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2022-05

Koskinen , S M , Ahveninen , J , Kujala , T , Kaprio , J , O'Donnell , B F , Osipova , D , Viken , R J , Naatanen , R & Rose , R J 2022 , ' Association of lifetime major depressive disorder with enhanced attentional sensitivity measured with P3 response in young adult twins ' , Biological Psychology , vol. 171 , 108345 . https://doi.org/10.1016/j.biopsycho.2022.108345

http://hdl.handle.net/10138/346816
https://doi.org/10.1016/j.biopsycho.2022.108345

Biological Psychology 171 (2022) 108345

Contents lists available at ScienceDirect

Biological Psychology

journal homepage: www.elsevier.com/locate/biopsycho

Association of lifetime major depressive disorder with enhanced attentional sensitivity measured with P3 response in young adult twins

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ARTICLE INFO

Keywords:
Young Adults
Major Depressive Disorder
Event-Related Potentials
P3
Twin Study

ABSTRACT

Major depression is associated with alterations in the auditory P3 event-related potential (ERP). However, the persistence of these abnormalities after recovery from depressive episodes, especially in young adults, is not well known. Furthermore, the potential influence of substance use on this association is poorly understood. Young adult twin pairs (N = 177) from the longitudinal FinnTwin16 study were studied with a psychiatric interview, and P3a and P3b ERPs elicited by task-irrelevant novel sounds and targets, respectively. Dyadic linear mixed-effect models were used to distinguish the effects of lifetime major depressive disorder from familial factors and effects of alcohol problem drinking and tobacco smoking. P3a amplitude was significantly increased and P3b latency decreased, in individuals with a history of lifetime major depression, when controlling the fixed effects of alcohol abuse, tobacco, gender, twins' birth order, and zygosity. These results suggest that past lifetime major depressive disorder may be associated with enhanced attentional sensitivity.

1. Introduction

Eight to ten percent of young adults suffer from depressive disorders, and more than half of young adults suffering from depressive disorders have a comorbid condition (Aalto-Setälä et al., 2001). Depressive symptoms in adolescence also predict early adulthood depressive disorders and problem drinking (Aalto-Setälä et al., 2002). Major depression is often comorbid with alcohol use disorder which appears to reflect shared genetic susceptibility (Andersen et al., 2017). Additionally, persons with depressive disorders are about twice as likely to smoke as persons without a psychiatric disorder (see Mathew et al., 2017, for a review). A recent study with twins suggested that cigarette smoking in early adolescence predicts depressive symptoms in later adolescence (Ranjit et al., 2019). Association between major depression and smoking may be influenced by genetic variations, which increases risk for both disorders (Yao et al., 2020). However, the way that adolescent depression, considering comorbid conditions including tobacco smoking and alcohol use, affects brain function later in life, is still poorly understood.

Major depressive disorder is a polygenic disorder in which multiple and partially overlapping sets of susceptibility genes interact with each other and with cumulative environmental factors, predisposing individuals to the development of the illness. Genetic and epigenetic processes, involved in neuroplasticity-related biological systems, are included in the development of major depression after exposure, for example, to early life stress (see Lopizzo et al., 2015, for a review). Animal models suggest that induction of depressive behaviors disrupts neuroplasticity and neuronal adaptation, by reducing synaptic plasticity and dendritic spines, and impairing neurogenesis (see Pittenger and Duman (2008), for a review). Consistent with these neural alterations in synaptic structure and function, major depression in humans has been associated with altered brain function as assessed by event related potentials (ERPs; Bruder et al., 2009; Chen et al., 2015; Zhang et al., 2007) in cross-sectional studies. However, the interpretation of a relationship between adolescent depression and brain function later in life is

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https://doi.org/10.1016/j.biopsycho.2022.108345
Received 3 May 2021; Received in revised form 29 April 2022; Accepted 1 May 2022
Available online 5 May 2022

confounded by comorbidities such as alcohol use and smoking. In our previous study, we found that both alcohol and smoking affected EEG responses related to auditory attention (Koskinen et al. 2011).

Neurophysiological effects of depressive, as well as alcohol and other substance abuse disorders, can be non-invasively studied by using auditory ERPs, stimulus-averaged electroencephalogram (EEG) epochs. The P3 is a very extensively studied and well-known ERP component, which is elicited by targets or by unexpected deviants embedded within a train of repetitive nontarget stimuli, and have different neural organizations, cognitive functions and neuropharmacological modulations (see Soltani and Knight (2000), for a review). The reliability of P3 measures has been proven quite high, especially in the case of its amplitude measures (Cassidy et al., 2012; Cofresi et al., 2022; Walhovd & Fjell, 2002). One of the subcomponents of P3, the novelty-related P3 or P3a, is thought to be associated with involuntary attention switching to stimulus changes (see Escera et al. (2000), for a review). The brain processes that underlie novelty-related P3 generation could comprise alerting, orienting, and executive control processes triggered by an unexpected stimulus (SanMiguel et al., 2010). Novelty-related responses including P3a are thought to originate from frontal areas, where stimulus driven disruption of attention arouses activation which is related to dopaminergic processes (Polich, 2007; Polich & Criado, 2006). However, brain responses to novelty seem to also involve the hippocampus (Lisman & Grace, 2005), a structure that has repeatedly been found to be abnormal in depressive disorders (see Kempton et al., (2011), for a review; see Pittenger and Duman (2008), for a review). The target-related P3 or P3b, the other subcomponent of the P3 wave, is thought to reflect conscious stimulus evaluation, target detection, and working memory functions, and is supposed to originate from temporal-parietal activity which is related to norepinephrine processes (Polich, 2007; Polich & Criado, 2006; Polich & Herbst, 2000) and may also be influenced by anti-depressant medications (d'Ardhuy et al., 1999; Sanz et al., 2001).

Only a small number of studies have examined the novelty-related P3a in depressed patients, mainly with adults. Some previous studies of children (Lepistö et al., 2004) and adult (Kähkönen et al., 2007) patients with major depressive disorder have suggested enhanced involuntary responses to stimulus changes, including the late stage of the novelty-related P3 component (Lepistö et al., 2004), which could reflect elevated sensory sensitivity and attentional distractibility in major depression. These findings are contrasted by studies that report diminished novelty-related P3 in depressed patients (Bruder et al., 2009), which is related to depression symptoms including retardation and blunted-affect (Partiot et al., 1993) and which is aggravated particularly in recurrent major depression (Chen et al., 2015). Depression can also reduce the P3b component (Roth et al., 1986; Zhang et al., 2007). Patients experiencing a major depression with melancholic features were especially likely to have reduced P3b (Urretavizcaya et al., 2003), and P3b has also been shown to be more reduced in patients having psychotic depression (Kaustio et al., 2002) and suicidality (Hansenne et al., 1996). This reduced P3b in depressed patients seems to be at least partially state-dependent and increase or normalize following treatment like antidepressants (Gangadhar et al., 1993). Reduced P3b is also suggested to be a risk marker that predicts increase in adolescent depression (Santopetro et al., 2020).

In general, adult patients with major depressive disorder seem to suffer a wide range of cognitive deficits, including in attention and cognitive control (see Austin et al., (2001), for a review; Hammar & Årdal, 2009; Nuno et al., 2021). Most studies suggest that these deficits are state dependent, or this impairment might be long lasting despite symptom reduction and recovery (see Hammar and Årdal (2009), for a review). In contrast, other studies propose that the impaired performance of patients with remitