values below .05 were considered significant, but p-values below .075 were also further examined. For **Studies II** and **III**, p-values were corrected with false discovery rate correction (for independent sample t-tests: Benjamini & Hochberg, 1995; for paired sample t-tests: Yekutieli & Benjamini, 2001) and values below .05 were considered significant and further examined. For the effect size estimate, partial eta squared (η^2_p) for MANOVA and ANOVA and Cohen's d for t-tests were applied. The sample demographics and applied statistical models of each study are presented in Table 1.

TABLE 1 Description of the sample demographics and methods for each study

Study	Sample	Responses	Statistics
I	N = 62 FE-dep (n = 16) age M = 41.4 ± 13.4 y Rec-dep (n = 25) age M = 43.7 ± 9.7 y control group (n = 21) age M = 40.0 ± 11.9 y	mean amplitudes N1: 90–140 ms MMN: 150–200 ms	repeated measures of MANOVA / MANCOVA with post-hoc tests (one-way ANOVA, independent samples and paired samples t-tests) Pearson's correlations
II	N = 72 YOUNG (n = 20) age M = 27.5 ± 6.6 y YOUNG-D (n = 16) age M = 27.9 ± 6.9 y OLD (n = 17) age M = 67.5 ± 4.0 y OLD-D (n = 19) age M = 68.0 ± 4.3 y	mean amplitudes N1: 80–130 ms MMN: 140–180 ms <u>intensity dependence:</u> N1 differential response <u>sensory gating:</u> N1 responses to deviant and standard sounds <u>MMN:</u> differential response	repeated measures of MANOVA / MANCOVA and ANOVA / ANCOVA with post-hoc tests (independent sample t-tests) Pearson's correlations
III	N = 54 <u>Baseline:</u> depressed (n = 27) age M = 48.4 ± 13.6 y control group (n = 27) age M = 45.4 ± 15.7 y <u>two-time-point comparison:</u> depressed (n = 25) <u>three-time-point comparison:</u> depressed (n = 17) <u>Treatment response comparison:</u> non-recovered (n = 8) recovered: (n = 16)	peak amplitudes P1: 80–150 ms N170: 130–210 ms <u>Baseline analysis:</u> P1 and N170 to sad, happy and neutral faces <u>Time point /treatment response analyses:</u> P1 differential responses (sad minus neutral face)	repeated measures of MANOVA / MANCOVA and One-way ANOVA / ANCOVA with post-hoc tests (paired sample t-tests) Pearson's correlations

FE-dep = first episode depressed, REC-dep = recurrent depressed, YOUNG = younger adult group, YOUNG-D = younger adult depression group, OLD = older adult group, OLD-D = older adult depression group, M = mean, y = years

3 RESULTS

In **Study I**, auditory intensity processing was investigated between depressed groups differing in the number of episodes and non-depressed controls. The N1 responses were found to be larger in FE-dep group (n = 16) compared to REC-dep group (n = 25) and Ctrl group (n = 21) to sounds deviating in intensity from the repeated sounds. No group differences were found in the MMN. **Study II** investigated depression- and aging-related brain responses to auditory intensity changes. Four groups were included: younger adults (n = 20, age range 19–39 years), younger depressed adults (n = 16, age range 18–40 years), older adults (n = 17, age range 63–80 years) and older depressed adults (n = 19, age range 62–76 years). Depression- and aging-related effects were both demonstrated as enlarged N1 responses. Intensity dependence showed only aging-related effects, responses being larger in amplitude for the older adults compared to the younger adults across the depression groups. In **Study III**, the negative bias in automatic face processing and the stability of it was investigated in depression. In addition, the differences in negative bias were investigated between the controls, depressed group that recovered and depressed group that did not recover after a brief psychological intervention. The early automatic bias was confirmed in the depression group (n = 27) in the form of larger P1 responses to sad faces compared to neutral faces, whereas it was not found in the control group (n = 27). The bias was reduced in the 2-m and 39-m follow-up measurements when depression symptoms were also reduced. The negative bias did not differ between those depressed who recovered (n = 16) and those who did not recover (n = 8) after the intervention, although the bias was significant in comparison to the control group only in the group that did not recover. The research questions, hypotheses and main results for each study are presented in Table 2.

TABLE 2 Summary of the research questions, hypotheses and main results of each study

Study	Research questions	Hypotheses	Results
I	Does auditory intensity processing differ between FE-dep, REC-dep and controls?	N1 and MMN responses are larger in one or both of the depressed groups compared to controls.	The hypothesis was partly supported; enhanced N1 responses were found in FE-dep group compared to the other groups, but no group difference was found in MMN.
II	Are depression-related alterations reflected in the N1 intensity dependence responses especially for older depressed adults?	Larger N1 intensity dependence responses in older adult depressed group compared to the other groups.	The hypothesis was not supported; greater intensity dependence was found related to aging, but not depression.
	Is sensory gating affected in aging?	Larger N1 responses in both older adult groups compared to the younger groups.	The hypothesis was supported; older adults had larger N1 responses than younger adults. Similar effect was found in depressed compared to non-depressed.
	Is change detection affected by aging or depression?	Altered MMN in older groups and possible in depressed.	The hypothesis was not supported: no aging- or depression-related effects were found.
III	Is the negative bias in depression found in the early automatic processing of facial expressions?	Larger P1 and/ or N170 response amplitude to sad faces than to neutral and happy faces in depressed group.	The hypothesis was partly supported; larger P1 responses to sad faces compared to neutral faces only in the depressed group.
	Can the bias change when depression symptoms subside?	The negative bias is reduced in follow-up measurements when depression symptoms are reduced.	The hypothesis was supported; the negative bias was reduced in the 2-m and 39-m follow-up measurements compared to the baseline.
	Does the initial negative bias associate to the response to psychological treatment?	Greater initial negative bias in those depressed participants who did not recover after intervention compared to the recovered and controls	The hypothesis was partly supported: greater negative bias was found in non-recovered group compared to controls, but no difference was found between recovered and non-recovered groups.

FE-dep = first-episode depressed, REC-dep = recurrent depressed group

3.1 Study I: N1 response to auditory intensity changes is enlarged in first-episode depression

In **Study I**, the brain responses to automatic auditory intensity changes were examined between the FE-dep, REC-dep and Ctrl groups in experimental conditions including intensity increments and decrement changes. The results showed that the FE-dep group had larger N1 (averaged over frontocentral electrode cluster from 90–140 ms after stimulus onset) responses to deviants (conditions collapsed) compared to the Ctrl and REC-dep groups (Figure 1). In addition, the responses to deviant sounds were larger than the responses to standard sounds in the FE-dep and REC-dep group, but did not differ significantly in the control group. The group difference approached significant (p-values were below .07) when controlling for medication status or when only non-medicated participants were examined. No group differences were found for the MMN responses (measured at frontocentral electrodes 150–200 ms after stimulus onset). There were no significant correlations between the N1 responses and the depression (BDI-II) scores.

The results indicate cortical excitability in the early pre-attentive processing phase for intensity changes in first-episode depression, which was not observed in recurrent depression.

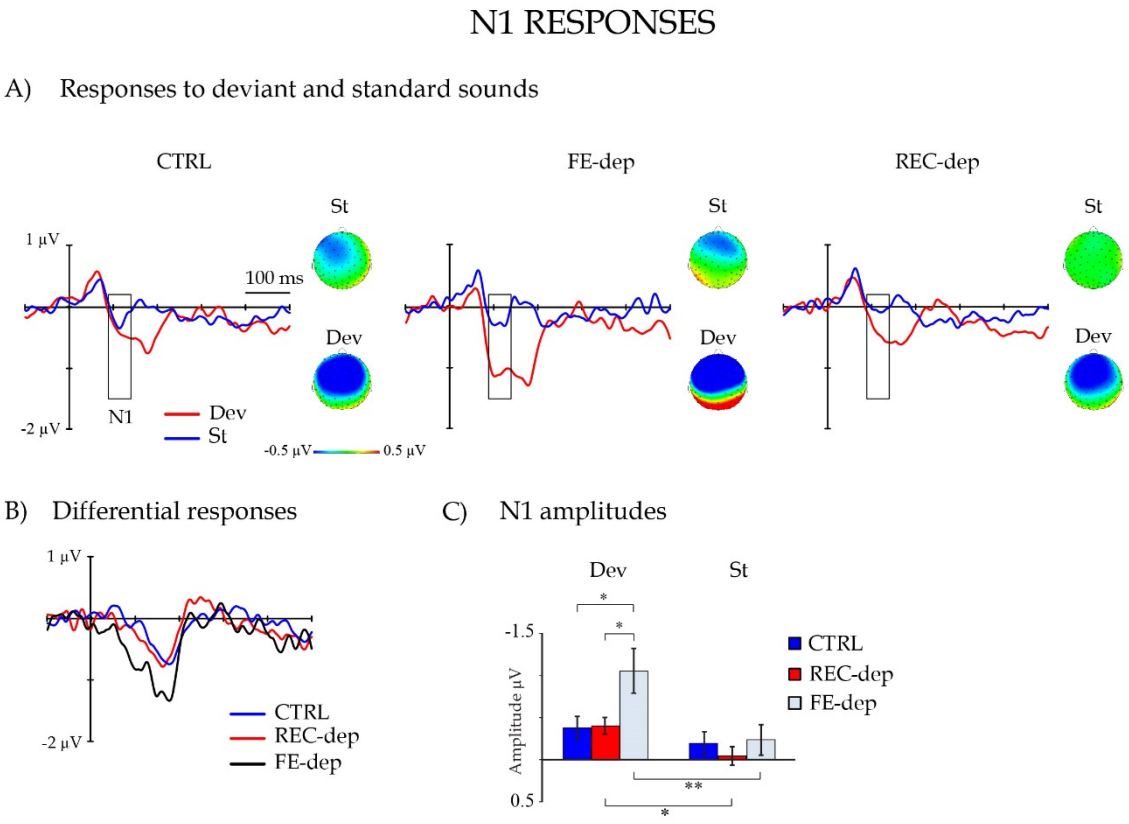

FIGURE 1 N1 responses in intensity oddball condition for Study I. A) Grand-averaged N1 responses and topographical maps of the responses to standard and deviant sounds (intensity conditions collapsed) for each group. The rectangles and the topographies show the time window from which the responses were averaged (90–140 ms after stimulus onset). B) Differential N1 responses (deviant minus standard) for each group (averaged over the intensity conditions). C) The mean amplitudes of N1 to deviant and standard sounds (averaged over the intensity conditions) in each group. Error bars represent standard error. CTRL = control group, FE-dep = first-episode depression group, REC-dep = recurrent depression group, St = standard, Dev = deviant. *p <.05, ** p <.01

3.2 Study II: N1 responses reveal cortical excitability related to depression and aging

In **Study II**, the effects of depression and aging on auditory intensity processing was examined with an intensity change detection paradigm (corresponding to **Study I**). The effects of aging (older vs. younger) and depression (depressed vs. non-depressed) on auditory responses were compared by including participants from four groups: younger adults, younger depressed adults, older adults and older depressed adults. Three analysis were conducted: the intensity dependence reflected by N1 differential responses to standard sounds (high-intensity minus

low-intensity), sensory gating reflected by N1 responses to deviants and standards and MMN as differential responses to sound increments and decrements.

The comparison related to intensity dependence revealed a larger N1 differential response in older groups, compared to the younger groups, but no depression-related effects were found. For the sensory gating analysis, depression- and aging-related N1 enhancement were both found as increased N1 responses. However, the aging-related enhancement was found for the repeated sounds and for the rare high-intensity sounds, whereas the depression-related enhancement was found over all the stimulus types. The depression-related effects were only found when controlling for medication. No group differences were found in the MMN responses. The results indicate cortical overexcitability in auditory intensity processing in depression and aging. The grand averaged waveforms for N1 sensory gating and the group differences in it are depicted in Figure 2.

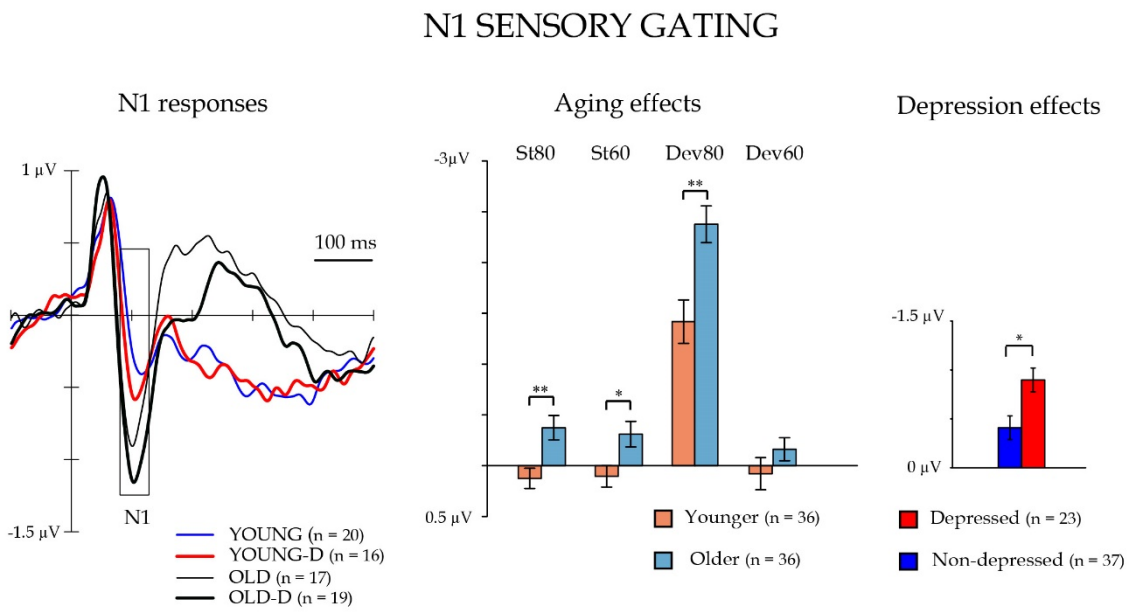

FIGURE 2 N1 sensory gating responses in Study II. Left panel: Grand averaged waveforms over all stimulus types (averaged over standards and deviants) for the groups (note that depression groups include both medicated and non-medicated participants). The rectangle shows the time window over which the responses were averaged (80–130 ms after stimulus onset). Middle panel: The mean amplitude values for the different stimuli in younger and older adult groups (averaged over the depressed and non-depressed groups). Right panel: The mean amplitude values for N1 (averaged over the conditions and deviant and standard stimuli) for non-depressed and non-medicated depressed participants. Error bars represent standard error. St80 = standard sound of 80 dB, St60 = standard sound of 60 dB, Dev80 = deviant sound of 80 dB, Dev60 = deviant sound of 60 dB, YOUNG = younger adult group, YOUNG-D = younger adult depression group, OLD = older adult group, OLD-D = older adult depression group. *p <.05, ** p <.01

3.3 Study III: The negative bias to sad faces in depression is state dependent

In **Study III**, the negative bias in brain responses to emotional facial expressions was studied in an oddball paradigm between depressed groups and controls. In addition, the changes in the brain responses over time were examined by following the depressed participants with the measurements two months and 39 months after the baseline measurement. The association of brain responses with the treatment response to psychological intervention was examined by comparing non-depressed controls and depressed groups who recovered and did not recover after a brief psychological intervention.

At the baseline measurement, the depressed group showed a larger P1 response to sad faces, but not to happy faces, compared to neutral faces, as indicative of a negative bias. No significant differences in the P1 responses to different expressions were found in the control group. Both groups showed larger N170 responses to the happy faces, compared to the neutral faces, but the responses to the sad faces did not differ from the responses to the neutral faces. There were no significant interaction effects with medication status (medicated vs. non-medicated) or the baseline BDI-II-scores reflecting depression symptoms when they were added to the model as covariates. At the 2-m measurement, approximately half of the depressed participant had received a psychological treatment intervention and the BDI-II-scores were significantly reduced at the whole group level. The P1 differential responses decreased in the depressed group from the baseline measurement to the 2-m measurement. For the smaller sample that was available for the three-time-point comparison (n = 17), the P1 differential response was found to decrease from the baseline measurement to the 39-m measurement, but no significant difference was found between the baseline and the 2-m measurement. The mean BDI-II-scores had remained low at the 39-m measurement. The analysis of the baseline P1 differential responses between the recovered, non-recovered and control groups indicated that the non-recovered group had a larger negative bias, compared to the control group, but the responses did not differentiate recovered from the non-recovered group. The P1 differential responses for the three-time-point comparison and the treatment response comparison are depicted in Figure 3.

To sum up the results for **Study III**, a negative bias was found in the depressed group at the baseline, but the bias was normalized in the follow-up measurements when depression symptoms were reduced. The results indicate that the bias is state dependent and not a permanent trait. The baseline negative bias did not differ between the recovered and non-recovered groups.

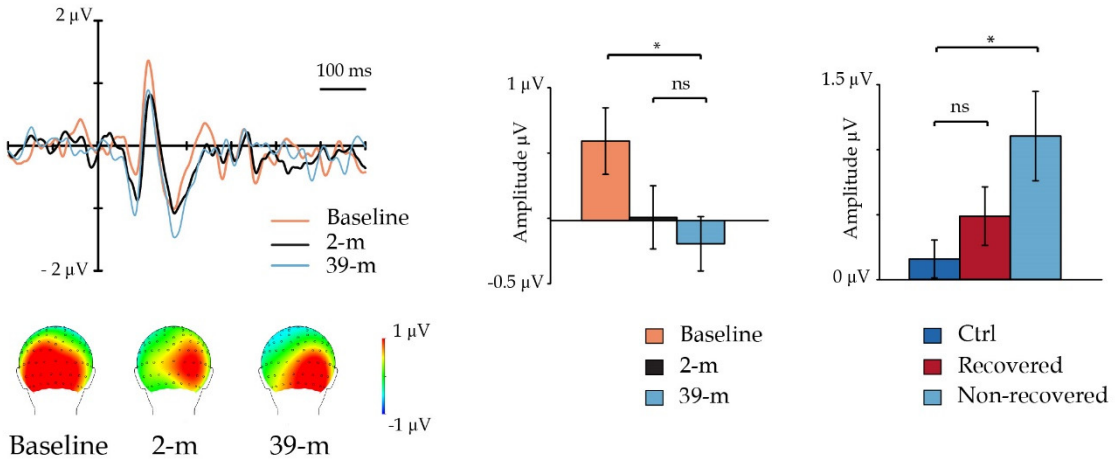

FIGURE 3 Negative bias reflected by P1 differential response (sad deviant face minus neutral standard face) in Study III. Left panel: Grand-averaged P1 differential responses and topographical maps of the responses (at 114 ms after stimulus onset) at the baseline, at 2-m and at 39-m measurement. The responses are averaged over the left and right occipital electrode cluster. Middle panel: The mean differential P1 responses (difference of the peak values; sad minus neutral) at the baseline, at 2-m measurement and at 39-m measurement. Right panel: The mean amplitudes for P1 differential responses (difference of the peak values; sad minus neutral) for recovered, non-recovered and control (Ctrl) groups. *p <.05, ns = non-significant. (Figure modified from Ruohonen et al., 2020)

In sum, the results of the studies indicate that the basic automatic processing of sound intensities as well as early processing of emotional visual information is affected in depression. The sound intensity processing was found to be more affected in first-episode depression than in recurrent depression, possibly indicating differences in the monoaminergic system between the subgroups. Depression- and aging-related effects in sound intensity processing were both demonstrated as augmented N1 responses. The findings on P1 response to the emotional facial expressions reflected depression-related negative bias in automatic information processing and suggested that the bias is not a permanent trait.

4 DISCUSSION

The focus of this dissertation was to investigate biomarkers for depression and aging in early electrical brain responses. In **Study I**, early ERPs to auditory intensity changes were examined between depressed participants with either first-episode or recurrent depression and non-depressed controls. Larger N1 responses were found in the first-episode depression group, compared to the recurrent depression group and control group, for rare sounds that deviated in intensity from the repeated sound. The finding indicates abnormal change detection and possible deficits in the monoaminergic neurotransmitter function in the first-episode depression group. In **Study II**, depressed and non-depressed younger adult and older adult groups were compared using ERPs to intensity changes. Compared to the younger groups, greater intensity dependence of the N1 responses was found in older adult groups indicating a possible deficit in the monoaminergic neurotransmitter function in aging. In addition, the depression- and aging-related effects were demonstrated as augmented N1 responses to rare and repeated stimuli, indicating deficits in the sensory gating of irrelevant stimuli. **Study III** investigated early automatic responses to facial expressions between depressed participants and controls, the stableness of the responses during symptom reduction and the association of the responses with treatment response to cognitive therapy. Larger P1 responses were found for sad faces, compared to neutral faces, in the depressed group, but not in the control group, indicating a negative bias in early information processing. The responses reflecting a negative bias decreased in the 2-month and 39-month follow-up when depression symptoms were reduced, indicating that the bias is not a stable trait. The negative bias did not differ between the depressed group that recovered and the group that did not recover after a brief cognitive therapy intervention.

4.1 Auditory intensity processing differs according to illness history

The finding of larger N1 responses to deviant sounds in **Study I** points to the altered processing of intensity changes in the first-episode depression group, compared to the recurrent depressed and control groups. Augmented N1 responses to intensity changes have been previously found in some subgroups of depressed participants (i.e., in atypical depression, see Lee, et al., 2014; in non-melancholic depression, see Fitzgerald et al., 2009), but recurrent and first-episode depression groups have not been compared before. The results provide support for the applicability of altered N1 intensity processing as a marker for identifying subgroups of depression based on illness history.

The findings indicate N1 may differ according to illness history because the responses were larger in the first-episode depression group, compared to the recurrent depression group. In fact, only the first-episode group differed significantly from the controls. Groups with different illness histories were examined here because recurrent depression has been associated with cumulative brain volume and biochemical alterations (Carvalho et al., 2014; Moylan et al., 2013), but it is not clear if the illness progression is also reflected in neurotransmitter function. Because N1 responses to intensity changes have been suggested to reflect monoaminergic function (Hegerl et al., 2001; Hegerl & Juckel, 1993; Lee et al., 2011; Pogarell et al., 2004), it was assumed that one or both of the depression groups may differ in their N1 responses. However, no specific hypothesis of the group difference could be made based on previous studies. The alterations found in N1 could reflect a difference in the monoaminergic neurotransmitter function between the recurrent depression and first-episode depression groups. There could be a difference between the groups in neurotransmission function, for example, because of the longer history with antidepressant treatment the recurrent depression group had. It could also be the case that the recurrent depression group included participants who are affected by some other neurotransmitter system—for example, participants with treatment-resistant depression that has been associated with the imbalance of GABAergic and glutamatergic neurotransmitter systems (Murphy, Sarris, & Byrne, 2017). Future studies should directly investigate if the differences found between first-episode and recurrent depression in N1 responses reflect differences in monoaminergic neurotransmission between the groups.

The intensity change detection protocol applied in the **Study I** was not similar to the previous studies that have investigated the intensity dependence of auditory responses (Gallinat et al., 2000; Jaworska et al., 2012a; Linka et al., 2007; Park et al., 2010), but it involves intensity changes and therefore could be assumed to measure similar processes. Previous studies on intensity dependence have employed a protocol wherein multiple stimulus intensities are presented with an equal number of sounds for each intensity (Fitzgerald et al., 2009; Gopal et al., 2004; Lee et al., 2014). Although these studies have highlighted the

relevance of intensity processing in depression, they have only focused on one aspect of it—that is, the augmentation or reduction of response relative to an increase in stimulus intensity. Here, with a change detection condition, we were able to show a specific alteration for rarely presented sounds in first-episode depression. The findings did not indicate depression-related augmentation of loud sounds in particular but indicate abnormalities in the intensity change detection, as larger responses were found in the first-episode group for both low- and high-intensity deviant sounds.

The present study was the first to investigate intensity dependence in depression with a change detection condition. A change detection condition offers the advantage of investigating the effect of stimulus presentation rate on the responses. In addition, the condition enables the study of the predictive coding mechanism of the brain, which has been suggested to be abnormal in many psychiatric disorders (Adams, Huys, & Roiser, 2016; Chekroud, 2015; Fletcher & Frith, 2009; Gradin et al., 2011; Kumar et al., 2008; Sterzer et al., 2018). Predictive coding theories postulate that the brain formulates top-down predictors of sensory input and compares the predictions to the bottom-up sensory inputs (Friston, 2005, 2010). When the input does not match the prediction, a prediction error occurs and the predictors are updated to match the bottom-up input. Brain responses to deviating stimuli among repeated stimuli are thought to reflect prediction errors (Friston, 2005; Wacongne, Changeux, & Dehaene, 2012).

As the augmented N1 responses in first-episode depressed participants were specific to rare stimuli, they could reflect alterations in change detection that have been previously found in depression in the MMN response that is elicited after N1. Although no depression-related modulation was found for MMN in **Study I**, it could be the N1 and MMN responses were partly overlapping. Previous studies have suggested that augmented change detection responses (MMN) in depression could reflect cortical overexcitability associated with deficits of inhibition (He et al., 2010; Kähkönen et al., 2007; Restuccia et al., 2015). Increased MMN responses have been previously associated with higher distractibility—for example, in patients with chronic alcoholism or head injury (review see, Näätänen et al., 2012). However, it could also be speculated that the enhanced N1 responses to deviant sounds in the first-episode depression group reflect the compensatory effects elicited by the first encounter with the illness. The first onset of depression is usually associated with major life stressors, whereas later episodes can be triggered by minor stressors because of sensitization (Post, 1992; Stroud, Davila, Hammen, & Vrshek-Schallhorn, 2011). Therefore, it could be that the larger N1 responses in the first-episode group reflect a reaction to the first encounter with the illness and an attempt to monitor potentially dangerous events in the environment. Similar overexcitability was not found in participants with a history of multiple episodes, perhaps because of spontaneous adaptation or a longer history of antidepressant treatment.

4.2 N1 responses to intensity changes demonstrate depression- and aging-related effects

Study II focused on the effects of depression and aging on intensity processing. Greater intensity dependence of N1 responses was found in older adults, compared to younger adult groups, while no depression-related effects were found for it. However, the sensory gating analysis revealed larger N1 responses in older adults and in depressed adults for both repeated and rare sounds. This latter finding thus indicates similar alterations in sound intensity processing for depression and aging.

The finding that intensity dependence was related to aging, but not to depression was unexpected. However, intensity dependence has not been studied before in old age. Some previous studies investigating young adult and middle-aged participants with samples including participants with and without psychiatric disorders (including depression) found no association between N1 intensity dependence and age (Linka et al., 2007; Linka et al., 2009; Park et al., 2010). However, one study found aging to be associated with weaker intensity dependence in depressed female participants (Min et al., 2012). Since the previous studies have not been conducted on older adults over 65 years of age, they are difficult to compare to the present study. The finding of enlarged N1 amplitude in older adults could indicate a deficit of the monoaminergic system in aging because a stronger N1 intensity dependence has been suggested to reflect weaker serotonergic neurotransmission (Hegerl et al., 2001; Hegerl & Juckel, 1993) and, possibly, dysfunctions in the dopamine system (Lee et al., 2011; Pogarell et al., 2004). Pronounced abnormalities in monoaminergic neurotransmission could be expected in older adults because aging has been associated with deficits in serotonin (Meltzer et al., 1998; Rodríguez et al., 2012) and dopaminergic neurotransmission (Barili et al., 1998). In agreement with previous studies that have been conducted on young adults and middle-aged adults (Jaworska et al., 2012a; Linka et al., 2007; Park et al., 2010; for contrary findings, see Gopal et al., 2004), we found no depression-related effect in intensity dependence. Since previous studies have found intensity dependence to differ between some subgroups of depression (Fitzgerald et al., 2009; Lee et al., 2014), it could be that the depression effects were not found in **the study II**, because the sample may have included participants with various depression subtypes.

It should be noted that intensity dependence was analyzed in this study with a novel method. As mentioned above, the change detection protocol differs from a typical intensity dependence study in the presentation rate of the stimuli. To make the analysis more comparable to previous studies, only the responses to standards following the deviants were investigated. This way, the effects of repetition on the responses should be reduced, since a deviant has disrupted the series. Future studies should confirm to what extent the intensity dependence response derived from the oddball condition resembles those from the traditional

intensity dependence condition by directly comparing the responses from the two conditions.

Another main finding of **Study II** was that both depression- and aging-related effects were found as augmented N1 responses to repeated and rare sounds, possibly reflecting sensory gating deficit. In older adults, the augmentation was found for the repeated sounds and high-intensity rare sounds, while in the depression groups the augmentation was found for all the stimulus types. The augmented N1 response for repeated sounds in older adults is consistent with the previous studies (Alain & Woods, 1999; Amenedo & Díaz, 1998; Anderer et al., 1996; Fabiani et al., 2006; Stothart & Kazanina, 2016; Strömmer et al., 2017), but surprisingly, the effect was also found for the high-intensity rare sounds. Since previous studies on sensory gating in aging have rarely investigated the processing of the infrequently presented sounds, it is difficult to explain the findings. However, one study found similarly aging-related N1 augmentation for both repeated and rare sounds (Tusch et al., 2016). The authors suggested that this early amplification of the responses could index an attempt to compensate for slowed processing speed in aging to monitor potentially relevant events in the unattended environment.

The depression-related effects for sensory gating were only found when controlling for medication or when examining only the non-medicated participants. In contrast to **Study I**, the N1 augmentation in depression in **Study II** was found for not only the rarely presented sounds but also the repeated sounds. However, the discrepancies between the studies could be related to differences in the sample—since in **Study II,** most of the participants had recurrent depression (over 60%) and in **Study I**, the effect was found only in the first-episode group. Furthermore, in **Study II,** the participants were older than in **Study I**, and age was also found to have an effect on the responses. The findings may indicate general cortical overexcitability in depression, as the effect was found for both repeated and rare stimuli and thus does not reflect typical sensory gating effects (i.e., failure to suppress responses to repeated sounds; Friedman, 2011). It could be speculated that the antidepressants may dampen the overexcitability, and therefore, the effect is not found when medicated participants are included in the comparison.

The findings of **Study II** are similar to **Study I** in the sense that the processing alterations, either related to depression or aging, were found as cortical overexcitability reflected by the enlarged N1 responses. It could be the case that the augmented N1 responses indicate higher distractibility and attentional deficits in depression and aging, since N1 has been suggested to reflect the preattentive triggering of attention (Näätänen, 1990). Furthermore, sensory gating deficit has been previously linked to attentional impairments (for a review, see Potter, Summerfelt, Gold, & Buchanan, 2006).

No differences between the groups were found in the MMN responses in either **Study I** or **Study II**. This stands in contrast to previous studies that have found altered MMN responses in depressed participants and older adults to frequency and duration changes (Chen et al., 2015; He et al., 2010; Kähkönen et

al., 2007; Naismith e al., 2012; Näätänen et al., 2011; Qiao et al., 2013; Restuccia et al., 2016; Takei et al., 2009). However, some previous studies have also failed to find depression- (Umbricht et al., 2003) or aging-related effects (Strömmer et al., 2017) in MMN. Depression- and aging-related alterations in the processing of stimulus intensity could show a specific pattern where early responses are affected (i.e., N1), whereas the later processing (i.e., MMN) remains intact. However, it is possible that the N1 and MMN responses may have overlapped in the present studies—as they were not separated, for example, with blind source separation methods, such as independent component analysis.

4.3 Facial expression processing as a state marker of depression

In **Study III**, a negative bias was found in the depression group for sad faces, compared to neutral faces, as indexed by enlarged P1 responses, indicating that the bias is already present in the automatic early processing stage. The negative bias decreased in the follow-up measurements when the depression symptoms were reduced, suggesting that the bias is not a permanent trait. The initial negative bias was larger compared, to the controls in the group who did not show clinically significant recovery after a brief cognitive therapy. However, since the brain responses did not directly differ between the recovered and non-recovered groups, there is no indication that P1 responses to sad faces could serve as a biomarker for treatment response.

The depression-related negative bias in early processing was revealed by employing a change detection condition wherein sad and happy faces were rarely presented among repeated neutral stimuli. A change detection condition allows for the investigation of automatic early processing, as it does not require attention from the participant. Furthermore, presenting the emotional faces as rare deviants was expected to bring out the processing bias because responses are typically larger for rarely presented stimuli, since rareness can increase the biological significance of a stimulus. Previous studies that have applied different experimental conditions have also found larger P1 for sad faces, compared to neutral faces, in depressed patients (Dai & Feng, 2012; Zhang et al., 2016). These studies have confirmed P1 alterations both in attended tasks where the faces were evaluated (Dai & Feng, 2012) and in subliminally presented faces (Zhang et al., 2016). Together, the findings support the theory that cognitive bias in depression is found in various stages of stimulus processing, including the automatic level, as Beck (2008) suggested.

In contrast to some previous studies that have found larger N170 responses to sad faces, compared to happy / neutral faces, in depressed participants (Zhang et al., 2016; Zhao et al., 2015), no group differences were found in the N170 responses in **Study III**. However, some studies have similarly not found depression-related negative bias in N170 responses (Jaworska, Blier, Fusee, & Knott, 2012b; Xu et al., 2018) or instead of finding a specific bias for negative faces have found alterations in change detection in general (Chang et al., 2010). The

discrepancies could be related to differences in the experimental tasks (e.g., attended vs. nonattended stimuli), protocols and stimuli (e.g., oddball condition vs. equal probability of stimulus types) or sample demographics. However, the finding of depression-related effects in P1 but not in N170 could indicate abnormalities in task-irrelevant facial expression processing are specific to the early stage of processing. Previous studies have indicated that P1 and N170 may reflect different stages of facial expression processing—with P1 reflecting the encoding of low-level visual features and early differentiation between emotional expressions and N170 reflecting slower, but more detailed, processing of emotional expressions (Batty & Taylor, 2003).

A decrease in the negative bias, mirroring symptom reduction, was found from the baseline to the 2-m and the 39-m measurements, supporting the state dependency of the negative bias. This finding suggests that the bias is not a permanent trait but is instead dependent on the depression symptoms. This was the first longitudinal study conducted on ERPs to facial expressions in depression, although some fMRI studies have been conducted and have shown alterations in facial expression processing following treatment with cognitive behavioral therapy (Fu et al., 2008) or antidepressants (Victor et al., 2010). Based on cross-sectional studies investigating ERPs to facial expressions in depression, some have argued negative bias is a stable cognitive vulnerability because it is also present in sub-clinically depressed participants (Dai & Feng, 2012; Dai et al., 2016). However, in the previous studies, the sub-clinically depressed groups also experienced clear depression symptoms, as measured by depression scores, and therefore, the studies did not give information on how the responses were affected by symptom reduction (Dai & Feng, 2012; Dai et al., 2016). In contrast, in the **study III,** the effect of symptom reduction could be investigated, since the depression scores had dropped below the cut-off limit for clinical depression in the majority of the participants (58% and 65% of the participants at the 2-m and 39-m measurements, respectively). It is, however, possible that the negative bias is more stable for attended processes wherein the stimuli are consciously evaluated, as was the case in the studies conducted by Dai and Feng (2012) and Dai et al. (2016). In contrast to this view, findings from other studies applying attended conditions suggest that the negative bias could be related to illness progression or depression severity. For example, Chen et al. (2014) found larger N170 responses to sad faces in the recurrent depression group, compared to the first-episode depression group, in an attended change detection condition. They suggested that N170 responses to sad faces may predict the sequential progression of the illness since the responses were positively correlated with depressive episodes. Further support for state-related negative bias comes from Wu et al.'s (2016) study, where the number of depression symptoms were found to correlate with N170 amplitudes to sad faces.

The brain responses were also investigated to find markers of response to brief cognitive behavioral therapy treatment. No differences in P1 were found between the recovered and non-recovered groups. The negative finding could, however, be related to the small sample size. Although the depression groups

did not differ, the negative bias was larger in the non-recovered group, compared to the controls, whereas the recovered group did not differ from the controls. There are no previous ERP studies that have investigated facial expression processing as a marker for treatment response to psychological treatment. However, one study found a larger late positive potential for aversive pictures to predict better treatment responses to cognitive behavioral therapy (Stange et al., 2017). In addition, fMRI studies have been conducted. The previous studies have shown mixed results, sometimes indicating a greater initial negative bias to predict better treatment response (Ritchey et al., 2011), whereas in some studies a lower negative bias predicted better response (Fu et al., 2008; Siegle et al., 2006). Fu et al.'s (2008) study is the most comparable to our study because it utilized facial expressions. Similar to our findings, the authors found that the group with a better treatment response had a more similar brain response pattern relative to the controls than the non-responder group.

The initial bias for sad faces could be speculated to hinder the responsiveness to intervention, for example, by affecting social interaction. Abnormal facial expression processing could increase feelings of social rejection and lead to social withdrawal. Issues of social interaction are common risk factors for depression (for a review, see Kupferberg, Bicks, & Hasler, 2016). The enhanced responses in the processing of sad faces could also be explained through the predictive coding framework, since negative schemas in depression can be thought of as prior representations or predictors (Adams et al., 2016; Chekroud, 2015). Because of the negative predictors, environmental cues related to rejection are given greater weight, whereas sensitivity to rewards is reduced. Participants with a greater negative bias could perhaps benefit from treatment that targets the negative bias. Previous studies have shown that attentional bias training may reduce depression symptoms and modify the bias (Dai, Hu, & Feng, 2019; Wells & Beevers, 2010). Wells and Beevers (2010) found that reductions in depression symptoms were mediated by reductions in negative bias, suggesting that bias may precede depression. It could also be the case that the participants with a larger perceptual negative bias would benefit more from some other treatment option, such as antidepressants (Roiser, Elliott, & Sahakian, 2012). They could also be slower in their treatment response and benefit from a longer treatment period. These aspects should be studied in the future.

4.4 Limitations of the studies

There are some limitations to the studies. The sample sizes were relatively small in all the studies. Therefore, some effects may have been masked. The findings in **Study III** related to treatment response comparison should be regarded as preliminary because of the small sample size and large imbalance in the number of participants between the groups.

Another limitation is the heterogeneity of the participants in the depression groups. This is an inherent issue for depression studies because depression is a

heterogeneous disorder with multiple pathways and underlying pathophysiologies (Hasler et al., 2004). For example, the presence of comorbid anxiety disorders in the sample could obstruct the findings, as anxiety and depression have been associated with distinct neural activity patterns (Etkin & Schatzberg, 2011) and differences in information processing biases (Gotlib & Joormann, 2010). Another concern relates to the categorization of the first-episode and recurrent depression groups. It is possible that some of the participants in the first-episode group may later experience recurrent episodes. Therefore, it cannot be confirmed that the groups differ only in the number of episodes (one episode or multiple episodes).

One factor that could be, in principle, controlled for in future studies is the medication status. All the studies of this doctoral thesis included both medicated and non-medicated participants, and in **Study II,** medication was found to affect the responses. Future studies should confirm the findings with non-medicated participants who have no previous medication history. There was also a gender imbalance in the studies, as most of the participants in **Studies I** and **III** and all the participants in **Study II** were women. Therefore, it is not known how well the findings generalize to men. On the other hand, focusing only on women (as in **Study II**) can reduce the heterogeneity in the data and be considered a strength.

4.5 Conclusions and future directions

Taken together, the studies in this thesis show depression-related alterations in auditory and facial expression processing, and aging-related effects for auditory intensity processing. The findings give support for early brain responses as potential markers of depression and aging. **Study I** indicated depression-related alterations in N1 responses to auditory intensity changes for certain subgroups of depressed participants. Enlarged N1 responses to rare sounds were indicated for first-episode depression, compared to recurrent depression. In **Study II**, a greater intensity dependence of N1 responses was found in older adults, compared to younger adults, but depression- and aging-related effects were similarly presented as augmented N1 responses. The findings support the measures of N1 intensity processing in reflecting depression- and aging-related alterations and suggest that aging and the number of depressive episodes should be taken into account when investigating biomarkers. **Study III** indicated that the P1 response to sad face processing could be used as a state marker of depression. The study showed that the alteration may not be a permanent trait related to depression but could mark the state of the illness. Mirroring the findings on auditory modality, the depression-related alterations were again found in the early stage of automatic processing (P1) but not in a later N170 response.

The heterogeneity of depression poses a challenge in finding depression biomarkers. In this thesis, the heterogeneity was taken into account by analyzing different subgroups of depressed participants (first-episode and recurrent and

different age groups). However, more data-driven categorizations could be used to define subtypes that can be expected to differ in the underlying pathophysiology. A recent fMRI study found, based on patterns of functional connectivity, four different neurophysiological subtypes for depression (Drysdale et al., 2017). The subtypes were associated with distinct symptom profiles, but the categorization could not have been done based only on the symptoms. The study illustrates a discrepancy between clinical categorization and categorization based on neurobiological findings. For example, a participant who has a generalized anxiety disorder diagnosis could be classified, based on the neuroimaging data, as fitting a depression subtype. Biomarkers could be used to find more homogenous subgroups of depression and more objectively define diagnostic groups based on etiology and pathophysiology. Combinations of different biomarkers could be used to identify various subgroups of depression (Quevedo & Yatham, 2018). Biomarker studies would benefit from a combination of different measures and large data sets and standardized protocols used across studies (Olbrich & Arns, 2013).

One possibility for a future study would be to combine intensity N1 responses and ERPs to facial expressions to predict if cognitive psychotherapy or antidepressant treatment would be more suitable for a patient. N1 responses have been used previously as predictors of antidepressant response (Gallinat et al., 2000; Jaworska et al., 2013; Juckel et al., 2007; Lee et al., 2015, Lee et al., 2005), whereas, in **Study III** we found some indications that a pronounced negative bias in sad face processing (at least compared to non-depressed controls) could be related to worse treatment response to psychological intervention. Antidepressants and psychological treatment have been suggested to differ in the way they affect cognitive and emotional processes, and therefore, the treatment effects may depend on the underlying bias (DeRubeis, Siegle, & Hollon, 2008; Roiser et al., 2012). Antidepressants have been suggested to affect emotions by dampening down low-level perceptual biases, whereas cognitive therapy is suggested to have more indirect effects by increasing cognitive control of emotions in a top-down manner (Roiser et al., 2012). Therefore, it has been suggested that cognitive therapy may work better for individuals who experience deficits in cognitive control reflected by biases in attentional processes, whereas antidepressants may be more suitable for individuals with low-level perceptual negative bias (Roiser et al., 2012). Considering this suggestion, it would be interesting to examine if the patients with intact automatic processing of sad faces and who benefit from cognitive therapy (the recovered group in **Study III**) experience negative bias in attentive conditions (i.e., a deficit in top-down control). Auditory N1 measures could be combined with measures of facial expression processing in both automatic and attentive conditions to investigate the proposed difference in predictors of antidepressant and cognitive therapy treatment effects.

Although ERP measures provide intriguing possibilities as biomarkers, they have still mostly been studied on a group level. Currently, ERP-measures have not provided a reliable way to diagnose depression or predict treatment

response based on a measure of the individual participant. This is partly due to large variability in the ERP responses between individuals that may reflect factors other than the investigated clinical marker. For example, differences in cortical folding and skull thickness and factors related to measurement errors can obstruct the findings (Luck et al., 2011). To be able to use ERPs in clinical settings, it is necessary to develop standardized protocols for the measurements and develop a methodology for analyzing individual data (Luck et al., 2011; Olbrich & Arns, 2013). One option would be to use a machine learning technique, a form of artificial intelligence, to predict treatment response at the level of a single participant. Machine learning has been used in a few studies to identify features from EEG for predicting response to antidepressants (for a review, see Wade & Iosifescu, 2016), but studies aimed at predicting treatment response to psychological intervention at the individual participant level are missing.

In conclusion, the studies in this thesis show that early brain responses reflect depression- and aging-related effects. In the auditory modality, the N1 responses were differently associated with depression subgroups that differed in illness history but showed somewhat similar effects for depression and aging. In the visual modality, the enlarged P1 responses to sad faces reflected depression state. However, in all the measurements where processing alterations were found, they were demonstrated as augmented early brain responses relative to typical processing. This could reflect neuronal overexcitability and may be related to the distractibility that is a common symptom in depression (World Health Organization, 2010) and aging (Hasher & Zacks, 1988; Weeks & Hasher, 2014) and could be linked to theories of predictive coding (Friston, 2005; Chekroud, 2015). The findings highlight the potential of early brain responses as markers to be developed for diagnosing depression.

YHTEENVETO (SUMMARY)

Sähköfysiologiset aivovasteet masennuksen ja ikääntymisen hermostollisina merkkeinä

Masennus on monimuotoinen mielenterveyden häiriö, joka voi ilmetä hyvin erilaisina oirekuvina ja jonka taustalla vaikuttavat monenlaiset tekijät. Viime vuosina aivotutkimuksen avulla on pyritty tunnistamaan masennukseen liittyviä muutoksia aivojen tiedonkäsittelyssä, sillä tätä tietoa voidaan mahdollisesti hyödyntää masennusdiagnostiikan kehittämiseen ja hoitovaikutusten ennustamiseen. Masennukseen tiedetään liittyvän vääristymiä paitsi tunnepitoisten ärsykkeiden käsittelyssä myös automaattisessa yksinkertaisten kuuloärsykepiirteiden käsittelyssä. Tämän väitöskirjan osatutkimuksissa pyrittiin tunnistamaan masennukseen liittyviä tiedonkäsittelyn muutoksia mittaamalla erilaisiin aistiärsykkeisiin syntyviä aivojen sähköisiä jännitevasteita.

Ensimmäisessä osatutkimuksessa tutkin, miten aivojen automaattinen kyky käsitellä äänen voimakkuuden muutoksia eroaa verrokkihenkilöiden sekä niiden masentuneiden välillä, joilla oli diagnosoitu joko yksittäinen masennustila tai toistuvan masennuksen masennusjakso. Äänen voimakkuuteen liittyvien aivovasteiden on esitetty heijastelevan masennuksen kannalta olennaisten välittäjäainejärjestelmien toimintaa. Lisäksi masennukseen on liitetty poikkeamia aivovasteissa, jotka heijastavat aivojen automaattista kykyä havaita äänisarjoissa tapahtuvia muutoksia. Käytimme nyt uudenlaista äänen voimakkuuden muutoksia sisältävää ärsykejärjestelyä aivovasteiden tutkimuksessa masentuneilla. Tulokset osoittivat suurentuneita varhaisia aivovasteita äänen voimakkuuden muutoksiin niillä masentuneilla, joilla oli diagnosoitu yksittäinen masennustila, mikä viittaa ylivirittyneisyyteen aivokuoren toiminnassa ja saattaa heijastaa puutteita monoamiinivälittäjäaineiden toiminnassa. Löydökset kannustavat tulevaisuudessa kehittämään äänen voimakkuuteen liittyviä mittareita, jotka hyödyntävät aivojen sähköisiä vasteita eri masennustyyppien diagnostiseen erotteluun.

Toisessa osatutkimuksessa pyrittiin löytämään masennukseen ja ikääntymiseen liittyviä vaikutuksia aivovasteissa äänen voimakkuuden muutoksiin. Tutkimuksessa vertailtiin aivovasteita neljän ryhmän välillä: masentuneet nuoremmat aikuiset, ei-masentuneet nuoremmat aikuiset, masentuneet iäkkäät aikuiset ja ei-masentuneet iäkkäät aikuiset. Tutkimuksessa tarkasteltiin aivovasteiden riippuvuutta äänen voimakkuudesta, sillä aiemmin on osoitettu, että aivovasteiden jyrkkä kasvu äänen voimakkuuden kasvaessa heijastaa puutteita serotoniinivälittäjäainejärjestelmässä. Vaikka suurin osa aiemmista tutkimuksista ei ole kyennyt osoittamaan eroja masentuneiden ja ei-masentuneiden välillä näissä vasteissa, on jyrkemmän aivovasteiden kasvun (mikä viittaa puutteelliseen serotoniinijärjestelmään) havaittu ennustavan hyötymistä serotoniiniin vaikuttavista masennuslääkkeistä. Lisäksi on löydetty eroja joidenkin masennuksen alatyyppien välillä. Äänen voimakkuuden

käsittelyä ei ole kuitenkaan aiemmin tutkittu ikääntyneillä masentuneilla. Koska sekä ikääntymiseen että masennukseen on liitetty serotoniinijärjestelmän puutoksia, arveltiin, että äänen voimakkuuteen liittyvät aivovasteet olisivat erityisesti poikkeavia ikääntyneillä masentuneilla verrattuna muihin ryhmiin. Odotusten vastaisesti jyrkempi aivovasteiden kasvu äänen voimakkuuden kasvaessa liittyi ikääntymiseen, muttei masennukseen. Kuitenkin sekä ikääntymisen että masennuksen vaikutukset ilmenivät suurentuneina varhaisina aivovasteina toistuvien ja harvoin esitettyjen äänten käsittelyssä, mikä viittaa puutteisiin kyvyssä suodattaa epäolennaista aisti-informaatiota.

Kolmannessa osatutkimuksessa selvitin masennukseen liitettyä negatiivista vääristymää kasvonilmeiden automaattisessa käsittelyssä. Tutkimuksessa verrattiin surullisiin, iloisiin ja neutraaleihin kasvonilmekuviin syntyviä aivovasteita masentuneiden ja ei-masentuneiden välillä. Aiemmin on osoitettu, että masennukseen liittyy tarkkaavuuden suuntautuminen surullisiin kasvonilmeisiin, mikä ilmenee myös suurentuneina aivovasteina surullisiin kasvonilmeisiin. Aiemmin ei ole kuitenkaan juuri tutkittu, ilmeneekö samanlaista vääristymää automaattisissa aivovasteissa silloin, kun kasvonilmeitä ei tietoisesti tarkkailla. Lisäksi tutkin tämän negatiivisen vääristymän pysyvyyttä 2 kuukauden ja 39 kuukauden seurannassa. Negatiivisen vääristymän on esitetty olevan pysyvä piirre masennuksen taustalla, mutta tämä päätelmä on perustunut pitkälti poikkileikkaustutkimuksiin, joissa on vertailtu kliinisesti masentuneita ja masennuksesta toipuneita henkilöitä tai henkilöitä, joilla masennusoireiden määrä ei täytä diagnostisia kriteerejä. Väitöskirjani kolmas osatutkimus on tiettävästi ensimmäinen tutkimus, jossa seurattiin muutosta aivojen sähköisissä vasteissa samoilla tutkittavilla masennusoireiden vähennyttyä. Näin voitiin tutkia, miten masennusoireiden väheneminen vaikuttaa aivovasteisiin. Tutkimuksessa selvitettiin myös, miten vasteet eroavat niiden masennusryhmien välillä, jotka hyötyvät ja jotka eivät hyödy psykologisesta hoidosta. Tulokset osoittivat negatiivisen vääristymän ilmenevän surullisiin kasvonilmeisiin syntyvissä varhaisissa automaattisissa aivovasteissa masentuneilla. Negatiivinen vääristymä poistui 2 kuukauden ja 39 kuukauden jälkeisissä seurannoissa, joissa masennusoireet olivat vähentyneet, mikä viittaa siihen, että negatiivinen vääristymä ei ole pysyvä piirre. Vertailu hoidosta hyötyneiden ja ei-hyötyneiden sekä ei-masentuneiden välillä osoitti, että surulliset kasvonilmeet herättivät suurempia aivovasteita kuin neutraalit ilmeet niillä masentuneilla, jotka eivät hyötyneet hoidosta, verrattuna ei-masentuneisiin henkilöihin. Vahvaa tukea hoitovaikutusten ennakointiin ei kuitenkaan saatu, sillä aivovasteet eivät suoraan eronneet hoidosta hyötyneiden ja ei-hyötyneiden masentuneiden välillä.

Tämä väitöskirja osoittaa masennukseen liittyvän poikkeamia varhaisissa automaattisissa aivovasteissa niin yksinkertaisten aistiärsykkeiden käsittelyssä kuin tunnepitoisten ärsykkeiden käsittelyssä. Ääniärsykkeiden käsittelyssä masennukseen liittyvät poikkeamat vastasivat osin ikääntyneillä havaittuja muutoksia, eikä masennuksen ja ikääntymisen vaikutuksia voitu siten erotella. Poikkeavat aivovasteet viittaavat vaikeuteen suodattaa epäolennaisia aistiärsykkeitä, mikä mahdollisesti liittyy masennuksessa usein ilmeneviin

tarkkaavuuden pulmiin ja häiriöherkkyyteen. Poikkeamat varhaisissa aivovasteissa saattavat vaikuttaa korkeampiin kognitiivisiin toimintoihin, sillä nämä rakentuvat varhaisempien tiedonkäsittelyn vaiheiden pohjalle. Tulokset antavat viitteitä mahdollisuudesta kehittää aivovastemittauksia diagnostisina työkaluina eri masennuksen alatyyppien erotteluun sekä masennustilan seurantaan.

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ORIGINAL PAPERS

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BRAIN RESPONSES TO SOUND INTENSITY CHANGES DISSOCIATE DEPRESSED PARTICIPANTS AND HEALTHY CONTROLS

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Brain responses to sound intensity changes dissociate depressed participants and healthy controls

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ABSTRACT

Depression is associated with bias in emotional information processing, but less is known about the processing of neutral sensory stimuli. Of particular interest is processing of sound intensity which is suggested to indicate central serotonergic function. We tested weather event-related brain potentials (ERPs) to occasional changes in sound intensity can dissociate first-episode depressed, recurrent depressed and healthy control participants. The first-episode depressed showed larger N1 amplitude to deviant sounds compared to recurrent depression group and control participants. In addition, both depression groups, but not the control group, showed larger N1 amplitude to deviant than standard sounds. Whether these manifestations of sensory over-excitability in depression are directly related to the serotonergic neurotransmission requires further research. The method based on ERPs to sound intensity change is fast and low-cost way to objectively measure brain activation and holds promise as a future diagnostic tool.

1. Introduction

Cognitive theories of depression have proposed that depression is associated with bias in information processing leading to selective attention to the negative aspects of experiences (Beck, 1967; Beck, 2008). This information processing bias is suggested to be automatic, rapid and involuntary (Beck, 2008). Many empirical studies give support for this theory by showing, for example, that depressed individuals have difficulty in disengaging from emotionally negative information and they show reduced inhibition of irrelevant emotional information (for a review, see Gotlib & Joormann, 2010). However, recent electrophysiological studies using event-related potentials (ERPs) suggest that depression-related bias in information processing is not restricted to emotional stimuli but can also be seen in the processing of basic sensory information (e.g. Chang et al., 2011; Kähkönen et al., 2007).

Auditory processing in depression has been under investigation because the primary auditory cortex is known to receive widespread projections from neurons using serotonin (Hegerl, Gallinat, & Juckel, 2001), a neurotransmitter that is closely associated with depression (Coppen, 1967; Leonard, 2000; Maes & Meltzer, 1995). A specific feature of auditory stimulus encoding, namely the intensity dependence of auditory evoked potentials (AEPs) may be relevant for depression, because it is suggested to reflect central serotonergic function (Hegerl et al., 2001; Hegerl & Juckel, 1993; Juckel, Hegerl, Molnár, Csépe, & Karmos, 1999; Juckel, Molnnár, Hegerl, Csépe, & Karmos, 1997; Strobel et al., 2003; Wutzler et al., 2008). Intensity dependence refers to a phenomenon where auditory responses increase when the intensity of an auditory stimulus increases (Hegerl et al., 2001). This reactivity can be seen when measuring early auditory evoked responses such as the N1. The N1 is an automatic response elicited in the auditory cortex at approximately 100 ms after the stimulus onset, and reflects stimulus encoding (Näätänen, 1990). Intensity dependence is measured in experimental designs where sinusoidal sound stimuli of different intensities are presented in a random order. There are considerable individual differences in the strength of intensity dependence (Hegerl et al., 2001). Some individuals show a steeper increase in N1 responses to increases in stimulus intensity while others show only weak intensity dependence. Studies have linked strong intensity dependence to low serotonergic activity while weak intensity dependence (only a small increase in amplitude in response to an increase in stimulus intensity) reflects high serotonergic activity (Hegerl et al., 2001; Hegerl & Juckel, 1993; Juckel et al., 1997). However the link between intensity dependence and serotonergic system is mainly based on animal studies and also other neurotransmitters, such as dopamine, have been suggested to modulate the intensity dependence of AEPs (Bruneau, Barthelemy, Jouve, & Lelord, 1986; Juckel et al., 2008, 1997; Lee et al., 2011; O'Neill, Croft, & Nathan, 2008; Strobel et al., 2003). However studies with depressed participants have shown that individuals with strong intensity dependence have better treatment response with SSRI

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medications (selective serotonin reuptake inhibitors) compared to those with weaker intensity dependence (e.g. Gallinat et al., 2000; Jaworska et al., 2013; Juckel et al., 2007; Lee, Park, Lee, & Shim, 2015; Lee, Yu, Chen, & Tsai, 2005).

Another auditory ERP-component that has been studied in depression is the mismatch negativity (MMN). MMN, an indicator of automatic change detection, is elicited by the temporofrontal network (Alain, Woods, & Knight, 1998) in response to a rarely presented deviant sound interspersed with frequently presented standard tones (Näätänen, Gaillard, & Mäntysalo, 1978). Alterations in MMN response are seen in many neuropsychiatric conditions, and they are thought to reflect cognitive decline or dysfunction (for a review, see Näätänen et al., 2011). Studies on depression have shown mixed results; some studies have reported decreased MMN response to duration and frequency changes in sound in the depressed group compared to the controls (Chen et al., 2015; Naismith et al., 2012; Qiao et al., 2013; Takei et al., 2009 for a negative result see Umbricht et al., 2003) while others have demonstrated increased MMN responses to frequency changes in individuals with depression (He et al., 2010; Kähkönen et al., 2007; Restuccia, Vollono, Scaloni, Buccelletti, & Camardese, 2015). The conflict in these findings could be explained by differences in depressed populations or in experimental designs employing changes in frequency or duration. However, to our knowledge intensity-MMN has not been previously studied, which is surprising since intensity dependency is associated with the serotonergic system affected in depression (Hegerl et al., 2001; Hegerl & Juckel, 1993; Juckel et al., 1997). However, Restuccia et al. (2015) compared the frequency-MMN between depressed and healthy controls in high- and low-intensity conditions. The MMN was increased in depressed patients compared to controls only when high-intensity stimuli were applied. This phenomenon is in line with the previously referenced intensity dependence studies that show larger responses to increasing stimulus intensities in a subgroup of individuals with depression (Gallinat et al., 2000; Hegerl et al., 2001; Jaworska et al., 2013; Juckel et al., 2007; Lee et al., 2015; Lee et al., 2005). Also in those MMN studies that used relatively high-intensity stimuli (60 dB above hearing threshold, or 80 dB), the MMN response increased in depressed participants compared to the controls (He et al., 2010; Kähkönen et al., 2007). Together these results hint that depressed individuals have sensory system that is particularly sensitive to high-intensity sounds. However, it is not clear whether brain responses to sound intensity as such or the change detection process is affected in depressed.

To this end, the present study capitalizes on previous findings on the intensity dependency of auditory evoked potentials (Gallinat et al., 2000; Hegerl et al., 2001; Jaworska et al., 2013; Juckel et al., 2007; Lee et al., 2015; Lee et al., 2005) and those on auditory change detection (He et al., 2010; Kähkönen et al., 2007; Restuccia et al., 2015). Namely, we will measure automatic ERP responses, N1 and MMN, to rare changes in intensity in depressed and control participants

We will compare the processing of intensity change between controls and participants with different depression diagnosis, namely first-episode depression and recurrent depression. Earlier studies have shown that compared to first-episode depression recurrent depression is associated with more severe cognitive dysfunction (see for example Chen et al., 2013; Fossati et al., 2004; Talarowska, Zajaczkowska, & Galecki, 2015) as well as more pronounced alterations in the structural (review McKinnon, Yucel, Nazarov, & MacQueen, 2009) and metabolic function (de Diego-Adeliño et al., 2013) within the hippocampus. However, there is only one ERP study comparing auditory change detection in first-episode and recurrent depression patients (Chen et al., 2015). In this study no differences between depression groups were found in MMN response to duration deviant sounds. Here we assumed that intensity deviant sounds presented in oddball condition would be particularly sensitive to depression-related dysfunction in sensory encoding and automatic change detection. Based on earlier intensity dependence studies on N1 (Gallinat et al., 2000; Hegerl et al., 2001; Jaworska et al., 2013; Juckel et al., 2007; Lee et al., 2015; Lee et al., 2005) and MMN-studies that used frequency deviant sounds but with high sound intensities (He et al., 2010; Kähkönen et al., 2007; Restuccia et al., 2015) we hypothesize that there will be increased N1 and MMN response amplitude in depressives compared to controls. However, we cannot predict whether the ERP effects will differentiate both the first-episode depression and recurrent depression groups from the control group or just one of the depression groups from the control group.

2. Methods and materials

2.1. Participants

The participants were a group of volunteers recruited with announcements in a local newspaper and via e-mail lists at the University of Jyväskylä. A written informed consent was obtained from the participants before their participation. The experiment was undertaken in accordance with the Declaration of Helsinki. The ethical committee of the University of Jyväskylä approved the research protocol.

The inclusion criteria for all participants were: aged 18–64 years, self-reported normal or corrected-to-normal vision, normal hearing, and right-handedness. The exclusion criteria for both depressive and healthy participants were an anamnesis of any neurological condition such as brain injury, epilepsy, migraine, or sleep apnea. The exclusion criteria for depressed participants also included depression with psychotic features and diagnoses of a psychiatric disorder other than depression, such as substance abuse or addiction within the past year, schizophrenia or other psychotic disorders or bipolar disorders. The information related to inclusion and exclusion criteria was collected with a questionnaire and was also confirmed in a psychiatric interview (see below). In the questionnaire the participants were asked about previous psychiatric diagnoses related to depression or other psychiatric disorders (what was the diagnosis, when diagnosed and in which health care institute). Three participants with self-reported previous psychiatric diagnoses other than depression were included to the sample: one with undefined anxiety disorder, one with anorexia nervosa and one with unclear diagnosis. The exclusion criterion for the control participants also included anamnesis of any psychiatric diagnosis and a mean score of more than 10 in the Beck Depression Inventory-II (BDI-II, Beck, Steer, & Brown, 1996).

Forty-three participants with depressive symptoms (15 males) and 22 healthy controls (eight males) volunteered to participate in the experiment. After this, the data of two depressed and one control participant were omitted due to excessive artefacts in the ERP recording. The mean age of the depressed participants was 42.8 (*SD* 11.2) years, ranging between 18 and 64 years. The mean age for the controls was 39.0 (*SD* 11.9) years, ranging between 21 and 64 years. There was no significant difference in age, $t(60) = 1.25$, $p = .217$, or gender, $x^2(1) = 0.95$, $p = .758$, between the depressed and non-depressed group. In the depression group, the mean score of the BDI-II self-report questionnaire was 23 (*SD* 8.48) and the range was 3–43. Two participants had low BDI-II scores (under 5 points), but they were included in the study because they were diagnosed as depressed in a psychiatric interview (see below). In the control group, the mean score in the BDI-II was 2.8 (*SD* 3.21, range 0–10).

A psychiatric interview, administered by a physician independent of the study, was used to establish the eligibility of participants of the depressed group and to examine the diagnostic status and other background information of them. The diagnosis of depression was based on the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10, World Health Organization, 2010) criteria and the information available from the interviewee. The diagnostic interview applied was the same that is commonly used in primary health care in Finland for diagnosing depression (structured interview based on ICD-10 criteria). The depression symptoms included

in ICD-10 definition of depression, were carefully gone through with a structured interview. The comorbidity was assessed by asking the participant about other psychiatric symptoms and previous diagnoses. However, the interview did not contain detailed questions on symptoms related to other psychiatric disorders than depression and therefore it was not possible to conduct a comprehensive differential diagnosis. It is thus possible that some participants could have had comorbid psychiatric disorders along with depression.

Eleven participants met the criteria for mild depression (*F*32.0), and two participants were diagnosed with a mild dysthymic disorder (*F*34.1). Fifteen participants were diagnosed with a recurrent depressive disorder with a mild current episode (*F*.33.0). Five participants met the criteria for moderate depression (*F*32.1), and eight participants were diagnosed with a recurrent depressive disorder with a moderate current episode (*F*33.1). Seventeen of 41 depressed participants used antidepressant medication during the study. If in the psychiatric interview or the other phases of the study concern about the participant's risk for suicide was raised, the participant was asked to contact the professionals in the local health care center, and they were provided with the contact information.

For the data analysis, the participants were further divided into healthy control group (CTRL-group; $n = 21$), first-episode depression (FE-dep; $n = 16$) and recurrent-episode depression group (REC-dep; $n = 25$). The two participants with a mild dysthymic disorder were included in the REC-dep group because they had experienced continuous long-term depression. In FE-dep group there was one depressed participant with previous diagnosis of anorexia nervosa. In REC-dep group there were two depressed participants with previous psychiatric diagnoses: one with undefined anxiety disorder and the other with unclear diagnosis. There were no significant differences in one-way ANOVA, $F(2,59) = 0.97$, in age between the FE-dep and CTRL-group, $p = 1.000$, or between the FE-dep and REC-dep group, $p = 1.000$, or between the REC-dep and CTRL-group, $p = .510$. The three groups did not differ in number of male and female participants, $x^2(1) = 1.08$, $p = .562$.

Further, the two depression groups did not differ significantly in medication status, $x^2(1) = 1.13$, $p = .288$ or depression severity (mild or moderate), $x^2(1) = 0.003$, $p = .960$. The difference between BDI-II scores, $t(38) = 2.02$, $p = .050$ was marginally significant. To assess anxiety symptoms in the depressed group the participants were asked to fill the DASS questionnaire (Depression, anxiety, stress scales; Lovibond & Lovibond, 1995) and the anxiety subscale was calculated from it. There was no difference between FE-dep and REC-dep group in DASS-anxiety scores $t(38) = -0.46$, $p = .648$. See further details in Table 1.

Table 1
Demographics and Clinical Measures for the Participant Groups. CTRL = control group, FE-dep = first-episode depression group, REC-dep = recurrent depression group, SD = standard deviation.

	CTRL ($n = 21$)	FE-dep ($n = 16$)	REC-dep ($n = 25$)
Male/Female	8/13	7/9	7/18
Age: Mean (SD) [range]	40.0 (11.9) [21-64]	41.4 (13.4) [18-64]	43.7 (9.7) [25-64]
Medicated/non-medicated	Na	5/11	12/13
Previously medicated/ previously non-medicated*	Na	4/11†	19/6
Medication type**	Na	3 SSRI 2 SNRI	5 SSRI 5 SNRI 2 other
Mild/Moderate depression	Na	11/5	17/8
BDI-II Mean (SD) [range]	2.8 (3.2) [0–10]	19.8 (8.5) [3–36]†	25.2 (8.11) [12–43]
DASS-anxiety (SD) [range]	Na	8.69 (6.8) [0–22]	9.92 (9.1) [0–31]

*Number of participants who reported having used/not having used antidepressants previously. **SSRI = selective serotonin reuptake inhibitor, SNRI = serotonin and norepinephrine reuptake inhibitors, other = other depression medication. † One participant's value missing.

2.2. Procedure

During the ERP experiment, the participants sat in a comfortable chair in a dimly-lit room. They were instructed to watch a movie and ignore the sounds that were presented from a loud speaker situated above them. Each participant was monitored during the ERP recordings via a video camera positioned on top of the screen.

2.3. Stimuli

During the brain activity measurement, sinusoidal sounds of 1000 Hz in frequency, and 50 ms (5-ms onset and offset ramps) in duration were presented. The experiment consisted of two different stimulus blocks whose order was counterbalanced across the participants. In the high-intensity condition, the standard sound was 60 dB (sound pressure level, SPL) and the deviant sound was 80 dB (SPL). In the low-intensity condition, the intensities between the standards and deviants were reversed. Standard and deviant sounds were presented pseudo-randomly with the restriction that no less than two standard sounds would occur between consecutive deviants. The stimulus-onset asynchrony (SOA) in the stimulus presentation was randomly set at 400, 450, or 500 ms. In each of the stimulus blocks, there were 50 deviant sounds among 450 standard sounds (the probability for the deviant sound was 10%).

The stimulus presentation was controlled with E-Prime 2.0 software (Psychology Software Tools, Inc., Sharpsburg, MD, USA). The sound pressure level was measured with a sound level meter (type 2235, Bruel & Kjaer, Nærum Denmark) with C-weighting (optimized for 40–100 dB measurement).

2.4. Electroencephalography recording and data analysis

The EEG data was recorded using a 128-channel EEG system. The amplifier used to amplify the electric activity of the brain was a Net Amps 200 (Electrical Geodesics Inc.), and the software for data recording was the Net Station version 4.2.1. The sampling rate for the EEG recording was 1000 Hz and the data were filtered online from 0.1 to 400 Hz. The HydroCel Geodesic Sensor Net was used. The EEG was online referred to the vertex electrode (Cz).

The EEG signal was analyzed with Brain Vision Analyzer 2.1. software (Brain Products GmbH, Munich, Germany). Offline, an average from all the channels was calculated and applied as a new reference. The electrode signals were filtered with 0.1 Hz low cut-off and 30 Hz high cut-off, both with 24 dB/octave roll-off. Also, a 50-Hz notch filter was applied. Six-hundred-ms time segments were extracted relative to the stimulus onset: from 100 ms before stimulus onset to 500 ms after the stimulus onset. The mean of a 100-ms pre-stimulus period served as a baseline for each segment. Eye movements were corrected with (independent component analysis (ICA) individually for each participant as implemented in the Brain Vision Analyzer. A detection algorithm was used to find ICA components for the blinks, and after this, the best representation for vertical or horizontal blinks was determined from the ICA components by visual inspection. After the ICA correction, bad channels were interpolated. Next, the remaining segments with signal amplitudes beyond the range between −150 μV and 150 μV in any recording channel within a 200-ms period were omitted. Also, segments with more than a 50 μV difference between two consecutive time points were deleted from further analysis.

For the averaging, only responses to standard sounds immediately preceding the deviant sounds were calculated. This procedure allows the same number of segments, and thus a similar signal-to-noise ratio,

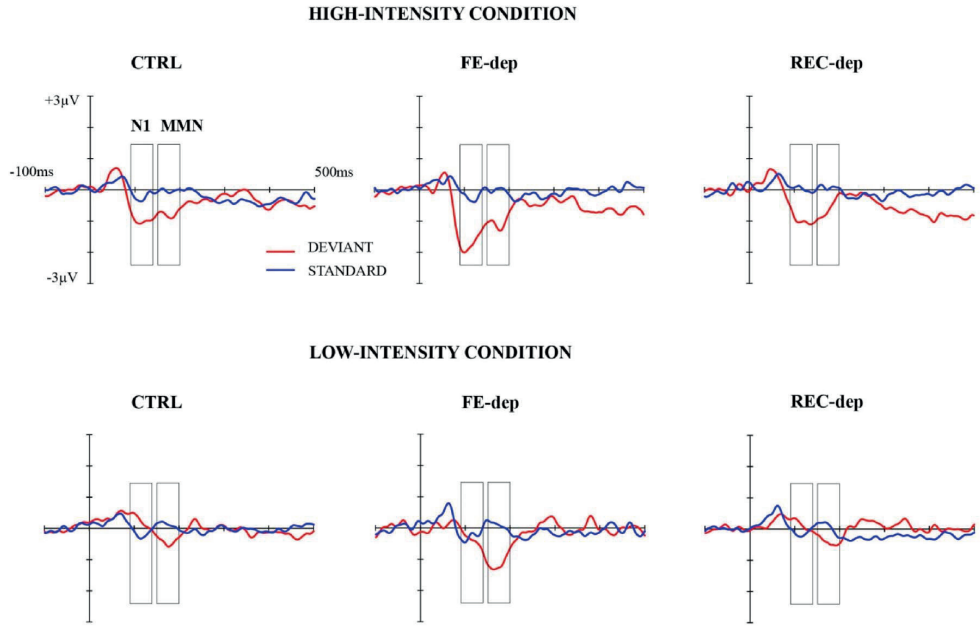

Fig. 1. Grand-averaged waveforms of responses to deviant and standard stimulus separately in each group and condition (averaged for analyzed electrodes). The rectangles represent the analysis windows for N1 (90–140 ms) and MMN (150–200 ms). The Y-axis shows the stimulus onset. CTRL = control group, FE-dep = first-episode depression group, REC-dep = recurrent depression group.

for both standard and deviant responses. Whenever there were less than 30 segments left for the averaging, the participant's data for the condition was not applied. On average, the number of analyzed trials for the deviants in high-intensity and low-intensity conditions was 47.0 and 46.6 in CTRL-group, 48.3 and 46.2 in FE-dep group, and 48.4 and 48.1 in REC-dep group, respectively. There were no group differences in One-way ANOVA in the number of analyzed trials in high-intensity, $F(2,59) = 1.93$, $p = .154$, or in low-intensity condition, $F(2,59) = 1.71$, $p = .191$.

Visual observation of the grand-averaged waveforms indicated that N1 and MMN responses were elicited, but P3a response was not evident. Accordingly, N1 and MMN amplitudes were analyzed. Based on the grand-averaged waveforms and previous literature (Näätänen, 1990), mean standard and deviant response amplitude values for the N1 and MMN were calculated for the latency of 90 − 140 ms and 150 − 200 ms after the stimulus onset, respectively. Both standard and deviant responses were extracted from the MMN time window, in order to investigate whether possible group difference is associated either to memory trace formation for the standard stimulus or to deviance detection. It has been recently acknowledged that taking stimulus type to statistical model can reveal the underlying mechanism of group differences in change detection (Kremláček et al., 2016). Since the MMN is traditionally analyzed as a differential response, also an analysis based on it was applied. The amplitude values were extracted from the fronto-central electrodes (channels 3, 10, 11, 15, 16, 18, 23, 24, 27, 123, and 124 in the EGI 128-channel system, Supplemental Fig. S1).

2.5. Statistical analysis

A three-way repeated measures of Multivariate Analysis of Variance (MANOVA) with within-subjects variables stimulus type (deviant, standard) and condition (high-intensity, low-intensity), and a between-subjects variable group (CTRL vs. FE-dep vs. REC-dep) was conducted separately for N1 and MMN. An additional two-way repeated measures of MANOVA was conducted for MMN by applying differential response (deviant minus standard) with condition (high-intensity, low-intensity) as a within-subjects variable and group (CTRL vs. FE-dep vs. REC-dep) as a between-subjects variable. Partial eta-squared η_p^2 presents effect size estimates for MANOVA and Cohen's d for *t*-tests. Cohen's d was computed using pooled standard deviations (Cohen, 1988). One-way Analysis of Variance (ANOVA) with Bonferroni correction was used as a post hoc test for between-group comparisons, and paired *t*-tests with Bootstrap statistics based on 1000 samples when within-group comparisons were applied.

Whenever an effect of a group or any of its interaction effect was found a further test with a variable 'medication status' as a covariate was conducted. 'Medication status' is a dichotomous variable indicating whether the depressed participant was currently taking medication for depression or not. In addition, an analysis with the participants without current medication was conducted (FE-dep, $n = 11$, REC-dep, $n = 13$). In MANOVA between-subjects variable was group (CTRL vs. FE-dep vs. REC-dep) and within-subjects variables were stimulus type (deviant, standard) and condition (high-intensity, low-intensity). Finally, Pearson's correlation coefficients were computed to examine the relationship between the ERPs and BDI-II and between ERPs and DASS-anxiety scores whenever the interaction effect with the group was indicated by MANOVA.

Bonferroni corrected or Bootstrap-based *P*-value smaller than .05 was considered significant, but marginally significant interaction effects ($p \leq .075$) were also further studied.

3. Results

Here we report significant group effects and interactions with it. The results describing other main effects and interactions are presented in supplementary materials (Tables S1–S3). In Fig. 1, grand-average waveforms are depicted separately for the two experimental conditions: the high-intensity condition (deviant sound 80 dB and standard sound 60 dB) and the low-intensity condition (deviant sound 60 dB and

standard sound 80 dB). Differential waveforms (deviant minus standard response) are presented in Fig. 2. Topographical maps of response amplitudes to deviant sounds in N1 and MMN time windows are shown in Fig. 3. Mean amplitude values and significant group differences in these are shown in Fig. 4.

3.1. N1 (90–140 ms)

In MANOVA a significant stimulus type x group interaction, $F(2,59) = 3.56$, $p = .035$, $\eta_p^2 = 0.11$, was observed.[1] For post hoc tests, a one-way ANOVA was performed to compare the responses to different stimulus types among the three groups. The ANOVA showed group difference in responses to deviant stimuli, $F(2,59) = 4.96$, $p = .010$, but no significant difference between groups in responses to standard stimuli, $F(2,59) = 0.59$, $p = .559$, was observed (Fig. 4).

Follow-up pairwise comparisons showed that the FE-dep group had larger negative responses to deviant stimuli ($M = -1.05$, $SD = 1.06$) compared to the REC-dep group ($M = -0.40$, $SD = 0.49$), $p = .020$, d = 0.866, and to CTRL-group ($M = -0.38$, $SD = 0.62$), $p = .020$, d = 0.821 (Fig. 4). No difference in deviant responses between REC-dep and CTRL-group was found, $p = 1.000$, d = 0.046. Mean difference in deviant response between FE-dep and REC-dep group was −0.65 μV, 95% CI [−1.27, −0.14], and between FE-dep and CTRL-group −0.67 μV, 95% CI [−1.32, −0.14].

Paired *t*-tests comparing deviant and standard stimulus responses (averaged over the conditions) were also performed separately in each group. Responses to standard and deviant stimulus differed in FE-dep, $t(15) = 4.11$, $p = .004$, d = 0.896, and in REC-dep group, $t(24) = 2.73$, $p = .012$, d = 0.697 but not in CTRL-group, $t(20) = 1.16$, $p = .266$, d = 0.296 (Fig. 4). Mean amplitude difference in FE-dep group was −0.81 μV, SD = 0.79 and 95% CI [−1.23, −0.48], in REC-dep group −0.36 μV, SD = 0.67 and 95% CI [−0.61, −0.12], and in CTRL-group −0.18 μV, SD = 0.73, 95% CI [−0.52, 0.13].

The stimulus x group interaction remained marginally significant when controlling for medication status $F(2,58) = 4.16$, $p = .050$, $\eta_p^2 = .098$. In a MANOVA between non-medicated depression groups and CTRL-group (FE-dep vs. REC-dep vs. CTRL) the stimulus type x group interaction was marginally significant, $F(2,42) = 2.95$, $p = .063$, $\eta_p^2 = .123$. For post hoc tests, a one-way ANOVA was performed. One-way ANOVA showed group difference in responses to deviant stimuli, $F(2,42) = 4.08$, $p = .024$, but no significant difference between groups were found in responses to standard stimuli, $F(2,42) = 0.28$, $p = .761$. Follow-up pairwise comparisons showed that FE-dep group had larger negative responses to deviant stimuli compared to CTRL-group, $p = .033$. Difference between FE-dep and REC-dep was marginally significant, $p = .059$. REC-dep and CTRL-group did not differ, $p = 1.000$.

No correlations were found between BDI-II scores and N1 responses or between DASS-anxiety scores and N1 responses (to the deviants or standards, or deviant minus standard differential response) within the depressed participants (all $p > .156$). In addition, no such correlations were found either in FE-dep group (all $p > .164$), or in the REC-dep group, (all $p > .321$) when the groups were studied separately.

3.2. MMN (150–200 ms)

In the MMN time window, both analyses, based on standard and deviant responses and on differential response, showed no group differences or interaction effects with the group (all $p > .200$).[2]

[1] Also the data without the two participants with low BDI-scores were analyzed. The stimulus type x group interaction was still marginally significant, $F(2,57) = 2.862$, $p = .065$, $\eta_p^2 = .091$

[2] Also the data without the two participants with low BDI-scores were analyzed. The results remained non-significant (all $p > .200$).

4. Discussion

Here we used an intensity change detection paradigm that allowed us not only to study the intensity dependency of ERPs (Hegerl et al., 2001; Hegerl & Juckel, 1993; Juckel et al., 1997), but also the function of the change detection mechanism that is known to be affected in many neuropsychiatric disorders, including depression (for the MMN, see Näätänen et al., 2011). We found that the first-episode depression group had larger ERP amplitudes to rare changes in sound intensity in the obligatory N1 response compared to control participants. The recurrent depression group did not differ in N1 responses to deviant sounds from the control group. However, both depression groups showed larger N1 amplitude to deviant than to standard stimuli while in the control group no such difference was found. MMN was elicited to both high- and low-intensity deviant sounds as expected but it did not reflect any group differences.

Previous studies have found increased intensity dependence in a subgroup of depressed patients responsive to antidepressants (see for example Gallinat et al., 2000; Jaworska et al., 2013; Juckel et al., 2007; Lee et al., 2015; Lee et al., 2005). This increased intensity dependence is thought to reflect, at least partly, low serotonergic neurotransmission (Hegerl et al., 2001; Hegerl & Juckel, 1993; Juckel et al., 1997, 1999; Wutzler et al., 2008). Therefore, our finding of increased N1 responses to intensity deviant sounds in first-episode depression may potentially indicate weaker serotonergic neurotransmission in that group comparing to the recurrent depression group and control group. However, the finding of statistically significant differential response (deviant vs. standard stimulus) in both depression groups, but not in the control group, may indicate a decreased threshold for a trigger to allocate attention towards changes in depression (Näätänen, 1990). Moreover, it indicates that it is, indeed, the change detection mechanism, not sound encoding in general, which is affected in depression. Considering this, it was surprising that the MMN response reflected no group differences. To our knowledge MMN responses to rare changes in intensity have not been previously measured in depression, but instead earlier studies have investigated alterations in the processing of duration or frequency changes. Our results are in contrast with the earlier MMN studies that found depression-related alteration of the MMN in response to duration and frequency changes in tones (Chen et al., 2015; He et al., 2010; K & hkönen et al., 2007; Naismith et al., 2012; Qiao et al., 2013; Restuccia et al., 2015; Takei et al., 2009).This discrepancy might be explained by the different neural sources the different sound features activate in the brain (Alho, 1995; Rosburg, 2003).

It is not clear why the first-episode depression group showed more pronounced auditory over-excitability to intensity changes than the recurrent depression group. Even if both depression groups had significant difference between the N1 response amplitudes to standard and deviant sound, the effect size for this difference was clearly larger for the first-episode depression group than for the recurrent depression group (d = 0.896 and d = 0.697, respectively). The previous studies investigating automatic change detection between first-episode and recurrent depression have not been able to dissociate first-episode and recurrent depression groups (Chen et al., 2015; Umbricht et al., 2003). To our knowledge no study related to change detection in sound intensity has previously compared first-episode and recurrent depression groups. The cortical over-excitability found in our experiment may thus be specifically related to automatic sensory processing of sound intensity.

One difference between the depression groups is the medication history. Because participants in the recurrent depression group had previous depression episodes, they also had more participants who had previously used antidepressants. Most of the participants in recurrent depression group had used antidepressants previously (19 out of 25 participants), while only a few participants in the first-episode depression group had previous medication history (4 out of 16 participants). It is not known, if the previous medication that was more often used in

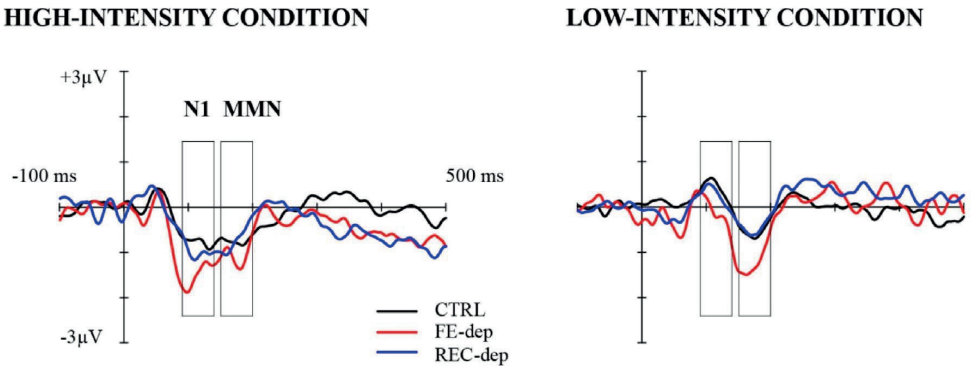

Fig. 2. Grand-averaged differential responses (deviant minus standard) for each group and condition (averaged for analyzed electrodes). The rectangles represent the analysis windows for N1 (90–140 ms) and MMN (150–200 ms). The Y-axis shows the stimulus onset. CTRL = control group, FE-dep = first-episode depression group, REC-dep = recurrent depression group.

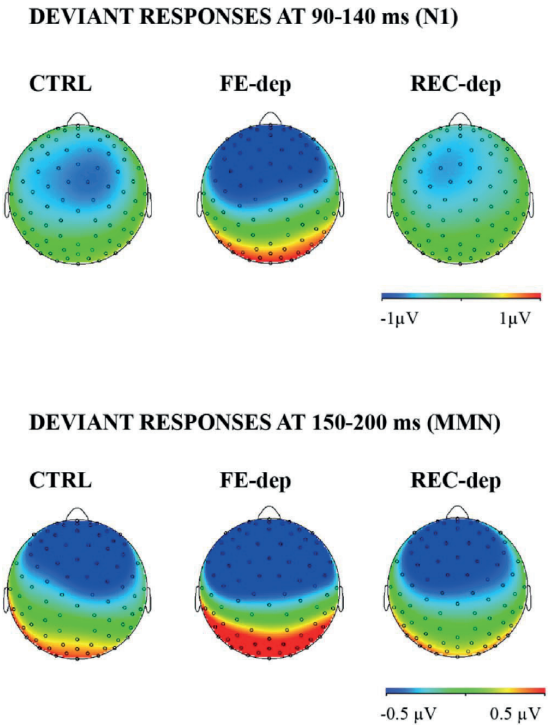

Fig. 3. Grand-averaged topographical maps of the N1 and MMN responses for the deviant sounds in each group (high-intensity and low-intensity conditions are averaged). CTRL = control group, FE-dep = first-episode depression group, REC-dep = recurrent depression group.

the recurrent depression group, could explain the differences between the ERP responses in first-episode and recurrent depression groups. One potentially relevant aspect related to previous medication is treatment resistance. It can be assumed that the recurrent depression group included participants who are treatment-resistant, e.g. unresponsive to at least two antidepressants (for a review, see Berlim & Turecki, 2007). In treatment-resistant depression also other neurotransmitter systems than serotonergic system have been suggested to be dysfunctional (e.g. glutamatergic, Berman et al., 2000; Zarate et al., 2013). This also supports the above mentioned interpretation that our ERP results may reflect more profound dysfunction of serotonergic system in first-episode depression compared to recurrent depression.

The participants in the recurrent depression group reported slightly more depression symptoms than the participants in the first-episode depression group. Therefore the larger N1 amplitudes in first-episode group compared to recurrent group and control group could not be explained by the amount of depression symptoms as such. Furthermore, we found no association between depression scores and the brain responses, suggesting that the alterations in brain responses are not related to the severity of depression. This is in line with previous MMN studies that found no correlations between the number of symptoms and brain responses to auditory changes (Kähkönen et al., 2007; Naismith et al., 2012; Pang et al., 2014; Takei et al., 2009).

This study is not without limitations. In our sample both depression groups had participants with medication, but the groups did not differ significantly in the amount of medicated vs. non-medicated participants. Furthermore, the medication status did not explain the observed group differences as the results remained mostly the same even after controlling for current medication status. An additional analysis with the subgroup of participants with no current medication for depression further suggested that the medication status did not explain the results.

One limitation is that the diagnostic interview was not a validated clinical interview, e.g. Structured Clinical Interview for DSM-IV, SCID (First et al., 2002), and it was not conducted by a psychiatrist. Instead, a structured interview based on ICD-10 criteria for depression was conducted by a physician. This procedure is, however, a common practice for diagnosing depression in primary health care context in Finland. Since the interview did not contain detailed questions about symptoms related to other psychiatric disorders than depression, it did not allow a comprehensive differential diagnosis. It is thus possible that some participants could have had comorbid psychiatric disorders along with depression.

Participants' hearing ability was not objectively measured and we did not evaluate their intelligence. Another limitation is related to the ERP analysis. We did not separate the N1 and MMN responses for example with blind source separation methods or using source localization, but through visual inspection of the grand-averaged waveforms. It is thus possible that the analyzed responses do not purely reflect N1 and MMN but they may partly overlap.

In sum, the method based on ERPs to rare changes in sound intensity was efficient to dissociate the depression groups from the control group, indicating potential deficits in the automatic auditory change detection in depression. Future studies should investigate to what extent the deficit in auditory change detection is directly associated to the function of serotonergic or other neurotransmission system in depression. In this study, we employed an intensity change

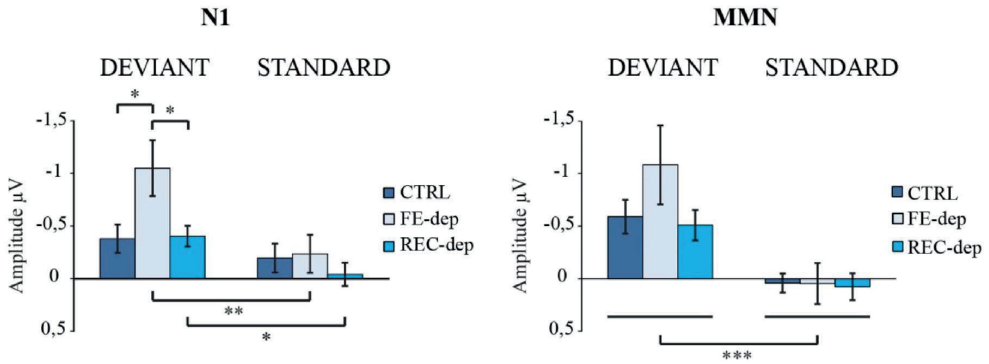

Fig. 4. Mean amplitudes for N1 and MMN to deviant and standard stimuli in each group (averaged for high-intensity and low-intensity conditions and analyzed electrodes). For the MMN only the main effect of stimulus type was significant. Error bars represent standard error. CTRL = control group, FE-dep = first-episode depression group, REC-dep = recurrent depression group, $*p < .05$, $**p < .01$, $***p < .001$.

detection paradigm to combine the benefits from previous intensity dependency and change detection studies, which both have shown promise in exploring cortical over-excitability in depression. This paradigm can quickly and cost-efficiently measure obligatory brain responses in depression which encourages to study further its possibility to be used as a diagnostic tool in future.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.biopsycho.2017.05.008.

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SUPPLEMENTAL INFORMATION

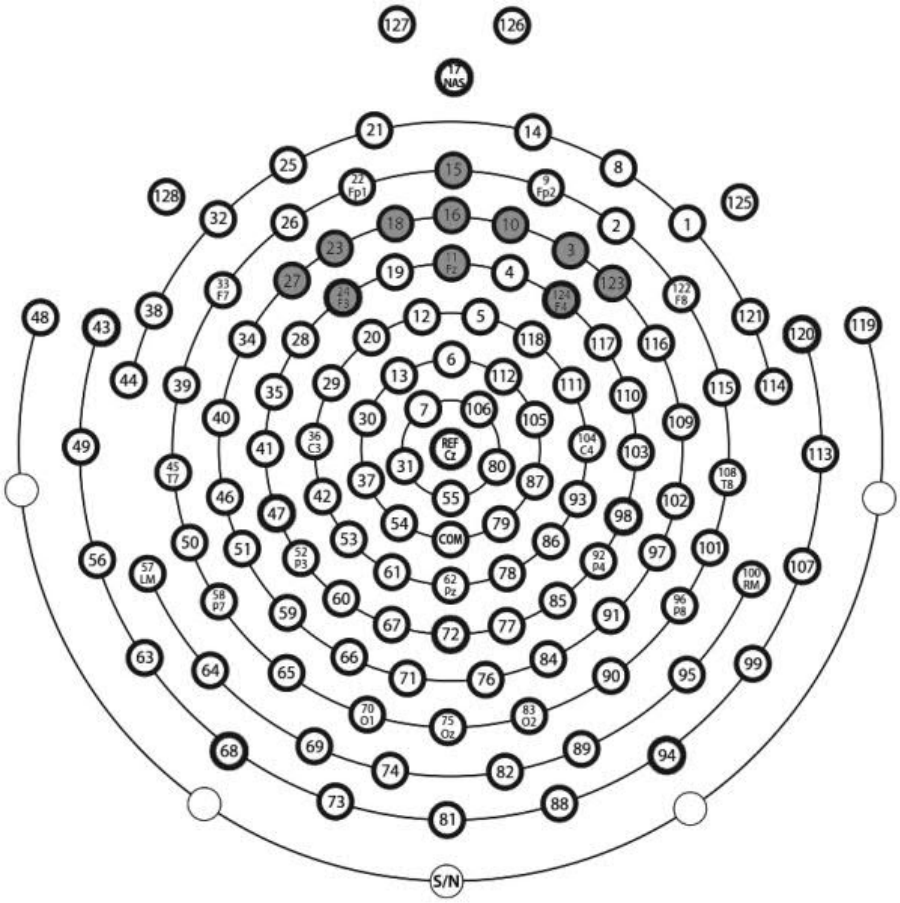

Figure S1. Map of 128 channel HydroCel Geodesic Sensor Net. The channels used in the analysis are marked with grey background.

Table S1. Main effect of stimulus type and its interaction effects in MANOVA for N1 and MMN.

Effect	N1	MMN
Stimulus type	$F(1,59) = 23.68$, **$p < .0001$**, $\eta_p^2 = .286$	$F(1,59) = 36.89$, **$p < .0001$**, $\eta_p^2 = .385$
Stimulus type x Condition	$F(1,59) = 54.05$, **$p < .0001$**, $\eta_p^2 = .478$	$F(1,59) = 0.18$, $p = .674$, $\eta_p^2 = .003$

P-values smaller than .05 are in bold. Please note that group effects are reported in Table S2.

Table S2. Interaction effects that include the group factor and stimulus type factor in MANOVA for N1 and MMN.

Group interaction	N1	MMN
Stimulus type x Group	$F(2,59) = 3.56$, **$p = .035$**, $\eta_p^2 = .108$	$F(2,59) = 1.64$, $p = .200$, $\eta_p^2 = .053$
Stimulus type x Condition x Group	$F(2,59) = 0.17$, $p = .841$, $\eta_p^2 = .006$	$F(2,59) = 0.32$, $p = .730$, $\eta_p^2 = .011$

P-values smaller than .05 are in bold.

Post hoc tests for N1

Interaction effect of stimulus type x condition was observed (see Table S1). Post hoc tests revealed that in the high-intensity condition deviants (M = -1.16 μV, SD = 1.07) elicited larger negative amplitudes compared to standards (M = -0.12 μV, SD = 0.72). In the low-intensity condition, no difference between responses to deviant (M = 0.03μV, SD = 0.78) and standard (M = -0.17 μV, SD = 0.69) sounds was observed. To test the effect of stimulus presentation rate, responses to deviant and standard stimuli of the same intensity presented in different conditions, were compared. High-intensity stimuli elicited larger negative amplitudes when presented as a rare deviant stimuli compared to when presented as a

repeated standard stimuli. Responses to low-intensity sounds presented as deviants or standards did not differ. See Table S3 for details.

Table S3. Paired t-tests comparing N1 responses to deviant and standard stimuli over the groups.

Interaction	df	t-value	M difference	SD	p-value	CI % 95	Effect size (Cohen's d)
80 dB-DEV vs. 60 dB-ST	61	7.65	-1.04	1.07	**.001**	-1.31, -0.77	1.140
60 dB-DEV vs. 80 dB-ST	61	1.73	0.20	0.91	.093	-0.023, 0.44	0.273
80 dB-DEV vs. 80 dB-ST	61	7.14	-0.99	1.09	**.001**	-1.27, -0.74	1.100
60 dB-DEV vs. 60 dB-ST	61	1.38	0.15	0.85	.197	-0.07, 0.36	0.197

Note: Two upper rows show t-tests between deviant and standard responses within high-intensity and low-intensity conditions, respectively. Two lower rows show t-tests between physically identical stimuli presented in different conditions. 80dB-DEV = 80 decibel sound presented as deviant, 60dB-ST = 60 decibel sound presented as standard, 60dB-DEV = 60 decibel sound presented as deviant, 80 dB-ST = 80 decibel sound presented as standard. Bootstrap based on 1000 samples. P-values smaller than .05 are in bold. DF = degrees of freedom, M difference = Mean difference in μV, SD = standard deviation, CI = confidence interval.

Post hoc tests for MMN

MANOVA for MMN showed a significant main effect of stimulus type (see Table S1). Larger negative amplitudes to deviant stimuli (M = -0.68, SD = 1.00) compared to standard stimuli were observed (M = 0.06, SD = 0.60).

II

EVENT-RELATED POTENTIALS TO SOUND INTENSITY CHANGES DEMONSTRATE AGING- AND DEPRESSION-RELATED CHANGES IN BRAIN FUNCTION IN FEMALES

by

Elisa M. Ruohonen, Saara Kattainen, Xueqiao Li, Anna-Elisa Taskila, Chaoxiong Ye & Piia Astikainen, 2017

Manuscript submitted for publication.

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III

EVENT-RELATED POTENTIALS TO TASK-IRRELEVANT SAD FACES AS A STATE MARKER OF DEPRESSION

by

Elisa M. Ruohonen, Veera Alhainen & Piia Astikainen, 2020

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Event-related potentials to task-irrelevant sad faces as a state marker of depression

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ABSTRACT

Negative bias in face processing has been demonstrated in depression, but there are no longitudinal investigations of negative bias in symptom reduction. We recorded event-related potentials (P1 and N170) to task-irrelevant facial expressions in depressed participants who were later provided with a psychological intervention and in never depressed control participants. Follow-up measurements were conducted for the depressed group two and 39 months later. Negative bias was found specifically in the depression group, and was demonstrated as enlarged P1 amplitude to sad faces, which normalized in the follow-up measurements when the participants had fewer symptoms. Because the P1 amplitude recorded at the baseline did not differ between the depression group that recovered and the group that did not recover after the intervention, this brain response did not show potential as a biomarker for treatment response. It could have potential, however, to serve as a state-marker of depression.

1. Introduction

Depression is a common and highly recurrent disorder, which is most typically characterized by lowering of mood and reduction of energy and enjoyment (World health organization, 2010). According to Aaron Beck's cognitive model of depression (1976, Beck, 1967, 1987), depressed individuals have a cognitive bias in information processing that predisposes them to selectively attend to negative stimuli. It could be a vulnerability factor that can affect the onset and recurrence of depression episodes (1976, Beck, 1967, 2008). Relevantly for the current study, this bias is suggested to occur also in automatic information processing facilitating the processing of negative stimuli already at early processing phases (Beck, 2008).

Negative bias in depression postulated in Beck's theory has been demonstrated empirically with different types of stimuli (for reviews, see Mogg & Bradley, 2005; Peckham, McHugh, & Otto, 2010), especially with facial expressions (Gollan, Pane, McCloskey, & Coccaro, 2008; Gotlib, Krasnoperova, Yue, & Joormann, 2004; Naranjo et al., 2011, for a review see, Delle-Vigne, Wang, Kornreich, Verbanck, & Campanella, 2014). Negative bias in these studies was found as bias in attention or in memory to sad faces.

Processing of facial expressions has been studied widely with event-related potentials (ERPs), which give accurate timing for the brain activity related to different processing stages in face perception. The first ERP component that is modulated by facial expressions is P1, and attentive negative bias in emotional face processing in depression has been found in P1. When participants evaluated emotion intensity in faces, sad faces elicited larger P1 responses than happy or neutral faces in the depressed group but not in the control group (Dai & Feng, 2012; for absent negative bias in P1, see Dai, Wei, Shu, & Feng, 2016; Zhao et al., 2015). Negative bias is also demonstrated in subliminally presented, but attended, faces. Sad faces elicited a larger P1 response compared to neutral faces in the depressed group while controls had a smaller P1 for sad faces compared to neutral faces (Zhang, He, Chen, & Wei, 2016).

There is also evidence for depression-related negative bias in the N170 ERP component (Zhang et al., 2016; Zhao et al., 2015), which reflects structural feature processing in faces, including facial expression processing (Batty & Taylor, 2003). In an attentive condition, including a condition where subliminally presented faces are presented, N170 was larger to sad faces than to happy and/or neutral faces in the depressed participants, whereas in the control participants the N170 was the largest to happy faces (Zhang et al., 2016; Zhao et al., 2015). Furthermore, a direct comparison between the N170 in the depressed and control groups showed that the responses to sad faces were larger in depressed participants compared to control participants (Wu et al., 2016), reflecting mood-congruent bias in facial emotion processing. However, sometimes no differences between depressed and non-

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depressed have been found in N170 responses to facial expressions (Jaworska, Blier, Fusee, & Knott, 2012).

Beck's cognitive model of depression suggests that negatively biased cognitive schemas function as automatic information processors (Beck, 2008). However, there is very little information on unattended or task-irrelevant processing of facial expressions in depression, especially with brain activity measurements that can reveal the time course for the processing (i.e. electroencephalography or magnetoencephalography studies, MEG; however, for a study applying functional magnetic resonance imaging, fMRI, see Suslow et al., 2010). In one study, ERPs were recorded for changes in emotional faces in depressed and control participants while participants attended faces with different colors (Chang, Xu, Shi, Zhang, & Zhao, 2010). In that study, the oddball condition was applied, in which the visual mismatch negativity (vMMN) component indexing cortical change detection is elicited (for reviews, see Kremláček et al., 2016; Stefanics, Astikainen, & Czigler, 2014). vMMN is calculated as the difference between responses to repeatedly presented standard stimuli and responses to rare deviant stimuli. In study by Chang et al. (2010), vMMN was found in two latencies reflecting mainly modulations in N170 and the following P250 component. Chang et al. observed smaller-amplitude vMMNs to happy and sad faces in the depressed group compared to the controls, thus showing no evidence of preattentive negative bias but instead an overall weakened cortical change detection related to facial expressions. However, in the study schematic faces, which have inevitably low ecological validity, were applied raising the question whether more naturalistic stimuli could reveal depression-related negative bias in task-irrelevant processing of facial expressions. In another study, task-irrelevant MEG responses were measured in participants with depression symptoms (dysphoric) and non-depressed controls to sad and happy faces presented in an oddball condition (Xu et al., 2018). Dysphoria-related negative bias was only found in later processing phase (M300 response), but no group differences were found in M100 or M170 responses, which correspond to P1 and N170 responses in ERPs, respectively.

Whether negative cognitive bias in depression is a trait-like characteristic or is state-dependent, that is, changes along with the degree of depressive symptoms, is unclear. Behavioral studies that have found similar processing bias in depressed and sub-clinically depressed participants (Dai et al., 2016) or in depressed and remitted participants (Joormann & Gotlib, 2007) or no change in negative bias in follow-up after remission (Bouhuys, Geerts, Mersch, & Jenner, 1996), have interpreted the result as reflecting a trait. However, some fMRI studies have shown normalization of brain activity for sad facial expressions after cognitive behavioral therapy (CBT; Fu et al., 2008) or after antidepressant treatment (Victor, Furey, Fromm, Ohman, & Drevets, 2010) suggesting state-dependency. Further support for state-dependency comes from an ERP study that found a correlation between depression symptom scores and negative bias in the N170 response (Wu et al., 2016) and from another study that found negative bias only in recurrent depressed individuals but not in first-episode depressed individuals suggesting that negative bias is associated with illness progression (Chen et al., 2014).

Brain responses to emotional faces may also have potential as indicators of treatment response. fMRI studies have shown that brain activation to sad expressions is associated with cognitive therapy treatment outcome in depressed participants (Costafreda, Khanna, Mourao-Miranda, & Fu, 2009; Fu et al., 2008). Costafreda et al. (2009) found that brain activity patterns related to sad facial expression processing, distinguish clinically remitted patients from non-remitted patients. Fu et al. (2008) included healthy control participants in comparisons and found better treatment response for patients who initially showed the most similar activity pattern to healthy controls in sad face processing. To best of our knowledge, ERP studies investigating treatment effect correlates of facial expression processing have not been reported, although they could be similarly feasible as the fMRI studies.

We aim to demonstrate automatic negative bias in depression reflected by ERP responses to pictures of real faces. If we find a negative bias related to depression, we will study the stability of the bias over time. In addition, we will investigate whether ERPs recorded in depressed participants for facial expressions can distinguish between those who recover and those who show no recovery after a brief psychological intervention.

We investigated P1 and N170 amplitudes to happy, sad and neutral faces presented in an oddball condition in which emotional faces were presented infrequently. The oddball condition was expected to be beneficial, because the responses to infrequent deviant stimuli could be expected to be enlarged compared to the frequently presented standard stimuli. We applied a stimulus condition where the identity of the faces, and thus, low-level visual features, changed trial-by-trial. Participants were instructed to attend to an audiobook during the face presentation. Since our adaptive behavior relies largely on preattentive cognition (Näätänen, Astikainen, Ruusuvirta, & Huotilainen, 2010) and cognitive negative bias is expected to exist already in the level of automatic processing (Beck, 2008), it is important to investigate task-irrelevant emotional face processing in depression.

Two groups of participants, depressed and age- and gender-matched non-depressed control participants, were enrolled in the study. We measured brain responses in the depressed group at three timepoints: at the baseline when all the participants were currently depressed and at 2-month (2-m) and at 39-month (39-m) follow-up measurements. At the 2-m measurement, approximately half of the depressed participants had received a brief psychological intervention for depression, and they were expected to have less depression symptoms (the other half of the group had been the first two months on a wait-list to receive the same intervention and they got the same intervention after the 2-m measurement). At the 39-m measurement, all of the depressed participants had received the intervention. Since it is very probable that some of the participants will have fewer symptoms after the intervention, this design allows us to study changes in brain responses in relationship to changes in depression symptoms. Clinical outcomes were assessed with questionnaires after the intervention for both groups to further divide the depressed participants into groups of recovered and non-recovered.

Based on previous attentive studies, we expect larger P1 and N170 amplitudes to sad faces compared to neutral and happy faces in the depressed group (Dai & Feng, 2012; Zhang et al., 2016; Zhao et al., 2015), reflecting negative bias in information processing in depression (1976, Beck, 1967, 1987). In addition, larger N170 responses to happy faces than to neutral faces are expected in the control group (Astikainen & Hietanen, 2009; Astikainen, Cong, Ristaniemi, & Hietanen, 2013; Zhao et al., 2015). Based on previous studies, we also hypothesize a positive correlation between depression symptom scores and negative bias (Chen et al., 2014; Wu et al., 2016) and normalization of the responses when depression symptoms are reduced (Fu et al., 2008; Victor et al., 2010). Furthermore, we expect depressed participants who benefit less from the brief psychological intervention to show more pronounced initial negative bias compared to those who respond better to the intervention, while those who recover would show similar processing compared to the controls (Fu et al., 2008).

2. Methods and materials

2.1. Participants

The participants were depressed and non-depressed volunteers recruited with an advertisement in the local newspaper and via email lists at the University of Jyväskylä. Written informed consent was obtained from each participant before he or she began. The experiment was undertaken in accordance with the Declaration of Helsinki. The ethical committee of the University of Jyväskylä approved the research protocol.

The depressed participants were recruited as part of a larger-scale

study in which the efficacy of a brief psychological therapy intervention was investigated. A total 119 depressed individuals were randomized to treatment and wait-list control group for the intervention study (Kyllönen et al., 2018), and of these individuals 37 volunteered for the ERP experiments reported here. Clinical depression and other inclusion and exclusion criteria were assessed in a psychiatric interview conducted by a physician independent of the study. The physician conducted a structured interview based on the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10; World health organization, 2010). Based on the interview made by the physician, participants were excluded for any of the following reasons: 1) serious suicide risk; 2) depression with psychotic features; 3) current substance abuse or addiction to drugs and intoxicants, including alcohol; and 4) diagnosis of psychotic disorder, bipolar disorder, eating disorder, or history of neurological injury or disease.

Age- and gender-matched non-depressed controls (n = 31) were recruited separately for the ERP study. The inclusion criteria for the ERP study for the depressed and control groups were age of 18–65 years, right-handedness, normal hearing and normal vision or corrected-to-normal vision. Exclusion criteria for the control group were self-reported 1) current substance abuse or addiction to drugs and intoxicants, including alcohol; and 2) current or previous diagnosis of psychiatric disorder, neurological disorder or neurological injury; 3) current symptoms of depression. For the control group, participants' eligibility to the study, in relation to the inclusion and exclusion criteria, was confirmed before the participation. Current depression symptoms were assessed for the depressed and control groups with Beck's Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996). Control participants with BDI-II scores of 10 or more were excluded from the study. This cut-off limit was chosen to make clearer difference between the groups and to ensure that the control group did not include participants with depression. In the depressed group, two participants had BDI-II-scores below 14 points, and they were excluded from further analysis because according to the BDI-II instruction manual, 14 points is the cut-off value for mild depression. Anxiety symptoms were assessed in the depressed group with the Depression, Anxiety, Stress Scales (DASS) questionnaire anxiety subscale (Lovibond & Lovibond, 1995).

There remained data of 27 non-depressed control and 27 depressed participants in the final sample after poor-quality data had been excluded (Table 1). There was no difference in age between the control and depressed groups, t(52) = 0.8, p = .456, 95% CI [-5.01, 11.01] (two-tailed independent sample *t*-test). There were ten depressed participants with current antidepressant medication. Of these participants, one participant had tricyclic antidepressants, four had selective serotonin reuptake inhibitors and five had serotonin-norepinephrine reuptake inhibitors medication. Seven participants were diagnosed with mild depression (*F32.0*), five with moderate depression (*F32.1*), two with mild dysthymic disorder (*F34.1*), nine with recurrent depression with a mild current episode (*F33.0*) and four with recurrent depression with a moderate current episode (*F33.1*).

Two follow-up measurements were conducted for the depressed participants: a short-term (~2-m) follow-up and a long-term (~39-m) follow-up. The control participants attended the baseline measurement only. Out of the 27 depressed participants whose data were available for the baseline comparison, 27 participants attended the 2-m measurement and 17 participants the 39-m measurement. After poor-quality data were excluded, data remained for 25 participants for the 2-timepoint comparison (baseline vs. 2-m measurement). For the 3-timepoint comparison (baseline vs. 2-m vs. 39-m measurement), data of 17 participants was available due to drop-out (n = 10). For the demographics of the participants within each comparison, see Table 1. To analyze the effect of drop out for the 3-timepoint sample, the demographics and clinical factors of participants included (n = 17) and unavailable (n = 10) for the 3-timepoint comparison were compared. Independent sample t-tests showed no significant group differences in the baseline BDI-II-scores, t(25) = -2.0, p = .062, 95 % CI [-10.09, 0.29] (included: M = 21.3, SD = 5.7; unavailable: M = 26.6, SD = 8.4), in age, t(25) = -0.2, p = .813, 95% CI [-12.66, 10.03] (included: M = 47.9, SD = 13.4; unavailable: M = 49.2, SD = 14.5) or in DASS-A scores, t(25) = -2.0, p = .058, 95% CI [-10,42, -0.19] (included: M = 3.6, SD = 5.0; unavailable: M = 8.7, SD = 2.7). Analysis of groups differences (two-tailed Fisher's exact test) for other demographics revealed no significant difference between the groups in number of participants according to gender, p = .535 (included: 16 females, 1 male, unavailable: 8 females, 2 males), depression severity (diagnosis of mild or moderate depression), p = 1.000 (included: 12 mild, 5 moderate; unavailable: 7 mild, 3 moderate) or medication status, p = 1.000 (included: 11 non-medicated, 6 medicated; unavailable: 6 non-medicated, 4 medicated).

2.2. Experimental design, psychological intervention and subgroups in the analyses

At the baseline measurement all the depressed participants were currently depressed, and their diagnoses had been recently confirmed. After the baseline measurement, the depressed participants were randomized into two groups because of the intervention study: One group received therapy intervention immediately (the treatment group) and the other group received the same intervention approximately 2 months later (the wait-list control group, W—L) (see Fig. 1). The 2-m ERP measurement was performed for both depressed groups after the treatment group's intervention, and there were on average approximately two months between the baseline measurement and the 2-m measurement (mean = 55 d, SD = 11.3, range 33–91 d). The third measurement was conducted approximately 39 months after the baseline measurement (mean = 38.9 m, SD = 0.3, range 38.5–39.5 m).

Both groups received a six-session psychological intervention based on acceptance and commitment therapy, which is a form of cognitive behavioral therapy (Hayes, Strosahl, & Wilson, 1999). The details of the intervention study are described in Kyllönen et al. (2018). Here we report results related to changes in brain responses in relation to changes in depression symptoms over time. The sample size did not allow us to investigate the effect of the intervention on brain responses separately in the treatment and wait-list control groups.

Table 1
Demographics and clinical measures at the baseline measurement for the participants included in the baseline, 2- and 3-timepoint comparisons.

Comparison	N	Mean age ± SD [range]	Male/ Female	Mild/ Moderate	Mean BDI-II ± SD [range]	DASS-A ± SD [range]	Non-med/ med
Baseline (Ctrl)	27	45.4 ± 15.7 [21-65]	4/23	Na	2.7 ± 3.0 [0-9]*	Na	Na
Baseline (Dep)	27	48.4 ± 13.6 [19-65]	3/24	18/9	23.3 ± 7.2 [15-42]	5.5 ± 6.8 [0-31]	17/10
2-timepoint comparison	25	50.0 ± 12.7 [19-65]	1/24	17/8	23.0 ± 7.2 [15-42]**	5.7 ± 7.1 [0-31]	15/10
3-timepoint comparison	17	47.8 ± 13.4 [19-65]	1/16	12/5	21.3 ± 5.7 [15-39]	3.6 ± 5.0 [0-18]	11/6

Mild/Moderate = diagnosis of mild/moderate depression; BDI-II = Beck's Depression Inventory-II at the baseline; DASS-A = Anxiety score subscale for DASS-questionnaire at the baseline; Non-med/med = no antidepressant medication/antidepressant medication; SD = standard deviation; Ctrl = non-depressed control group; dep = depressed group; Na. = Not applicable. *Missing data for three participants; ** Missing data for one participant.

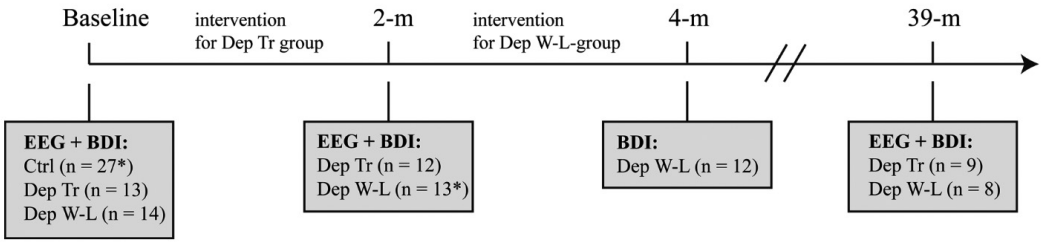

Fig. 1. Outline of the study protocol including EEG measurements, measurement of the BDI-II scores and intervention (brief psychological intervention for depression). The number of participants included in the EEG-analysis and whose BDI-II data was available at each timepoint are indicated in the grey boxes. Ctrl = non-depressed control group; Dep Tr = Depressed group that was a treatment group in the intervention study; Dep W–L = Depressed group that served as a wait-list group in the intervention study; m = months from the baseline. *Missing BDI-II score information at the baseline for three participants in the Ctrl group and at 2-m measurement for one participant in Dep W–L. Note that BDI-II at the 4-m (W–L group) is the post-intervention measurement for the Dep W–L group and is used to classify the depressed in W–L to recovery groups.

BDI-II and DASS anxiety questionnaire information was collected for all the depressed participants at the baseline, 2-m and 39-m measurement, and for the wait-list group after they had received the intervention, approximately four months after the baseline measurement (see Fig. 1). Pairwise t-tests (two-tailed) showed a statistically significant reduction in BDI-II-scores from the baseline (M = 22.8, SD = 7.4) to the 2-m measurement (M = 14.0, SD = 9.1), t(23) = 4.5, $p < .001$, 95 % CI [4.77, 12.81], Cohen's d = 1.06 (there was missing BDI-II data for one participant at the 2-m measurement). When the changes in the BDI-II-scores from the baseline measurement to 2-m measurement and to the 39-m measurement were compared, repeated measures of multivariate analysis of variance (MANOVA) showed a significant main effect of time, F(2,15) = 14.9, $p < .001$, $\eta_p^2 = .665$. Paired samples t-tests (two-tailed) with false discovery rate correction (FDR; Benjamini & Yekutieli, 2001) showed a decrease in the BDI-II-scores from the baseline (M = 21.3, SD = 5.7) to the 2-m measurement (M = 12.4, SD = 6.2), t(16) = 5.0, $p < .001$, 95% CI [5.14, 12.63], Cohen's d = 1.49, but no significant change from the 2-m to the 39-m measurement (M = 9.6, SD = 7.6), t(16) = 1.7, $p = .216$, 95% CI [-0.80, 6.44], Cohen's d = 0.40. However, the BDI-II-scores were higher at the baseline measurement, t(16) = 6.4, $p < .001$, 95% CI [7.83, 15.59], Cohen's d = 1.76, than at the 39-m measurement. The change in the BDI-II-scores from the baseline to the 2-m measurement and to the 39-m measurement is presented in the Fig. 2.

To evaluate the response to treatment, the depressed group was divided into recovered and non-recovered groups based on the change in the BDI-II-scores from the baseline to the measurement after the intervention. The clinical significance of the change in the BDI-II-score was evaluated by using the method suggested by Jacobson and Truax (1991). First, a reliable change index (RCI) was calculated, which assesses whether the change is large enough not to be regarded as a measurement error. Next, a cutoff was calculated that estimates the weighted midpoint between the means of the depressed and non-clinical populations. For the calculations, the normative values of the non-clinical population (i.e. a BDI-II mean score of 5.7 and a standard deviation of 6.8) and Cronbach's alpha for the BDI-II (0.86), were derived from the Kjaergaard, Arfwedson Wang, Waterloo, and Jorde (2014) article. Values for the clinical population were derived from the present study from all the depressed participants whose data were available for the baseline ERP analysis (n = 27, BDI-II mean 23.3, SD = 7.2). The RCI value and the cutoff values were used to classify participants into two groups: recovered and non-recovered. A participant was regarded as recovered if the RCI value was lower or equal to -1.96 (which indicates a significant clinical change) and the post-intervention BDI-II value was lower than the calculated cutoff value (which was 14.2). Participant was regarded as non-recovered if both criteria were not met. Because the method considers the RCI value and the cutoff value, the non-recovered group includes participants with post-intervention BDI-II values similar to those of the recovered group (i.e., below the cutoff point). However, in these cases, the RCI value indicated that the change from the baseline to post-intervention measurement was not large enough to be clinically significant.

Twenty-four participants out of 27 were classified as recovered or non-recovered (three were excluded, because of missing data). Sixteen participants were classified as recovered and eight as non-recovered. In the recovered group, there were five participants diagnosed with mild depression (*F32.0*), four with a moderate depression (*F32.1*), five with recurrent depression with a mild current episode (*F33.0*) and two with recurrent depression with a moderate current episode (*F33.1*). In the non-recovered group, there were two participants with a mild depression (*F32.0*), two with mild dysthymic disorder (*F34.1*), three with recurrent depression with mild current episode and one with recurrent depression with moderate current episode.

One-way univariate analysis of variance (ANOVA) revealed no significant difference between the recovered, non-recovered and control groups in age, F(2,48) = 1.0, $p = .404$, $\eta_p^2 = 0.04$. There was no significant difference in the baseline BDI-II scores, t(22) = 0.8, $p = .537$, 95% CI [-11.92, 6.67], Cohen's d = 0.36, or in the DASS anxiety scores, t(22) = 0.6, $p = .570$, 95% CI [-4.71, 8.33], Cohen's d = 0.26, between the recovered and non-recovered groups. In addition, no difference was found between the groups in number of participants with mild or moderate depression, $p = .352$ (two-tailed Fisher's exact test) or in the number of medicated or non-medicated participants, $p = .325$ (two-tailed Fisher's exact test) (Table 2).

2.3. Stimuli

Neutral, sad and happy faces derived from the Ekmanös and Friesenös pictures of Facial Affect (1976) were used as the stimuli in the ERP measurement. Four identities were used (male actors EM and JJ, female actors PF and NR). The expressions in this series of pictures present the basic expressions that have been found to be universally recognized regardless of the person's cultural background (Ekman & Friesen, 1971). E-Prime software version 2.0.8.90 (Psychology Software Tools, Inc, Sharsburg, MD, USA), a Dell 5500 computer and a 23″ monitor (Asus VG236 series H; refresh rate = 120 Hz; display resolution = 1920 × 1080) were used to present the stimuli. The pictures were presented at a visual angle of 11° × 16°.

Two separate oddball stimulus conditions were applied in a counterbalanced order where the frequently presented 'standard' stimulus was always a neutral face. The neutral standard stimulus (p = 0.86) was rarely replaced by a 'deviant' stimulus (p = 0.14) which was either a sad (Sad condition) or a happy face (Happy condition). The standard and deviant stimuli were presented pseudo-randomly with a restriction that at least two standards were presented between two deviant stimuli and the identity of the face was always different between consecutive

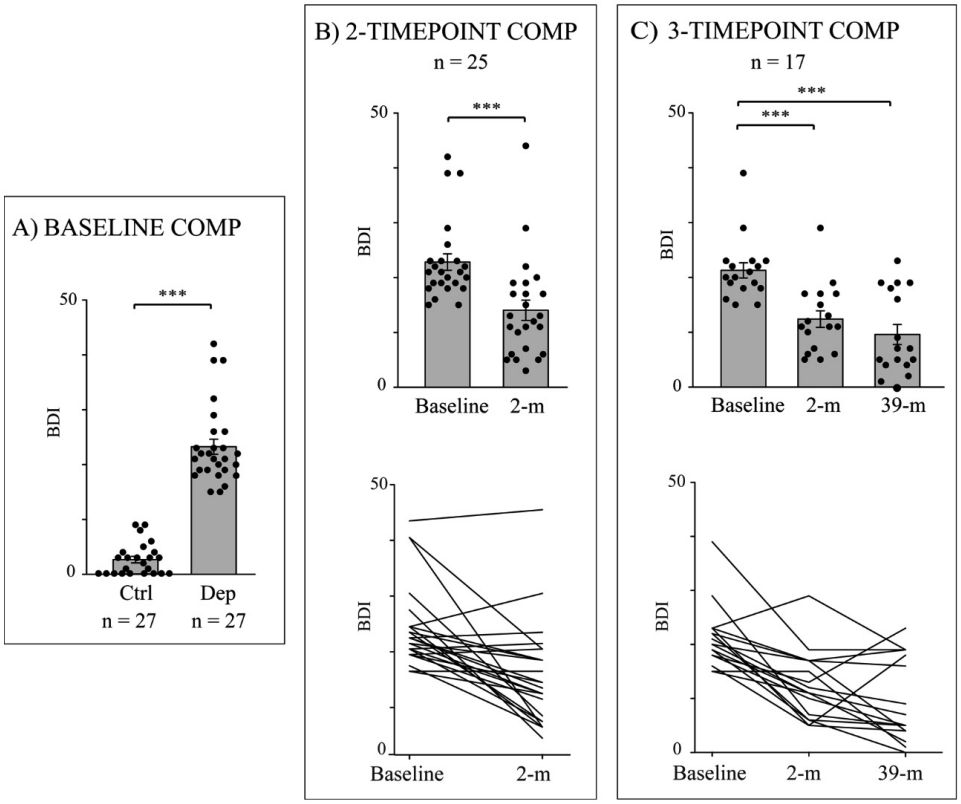

Fig. 2. The BDI-II-scores at different timepoints. A) BDI-II-scores for the control and the depressed group at the baseline measurement. B) The BDI-II-scores at the baseline and at the 2-m measurement for the depressed participants included in the 2-timepoint comparison. Note that data is missing for one participant. C) The BDI-II-scores at the baseline, the 2-m and the 39-m measurement for the participants included in the 3-timepoint comparisons. A, and upper panels of the B and C: The mean values, standard deviations and individual participants' values. Lower panel in B and C: Line graphs showing individual participants' BDI-II-score at different timepoints. Note that approximately half of the individuals in the depressed group (i.e. the wait-list group) had not yet received the intervention at the 2-m measurement. Baseline = before treatment, 2-m = 2-m after the baseline, when approximately half of the participants had received treatment, 39-m = 39 m after the baseline measurement. Comp = comparison, Ctrl = the control group, Dep = the depressed group; * $p < .05$, ** $p < .01$, *** $p < .001$.

stimuli. In both Happy and Sad conditions 480 standard stimuli and 80 deviant stimuli were presented. The stimulus duration was 200 ms, and the randomly assigned stimulus onset asynchrony was 400, 450 or 500 ms.

2.4. Procedure

During the experiment, the participants sat on a chair in a dimly lit, soundproof and electrically shielded room and were monitored via a video camera. Participants were presented with the facial stimuli on a screen 1 m in front of them. Simultaneously, the participants were listening to an audiobook from a loudspeaker above them. The participants were instructed to keep their gaze in the middle of the screen, focus on the story and ignore the visual stimuli. To ensure that participants focused on the story, they were asked questions about it between the stimulus conditions.

2.5. EEG recording and preprocessing

The EEG and electro-oculogram (EOG) was recorded with a high input impedance amplifier, i.e. Net Amps 200 amplifier, with 128-channel HydroCel Geodesic Sensor Net (Electric Geodesic Inc; Eugene;

Table 2
The demographics and clinical measures at the baseline measurement for the control, recovered and non-recovered groups.

Group	N	Mean Age ± SD [range]	Male/ Female	Mild/ Moderate	Mean BDI-II ± SD [range]	Mean DASS-A ± SD [range]	Non-med/med	TR group/ W-L group
Ctrl	27	45.4 ± 15.7 [21-65]	4/23	Na.	2.7 ± 3.0 [0-9]	Na.	Na.	Na.
Recovered	16	44.5 ± 13.4 [19-64]	2/14	10/6	22.5 ± 5.4 [16-39]	6.4 ± 8.4 [0-31]	11/5	8/8
Non-recovered	8	52.6 ± 13.0 [33-65]	1/7	7/1	25.1 ± 10.9 [15-42]	4.6 ± 3.7 [0-11]	4/4	5/3

Mild/Moderate = diagnosis of mild/moderate depression; BDI-II = Beck's Depression Inventory-II scores at the baseline; DASS-A = Anxiety score subscale for DASS-questionnaire scores at the baseline; Non-med/med = no antidepressant medication/antidepressant medication; SD = standard deviation; Na. = Not applicable. TR = treatment group in the intervention study; W–L = wait-list group in the intervention study; Ctrl = the non-depressed control group; for the definition of Recovered and Non-recovered see 2.2 Experimental design, psychological intervention and subgroup analyses.

USA) and Net Station software (version 4.2.1). The impedances were kept below 50 kΩ during the recording, as recommended by EGI Inc. The data was recorded at a 1000 Hz sampling rate, filtered online from 0.1 to 400 Hz and referenced to vertex electrode (Cz).

The analysis of the EEG data was conducted with Brain Vision Analyzer 2.1 (Brain Products GmbH, Munich, Germany). First, all bad channels with notable noise were interpolated. Next, the Gratton-Coles algorithm (Gratton, Coles, & Donchin, 1983) as implemented in Brain Vision Analyzer was used to reject artifacts originating from eye movements. The electrode signals were filtered with the low cutoff at 0.1 Hz and the high cutoff at 30 Hz, both with 24 dB/octave roll-off. In addition, a 50 Hz notch filter was applied. Offline, the data were re-referenced to average over all channels.

In the oddball condition, only the responses to standard stimuli immediately preceding the deviant stimuli were averaged. Eight hundred millisecond segments were extracted relative to the onset of the stimulus: from 200 ms before the onset of the stimulus to 600 ms after onset of the stimulus. The mean of a 200-ms pre-stimulus period served as a baseline for each segment. Segments with a voltage difference of more than 200 μV within a 200-ms time period were removed. The segments were averaged separately for the standard and deviant stimuli.

Data were excluded from further analysis if fewer than half of the trials were available for averaging. The mean number of accepted trials over all groups and conditions varied from 75.9 (SD = 8.3) to 77.8 (SD = 2.4) per condition. There were no significant differences in the number of accepted trials between the groups or between the measurement timepoints, $p > .148$.

Based on visual inspection of the data and previous findings for the P1 and N170 (e.g. Astikainen et al., 2013; Batty & Taylor, 2003), electrodes at the left and right occipital sites for P1 and at left and right parieto-occipital sites for N170 were selected (see Supplementary Figure S1). Two electrode clusters (left and right) were created for the analyses of P1 and N170 in order to examine the responses separately for both hemispheres. The most positive peak within 80–150 ms after the onset of the stimulus for P1 and the most negative peak within 130–210 ms after the onset of the stimulus for N170 were detected separately for each channel. The peak values were averaged over an electrode cluster separately for the left and right site.

2.6. Statistical analysis

The statistical analysis was conducted with the IBM SPSS Statistics 24.0 program (Armonk, Ny: IBM corporated). Repeated measures of MANOVA were applied at the baseline measurement to assess differences within the stimulus type (happy vs. sad vs. neutral), hemisphere (left vs. right) and component (P1 vs. N170) between the control and depressed groups. As described above (see Stimuli), there were two experimental conditions, which included different deviant stimuli (sad or happy) among standard neutral stimuli, and the neutral stimuli was always the same for both conditions. For the baseline comparison, an average of the responses to neutral faces derived from the two conditions (sad and happy collapsed) were calculated, to reduce the levels in the repeated measures of MANOVA analysis. At the baseline the amplitude values for each stimulus types (sad vs. happy vs. neutral) were applied to inspect in which stimulus type the depression-related alterations would arise. Whenever significant interaction effects of group x stimulus type or group x stimulus type x component were found they were followed with a further repeated measures of MANOVA analysis separately for the components and/or the groups. Two-tailed independent-samples t-tests were applied whenever a stimulus type difference was found between the groups and paired-samples t-tests whenever a stimulus type difference was found within the groups.

The sad negative bias found in the depressed group at the baseline measurement was analyzed in the follow-up timepoint comparisons with separate repeated measures of MANOVAs for the 2- and 3-timepoint comparisons. The 2-timepoint comparison included the available data from participants who participated to both baseline and 2-m measurements (n = 25) and the 3-timepoint comparison included the data from those who participated to baseline, 2-m and 39-m measurements (n = 17). Because some of the participants dropped out before the 39-m measurement, the samples are only partly overlapping. The negative bias was operationalized as a difference between the peak amplitude to the sad faces and that to the neutral faces preceding the sad faces (sad – neutral differential response). In the 2-timepoint repeated measures of MANOVA for the differential response the within-subject variable was timepoint (baseline vs. 2-m). The timepoint variable in repeated measures of MANOVA for the 3-timepoint comparison had three levels (baseline vs. 2-m vs. 39-m). To further investigate the timepoint effects, two-tailed paired sample t-tests were conducted comparing differential responses between the timepoints, whenever repeated measures of MANOVA indicated a main effect of time.

To further investigate group differences in negative bias, a one-way ANOVA comparing the differential responses (sad minus neutral) between the groups (recovered vs. non-recovered vs. control group) was conducted.

The p-values for multiple t-tests were corrected with an FDR-correction (for independent sample t-tests; Benjamini & Hochberg, 1995); for paired samples t-tests: Benjamini & Yekutieli, 2001). For the baseline group comparison, only the significant main effects of group or stimulus type or their interaction effects are reported. For repeated measures of MANOVA, partial eta squared (η_p^2) and for t-tests Cohen's d with pooled standard deviation are reported as effect size estimates.

Two-tailed Pearson's correlation coefficient were used to examine the correlations between the P1 differential responses (indicating negative bias) and BDI-II-scores. In addition, baseline BDI-II-scores were correlated with post-intervention BDI-II-scores and with BDI-II-score change from baseline to post-intervention (baseline BDI-II-scores minus post-intervention BDI-II-scores), to investigate the effect of number of the initial depression symptoms on treatment response. For the correlation tests, a bootstrap based on 1000 iterations and CI of 95% were applied.

For all tests, *P*-values of less than .05 were considered significant.

2.7. Analysis of reliability of the ERPs

The split-half reliability of the ERPs were investigated for the baseline measurement by comparing the P1 amplitudes between the even and odd trials of the neutral faces derived from the Sad condition. There was a large correlation between the even and odd incidences of the P1 responses in the left hemisphere, r = .923, n = 54, $p < .001$, 95% CI [0.87, 0.96] and in the right hemisphere, r = .892, n = 54, $p < .001$, 95% [0.79, 0.94]. Paired samples t-tests (FDR corrected) showed no significant differences between the even trials (M = 4.3, SD = 3.0) and the odd trials (M = 3.9, SD = 2.9) in the left hemisphere, t(53) = -2.0, $p = .144$, or between the even (M = 4.0, SD = 2.7) and the odd trials (M = 3.9, SD = 2.8) in the right hemisphere t(53) = -0.5, $p = .963$.

3. Results

3.1. Baseline comparison between depressed and control participants

Results for the P1 and N170 amplitudes are reported at the baseline measurement, when all the participants in the depressed group had a recently confirmed depression diagnosis and self-reported symptoms of depression (BDI-II-scores ≥ 14). The peak amplitude values for P1 and N170 are presented in the Fig. 3 and the waveforms for P1 and N170 in the Figs. 4 and 5, respectively.

Repeated measures of MANOVA investigating peak amplitude values (sad vs. happy vs. neural) showed a main effect of stimulus type, F(2,51) = 8.8, $p = .001$, $\eta_p^2 = .257$, and stimulus type x component

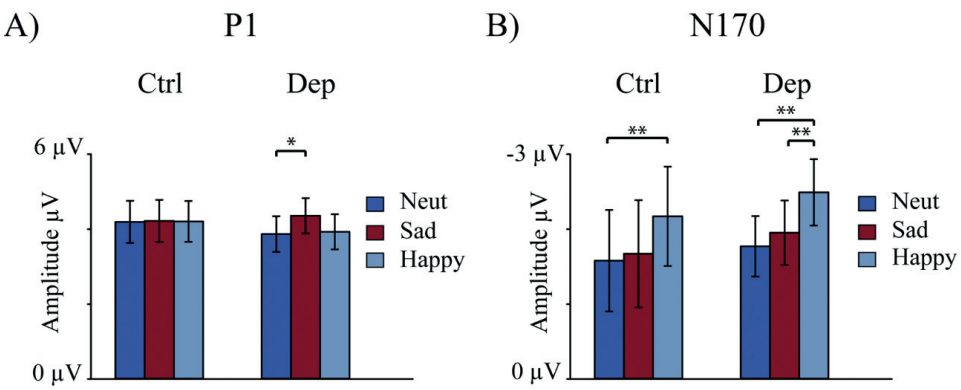

Fig. 3. The peak amplitude values and standard deviations for the neutral standard, sad deviant and happy deviant faces for the control and depressed groups for P1 (A) and N170 (B). Error bars represent standard error. Ctrl = the control group, Dep = the depressed group; * p < .05, ** p < .01.

interaction effect, F(2,51) = 27.8, p < .001, η_p^2 = 0.522, and stimulus type x component x group interaction effect, F(2,51) = 4.2, p = .022, η_p^2 = 0.139.

The stimulus type x component x group interaction was followed with separate repeated measures of MANOVAs for each component. The stimulus x group interaction was non-significant for P1, F(2,51) = 2.2, p = .122, η_p^2 = .08, and for N170, F(2,51) = 0.52, p = .597, η_p^2 = 0.02. Follow-up repeated measures of MANOVAs with within-subjects factors stimulus type (sad vs. neutral vs. happy) and component (P1 vs. N170) were conducted separately for the groups. Repeated measures of MANOVA showed a significant stimulus x component interaction within the control group F(2,25) = 5.7, p = .009, η_p^2 = .313, and within the depressed group F(2,25) = 28.7, p < .001, η_p^2 = .697. Therefore, repeated measures of MANOVAs with within-subjects factor of stimulus type (sad vs. neutral vs. happy) were conducted separately for the groups and components.

For the P1, the repeated measures of MANOVA showed a significant stimulus type effect in the depressed group, F(2,25) = 4.2, p = .026, η_p^2 = 0.253, but not in the control group, F(2,25) = 0.01, p = .987, η_p^2 < 0.01. The following paired-samples t-tests in the depressed group showed that the sad faces elicited larger P1-responses than the neutral faces (see Table 3). The effects of medication and baseline BDI-II-scores on the responses was investigated within the depressed group, by adding medication status (medicated vs. non-medicated) and the baseline BDI-II-scores as covariates to the repeated measures of MANOVA model for the depressed group. The medication x BDI x stimulus type interaction was non-significant, F(2,22) = 0.02, p = .977, η_p^2 = 0.120. Next, the medication and BDI-II-scores were inspected independently by adding them as covariates to separate repeated measures of MANOVAs. Both the stimulus type x medication interaction, F(2,24) = 2.6, p = .775, η_p^2 = .021, and the BDI x stimulus type interaction, F(2,24) = 0.4, p = .658, η_p^2 = 0.03, were non-significant.

The repeated measures of MANOVA for the N170 showed a main effect of stimulus type for the control, F(2,25) = 6.5, p = .005, η_p^2 = 0.342, and the depressed group, F(2,25) = 13.5, p < .001, η_p^2 = 0.520. The paired-samples t-tests within both groups showed larger N170 responses for the happy faces compared to the neutral faces. In the depressed group, responses for the happy faces were also larger than those to the sad faces (see Table 3). The covariate analysis with medication and BDI-II-scores showed no significant medication x BDI x stimulus type interaction in the depressed group, F(2,22) = 0.6, p = .569, η_p^2 = 0.05. There was no significant stimulus type x medication interaction, F(2,24) = 0.7, p = .520, η_p^2 = 0.05 or BDI x stimulus type interaction, F(2,24) = .0.4, p = .717, η_p^2 = 0.03, when covariates were added separately to the model.

There was no significant correlation between the amplitude of the P1 differential responses (sad minus neutral) and the BDI-II-scores within the whole sample, r = .207, n = 51, p = .146, 95% CI [-0.05, 0.45] or within the depressed group, r = -0.170, n = 27, p = .396, 95% CI [-0.56, 0.39].

3.2. The 2-timepoint comparison within the depressed group

In this section, the changes in the P1 differential responses (sad minus neutral) from the baseline measurement to the 2-m measurement in the Sad condition are reported. At the 2-m measurement, 48 % of the participants had completed the intervention. The P1 responses for the Sad condition at the baseline measurement and at the 2-m measurement are presented in the Fig. 6.

Repeated measures of MANOVA for the P1 differential response, showed a main effect of time, F(1,24) = 4.4, p = .046, η^2 = 0.155. The differential response decreased from the baseline measurement (M = 0.6 μV, SD = 0.9) to the 2-m measurement (M = -0.03 μV, SD = 1.1).[1]

To control for the possible effect of between-subjects variability in the time-interval between the baseline and the 2-m measurements (mean = 55 d, SD = 11.3, range 33–91 d), a repeated measures of MANOVA was conducted for the differential responses with time-interval as a covariate. The time x time-interval interaction was non-significant, F(1,23) = 0.5, p = .469, η^2 = 0.02. To control for the effect of anxiety, a repeated measures of MANOVA was conducted with DASS-A scores (at the baseline) as a covariate. The time x DASS-A interaction was non-significant, F(1,23) = 0.3, p = .584, η^2 = 0.01.

3.3. The 3-timepoint comparison within the depressed group

In this section, the significant changes in P1 differential responses (sad minus neutral) from the baseline measurement to the 2-m measurement and the 39-m measurement in the Sad condition are reported (Fig. 7).

In repeated measures of MANOVA a significant effect of timepoint was found for the differential response, F(2,15) = 5.2, p = .019, η^2_p = 0.411. The paired-samples t-test showed a significant decrease in the P1 differential response from the baseline measurement (M = 0.6 μV, SD = 1.0) to the 39-m measurement (M = -0.2 μV, SD = 0.8), t (16) = 3.4, p = .022, 95% CI [0.27, 1.21], Cohen's d = 0.82. No

[1] Repeated measures of MANOVA for the P1 differential response was also computed without the data of the participant with missing BDI-II scores at 2-m. There was a main effect of time, F(1, 23) = 4.4, p = .048, η^2 = 0.160. The differential response decreased from the baseline measurement (M = 0.6 μV, SD = 0.9) to the 2-m measurement (M = 0.0 μV, SD = 1.1).

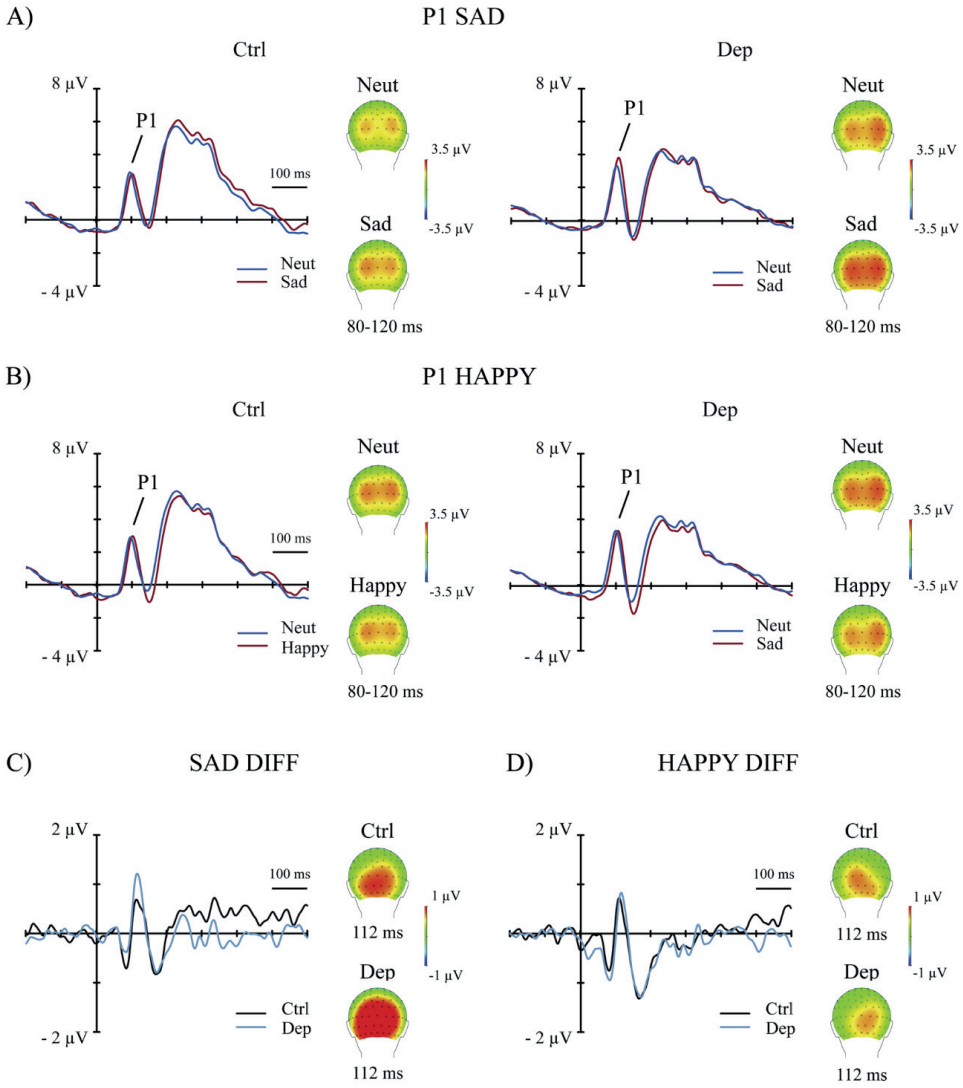

Fig. 4. The grand-averaged P1 waveforms averaged for the left and right occipital electrode cluster for the control (n = 27) and the depressed (n = 27) groups at the baseline measurement. Responses to sad (A) and happy (B) deviant faces and neutral faces and differential responses (emotional minus neutral) (C–D).The topographical maps for A and B show mean amplitude value from 80 to 120 ms after stimulus onset to the emotional faces and neutral faces preceding the emotional face (neut). The topographical maps for C and D show the differential response between emotional faces and neutral faces preceding the emotional face (peak value at 112 ms after stimulus onset). Ctrl = control group; Dep = depressed group.

change in the P1 differential response was found between the baseline and 2-m measurement (M = 0.02 μV, SD = 0.9), t(16) = 1.5, p = .457, 95 % CI [-0.25, 1.35], Cohen's d = 0.61 or between the 2-m and 39-m measurement, t(16) = 0.5, p = 1.000, 95% CI [-0.57, 0.95], Cohen's d = 0.26. To control for the effect of anxiety, a repeated measures of MANOVA for the differential responses was conducted with DASS-A scores (at the baseline) as a covariate. The time x DASS-A interaction was non-significant, F(2,14) = 0.03, p = .968, $\eta^2 < 0.001$.

3.4. Treatment response

In this section, the significant group differences in P1 differential responses (sad minus neutral) at the baseline measurement between the recovered, non-recovered and control groups are reported. A one-way ANOVA was performed to compare the groups in P1 differential responses.

The ANOVA showed significant group differences, F(2,48) = 4.0, p = .024, η_p^2 = .144. The post hoc independent sample t-tests between the groups showed a larger differential response in the non-recovered group (M = 1.1 μV, SD = 1.0) compared to the control group (M = 0.2 μV, SD = 0.8), t(33) = 2.9, p = .021, 95% CI [0.28, 1.61], Cohen's d = 1.10, but no significant difference in responses was found between the recovered (M = 0.5 μV, SD = 0.9) and non-recovered group, t(22) = -1.5, p = .203, 95% CI [-1.44, 0.21], Cohen's d = 0.67, or between the recovered and control group, t(41) = 1.3, p = .203, 95% CI [-0.19, 0.85], Cohen's d = 0.37. The averaged P1 differential responses for the three groups are presented in the Fig. 8.

To control for potential effects of medication and baseline BDI-II-

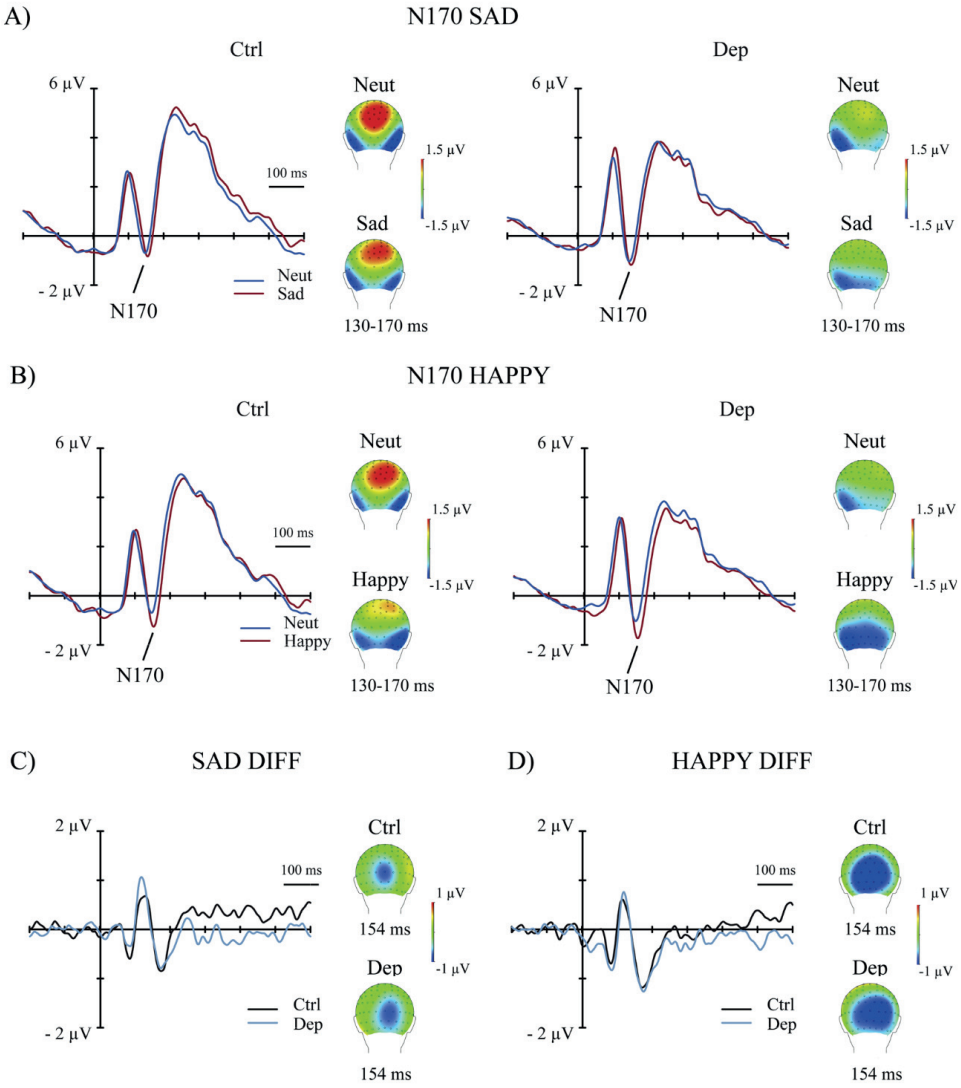

Fig. 5. The grand-averaged N170 waveforms averaged for the left and right parieto-occipital electrode cluster for the control (n = 27) and the depressed (n = 27) groups at the baseline measurement. Responses to sad (A) and happy (B) deviant faces and neutral faces and differential responses (emotional minus neutral) (C–D).The topographical maps for A and B show mean amplitude value from 130 to 200 ms after stimulus onset to the emotional faces and neutral faces preceding the emotional face (neut). The topographical maps for C and D show the differential response between emotional faces and neutral faces preceding the emotional face (peak value at 154 ms after stimulus onset). Ctrl = control group; Dep = depressed group.

scores on the differential responses, medication status and BDI-II-scores were added as covariates to the ANOVA model. There was no significant medication x BDI x group interaction, $F(2,41) = 1.0$, $p = .790$, $\eta_p^2 = 0.01$. When the effect of medication and BDI-II-scores were studied in separate ANOVA models, there was no significant BDI x group interaction, $F(2,42) = 3.0$, $p = .062$, $\eta_p^2 = 0.12$, or medication x group interaction, $F(1,46) = 0.2$, $p = .648$, $\eta_p^2 < 0.01$.

The effect of the baseline BDI-II-scores on treatment response was further investigated with Pearson correlation. There was no significant correlation between the baseline BDI-II-scores and the post-intervention BDI-II-scores (2-m measurement for the treatment group and 4-m measurement for the wait-list control group), r = .245, n = 24, p = .249, 95% CI [-0.35, 0.62]. There was a positive correlation between the baseline BDI-II-scores and the baseline minus post-intervention BDI-II difference, r = .769, n = 24, p = .001, 95% CI [0.57, 0.89], indicating that those with larger baseline BDI-II-scores had larger change in the BDI-II-scores from baseline to post-intervention.

There were no significant correlations between the P1 differential response (at the baseline) and the BDI-II-scores at the post-intervention, r = .327, n = 24, p = .119, 95% CI [-0.03, 0.64] or between P1 differential response and the change in the BDI-II-score from the baseline measurement to the post-intervention measurement, r = -0.124, n = 24, p = .563, 95% CI [-0.56, 0.29].

4. Discussion

The purpose of the present study was to investigate whether there is negative bias in task-irrelevant processing of facial expressions in

Table 3
The mean amplitude values (μV) and standard deviations (SD) of the P1 and N170 responses and the results of the follow-up paired-samples t-tests investigating the significant effects in repeated measures of MANOVA at the baseline.

			P1					
Group	Condition	Mean neutral ± SD	Mean emotional ± SD	df	t	*P*	d	95% CI
Dep	Sad	3.9 ± 2.5	4.4 ± 2.4	26	2.9	.039*	0.20	0.14, 0.84
	Happy	3.9 ± 2.5	3.9 ± 2.4	26	0.4	1.000	0.02	−0.22, 0.34
			P1 sad vs. happy deviant					
Group				df	t	*P*	d	95% CI
Dep				26	2.5	.052	0.21	0.08, 0.78
			N170					
Group	Condition	Mean neutral ± SD	Mean emotional ± SD	df	t	*P*	d	95% CI
Ctrl	Sad	−1.6 ± 3.5	−1.7 ± 3.7	26	0.6	1.000	0.03	−0.39, 0.21
	Happy	−1.6 ± 3.5	−2.2 ± 3.4	26	3.6	.006*	0.17	−0.93, -0.26
Dep	Sad	−1.8 ± 2.1	−2.0 ± 2.2	26	1.3	.400	0.09	−0.48, 0.11
	Happy	−1.8 ± 2.1	−2.5 ± 2.3	26	5.3	.008*	0.32	−1.00, -0.44
			N170 sad vs. happy deviant					
Group				df	t	*P*	d	95% CI
Ctrl				26	2.3	.091	0.14	−0.94, -0.05
Dep				26	3.3	.008*	0.22	−0.87, -0.21

Ctrl = control group; Dep = depressed group; Sad = Sad condition; Happy = Happy condition; SD = standard deviation; df = degrees of freedom; d = Cohen's d; CI = confidence intervals; P = p-value, * significant ($p < .05$).

depression and whether the bias remains if depression symptoms subside. In addition, it was investigated whether the brain responses recorded at the baseline when all the participants were currently depressed are associated with recovery after a brief psychological intervention. Consistent with our hypothesis, we found a negative bias in depressed participants in the P1 responses to sad faces. The bias normalized when the depression symptoms alleviated, suggesting that the bias is state-related rather than a permanent trait. The brain responses recorded at the baseline did not differ between those depressed participants who recovered and those who did not recover after the brief psychological intervention.

Negative bias was demonstrated as increased P1 amplitudes to rare sad faces compared to frequent neutral faces in the depressed group, whereas in the control group no differences between the responses to the different facial emotions were found. P1 has been suggested to reflect early global processing of faces (Itier & Taylor, 2002, 2004; Taylor, 2002). In accordance with absent modulation of the P1 to emotional faces in the control group, previous studies conducted in healthy participants have not found differences between P1 amplitude for neutral and emotional faces when an ignore oddball condition was applied (fearful and happy deviant faces and neutral standard faces: Astikainen & Hietanen, 2009) or have reported it to fearful deviant face, but not for happy faces (fearful and happy faces as standard and deviant stimuli: Stefanics, Csukly, Komlósi, Czobor, & Czigler, 2012). Also in line with our finding, in an attended task, where the participant was asked to evaluate the expressions, depression-related negative bias was found in the P1 response to sad faces, while no such difference was found in the control group (Dai & Feng, 2012). However, in one study, subliminally presented attended sad faces elicited a larger P1 response compared to neutral faces in the depressed group, while controls had a smaller P1 for sad faces compared to neutral faces (Zhang et al., 2016).

We did not find depression-related negative bias in N170, similarly to Jaworska et al. (2012) who applied sad, neutral, joyful and surprised faces with varying emotional intensities and with a task to detect the surprised faces. However, in a few previous studies negative bias has been found in N170 amplitudes to sad faces in depressed participants (Wu et al., 2016) or in early vMMN which occurred in the latency of the N170 (Chang et al., 2010). Chang et al. (2010) found decreased vMMN amplitudes to happy and sad faces in the depressed compared to the control group in the N170 latency range. However, the stimuli in Changös et al. (2010) study were schematic faces, and it is possible that more naturalistic faces, as applied in the present study, enables elicitation of a normal N170 in depressed participants. In addition, by using the oddball condition, Wu et al. (2016) found a larger N170 in response to sad faces in the depressed group compared to the control group. In contrast to our study, their results reflected attentive processing. The N170 response has also been studied in stimulus conditions other than the oddball paradigm with a task to discriminate emotional faces from non-emotional faces (Zhang et al., 2016) or to attend to the emotion of the face cue and then respond to a number target presented after the face cue (Zhao et al., 2015). These studies showed negative bias as reflected by increased N170 amplitude to sad faces compared to neutral faces in the depressed group (Zhang et al., 2016; Zhao et al., 2015) or decreased amplitude for happy faces in the depressed group relative to the control group (Zhao et al., 2015). The discrepancy between the previous results and the results of the present study can thus be possibly explained by differences in the experimental tasks (attend vs. ignore condition). Although in Zhangös et al. (2016) study the faces were presented subliminally, the task was to identify the emotion. Thus, it is possible that the depression-related negative bias in N170 is more evident with task-relevant stimuli but may not arise when the stimuli are task-irrelevant.

Although we did not find depression-related negative bias in the N170 response, we found in both groups an emotional modulation of it, which was demonstrated as larger amplitudes to rare happy faces compared to frequent neutral faces. In the depression group the responses were also larger for happy compared to the sad faces. The finding of no negative bias in the depression group is similar to a previous study that also found no depression-related negative bias in N170, but a larger response to joyful compared to sad and neutral faces

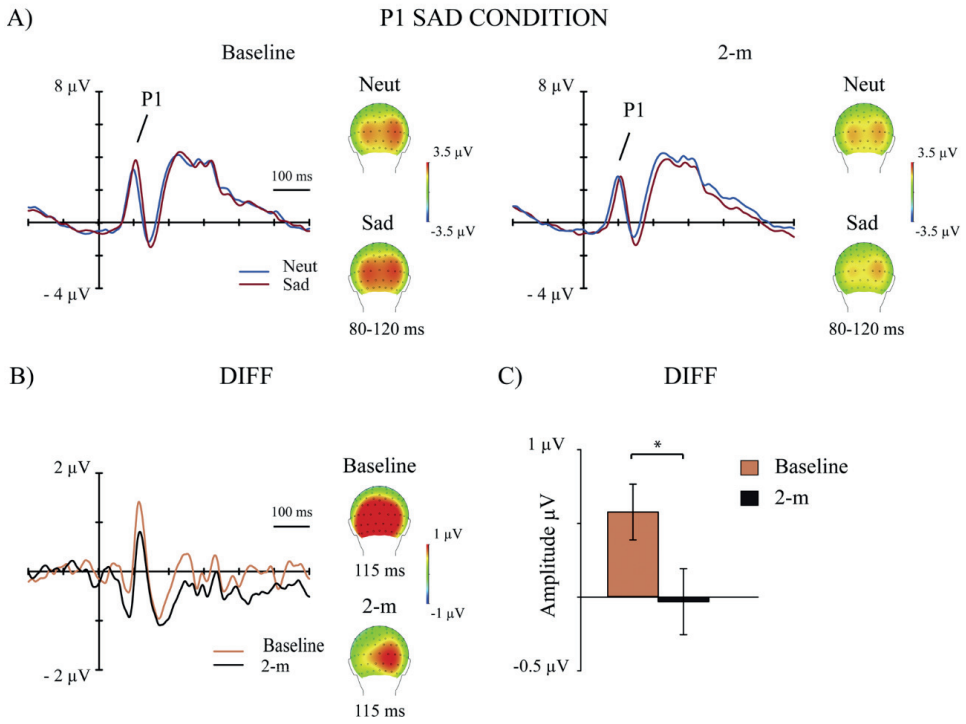

Fig. 6. The grand-averaged P1 responses in the Sad condition for the depressed group (n = 25) at the baseline measurement and at the 2-m measurement. A) The waveforms averaged for the left and right occipital electrode cluster and the topographical maps of the P1 responses (mean amplitude value at 80–120 ms after stimulus onset) to the sad faces and the neutral faces preceding the sad face (neut). B) Differential waveforms (Diff; sad minus neutral) and the topography of the differential responses (peak value at 115 ms after stimulus onset) at the baseline measurement and at the 2-m measurement. C) The amplitude values for the differential responses for the baseline and the 2-m measurements. Error bars represent standard error. * $p < .05$.

(Jaworska et al., 2012). Also in a MEG study in which task-irrelevant changes in emotional faces were presented in the oddball condition no negative bias in M170 was found for the dysphoric group (Xu et al., 2018). However, in that study a larger M170 response was found at the whole sample level for rare sad than to rare happy faces. The stimulus condition in Xu et al. (2018) was different to that of the present study, since it applied only emotional faces (both sad and happy faces as deviant and standard). Our finding of a larger N170 amplitude to happy than neutral faces is also in line with the previous oddball studies conducted in healthy participants (Astikainen & Hietanen, 2009; Astikainen et al., 2013; Stefanics et al., 2012; Stefanics, Heinzle, Attila Horváth, & Stephan, 2018; Zhao & Li, 2006) and also with the studies using stimulus conditions other than the oddball condition (Batty & Taylor, 2003; Japee, Crocker, Carver, Pessoa, & Ungerleider, 2009; Miyoshi, Katayama, & Morotomi, 2004; Wronka & Walentowska, 2011).

The second aim of the present study was to investigate the dependence of negative bias on the state of the depression. To study this, we investigated the changes in negative bias (reflected by P1 differential response, i.e. sad-neutral) from the baseline measurement to the 2-m measurement and the 39-m measurement in the depressed group. At the 2-m measurement, approximately half of the depressed participants had received a brief psychological intervention, and the depression symptoms had been significantly reduced at the whole group level (BDI-II mean at the baseline measurement 22.8 ± 7.4, mean at the 2-m measurement 14.0 ± 9.1). A decrease in the P1 differential responses to sad faces was found at the 2-m measurement. In addition, the differential responses decreased from the baseline measurement to the 39-m measurement, when all the depressed participants had received the intervention and the BDI-II scores were low (mean at the 39-m measurement 9.6 ± 7.6). The results resemble previous fMRI findings that showed normalized facial expression processing after cognitive behavioral therapy (Fu et al., 2008) or after antidepressant treatment (Victor et al., 2010). The present results indicate that as depression symptoms decrease, negative bias normalizes.

The third aim was to examine whether the negative bias in face processing in depression can distinguish between the depressed group who recovers and the group who shows no recovery after a brief psychological intervention. Finding predictors of treatment response is important, because the remission rate after antidepressant treatment or psychotherapy treatment is usually less than 50 % (Thase, Entsuah, & Rudolph, 2001, for reviews, see Cuijpers et al., 2014; De Maat, Dekker, Schoevers, & De Jonghe, 2006). If reliable predictors for treatment responses could be found, better treatment options could be selected individually in the future. Several fMRI studies (Fu et al., 2008; Ritchey, Dolcos, Eddington, Strauman, & Cabeza, 2011; Siegle, Carter, & Thase, 2006) have found potential brain correlates for treatment response to psychotherapy, but ERP studies are rare (see, however, Stange et al., 2017, who reported that the late positive potential to aversive pictures predicts the response to cognitive behavioral therapy). Studies on ERPs are warranted, because compared to fMRI measures, EEG is cost-efficient and widely available in public health care and therefore has more potential for clinical use.

The brain responses recorded at the baseline did not differ between the depression group who recovered and the group that did not recover after the intervention. It is possible that this null finding may be related to small sample size. Group difference was only found when comparing the non-recovered group to non-depressed controls. We found larger

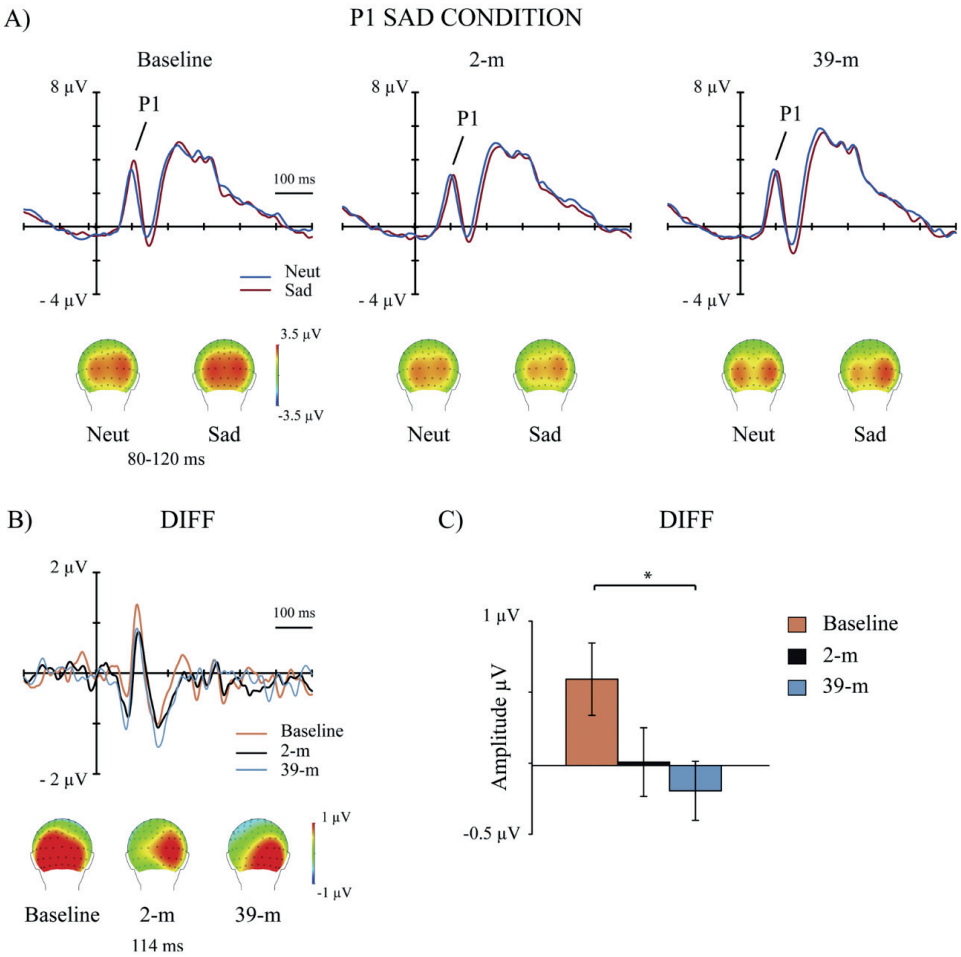

Fig. 7. The grand-averaged P1 responses in the Sad condition for the depressed group (n = 17) at the baseline, 2-m and 39-m measurements. A) The waveforms averaged over the left and right occipital electrode cluster and the topographical maps of the P1 responses (mean amplitude value at 80–120 ms after stimulus onset) to neutral (neut) and sad faces at the baseline, 2-m and 39-m. B) The P1 differential waveforms (Diff; sad minus neutral) and the topographies of the differential responses (peak value at 114 ms after stimulus onset) in the depressed group at the baseline, 2-m and 39-m measurements. C) The amplitude values for the differential responses for the baseline, 2-m and 39-m measurements. Error bars represent standard error. * $p < .05$.

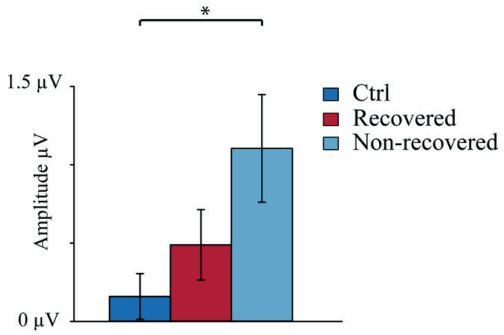

Fig. 8. The amplitude values of the differential responses (sad minus neutral) for each group at the baseline measurement. Error bars represent standard error. * $p < .05$, Ctrl = control group, Recovered = recovered group, Non-recovered = non-recovered group.

negative bias at the baseline, as reflected by the P1 differential response (sad minus neutral), in the group who did not recover after intervention compared to the control group, while the recovered group did not show larger negative bias than the control group. To best of our knowledge, this is the first ERP study to investigate facial expression processing in association with treatment response for psychological intervention.

Our finding that only the non-recovered group differed from controls in negative bias may not be explained by the initial number of depression symptoms, although some previous studies have found that greater number of depression symptoms can predict poorer treatment response for CBT (Elkin et al., 1989; Thase, Simons, Cahalane, McGeary, & Harden, 1991, however, more recent meta-analyses found no effect of baseline depression symptoms on treatment outcomes to CBT: Furukawa et al., 2017; Weitz et al., 2015). Namely, the recovered and non-recovered groups did not differ in number of symptoms at the baseline and there was no significant interaction effects between the number of the baseline depression symptoms and the P1 responses. Correlation analysis revealed that participants with greater baseline depression symptoms showed actually better treatment response

(change in BDI-II scores) as indicated by change in depression symptoms. This direction of the correlation is in discrepancy with the previous findings of poorer CBT treatment response in those with greater baseline symptoms (Elkin et al., 1989; Thase et al., 1991).

It is unlikely that the larger negative bias in the non-recovered group relative to controls is explained by this group having lower number of participant with antidepressants, because there was no significant difference between the recovered and non-recovered groups in the number of medicated and non-medicated participants. Furthermore, no interaction effects of medication were found in the group comparison analyses. It can be speculated that negative bias can undermine the therapist–patient interaction, which is one factor that can affect the outcome of therapy (for reviews see, Horvath & Symonds, 1991; Martin, Garske, & Davis, 2000). Problems in social interaction are common in depression and can increase risk for depression (Chou, Liang, & Sareen, 2011; Teo, Choi, & Valenstein, 2013, for a review see Kupferberg, Bicks, & Hasler, 2016).

It remains an open question whether negative bias can cause depression or whether negative bias is a symptom of depression. If negative bias can maintain depression as Beckös (1967, 1976) model suggests, then modification of the bias may affect depression symptoms. It can be speculated that those patients with greater negative bias could benefit from treatments that specifically target perceptual and attentive negative bias. Several studies showed a reduction in depression symptoms after attentional training where participants are taught to direct attention toward positive emotional stimuli and away from negative stimuli (see e.g. Wells & Beevers, 2010; Yang, Ding, Dai, Peng, & Zhang, 2015, for reviews, see Gold, Montana, Sylvia, Nierenberg, & Deckersbach, 2016; Hallion & Ruscio, 2011).

The small sample size, especially in the comparison including all the three timepoints and in the comparison of the recovered and non-recovered groups, as well as the uneven gender distribution with the significant majority of the participants being female, must be taken into account when generalizing the results of the study. In contrast, a definite strength of this study was the longitudinal study design that was utilized to investigate the changes in facial expression processing over time in the depressed group. However, the limitation is that the control group was assed only once.

Another limitation of the study is that we cannot disentangle the effects of rareness and emotional modulation in the face processing. This is because we applied the oddball paradigm where emotional faces were always presented as infrequent deviant stimuli. Therefore, it is possible that the enhanced responses to the stimuli can also reflect deviance detection as indexed by the vMMN (Astikainen & Hietanen, 2009; Astikainen et al., 2013; Stefanics et al., 2012, 2018; Zhao & Li, 2006) instead of (or in addition to) emotional modulation of the canonical ERP components (Batty & Taylor, 2003; Japee et al., 2009; Miyoshi et al., 2004; Wronka & Walentowska, 2011). However, the main focus in this study was finding ERP markers related to the illness course and treatment outcome.

In sum, the present results indicate negative bias in early automatic processing of sad faces in depression. This finding adds to the literature that has shown attentional bias towards sad emotions in depression. The results also indicate that early negative bias is state-dependent; in other words, the bias is reduced when the depression symptoms decrease. The results show that alleviation of negative bias in face processing can be detected very rapidly after depression symptoms subside. However, since the brain responses recorded at the baseline did not differ between the recovered and non-recovered depression groups, there is no indication that negative bias in P1 could serve as a biomarker for treatment response.

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All the authors had full independence from the funders.

Declaration of Competing Interest

The authors report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.biopsycho.2019.107806.

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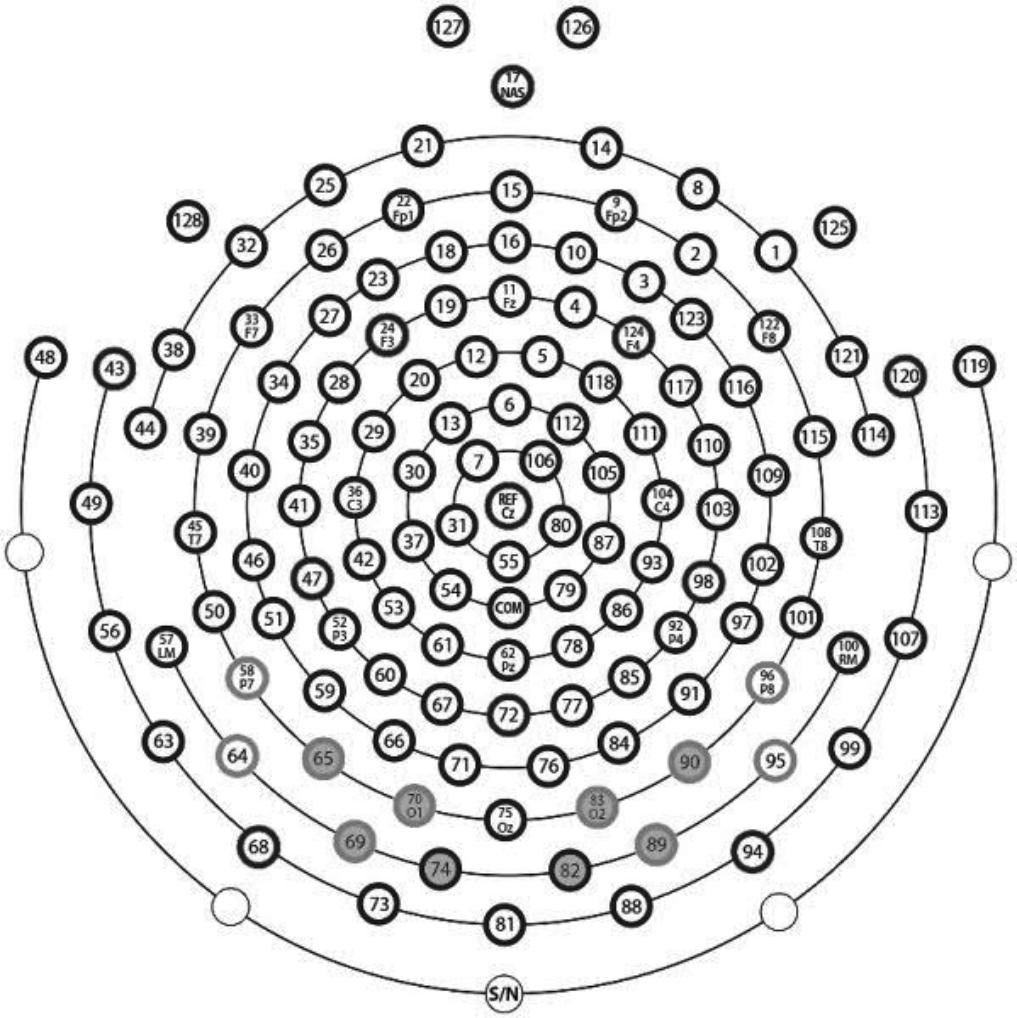

ERP component	Electrode pool left	Electrode pool right
P1	65, 69, 70, 74	82, 83, 89, 90
N170	58, 64, 65, 69, 70, 74	82, 83, 89, 90, 95, 96

Supplementary Figure S1. Hydrogel Geodesic Sensor Net 128-channel arrangement. The selected channels for P1 are marked with grey filling and channels for N170 with grey outline circles. Note that channel choices for P1 and N170 are partly overlapping (marked with grey filling and grey outline circle).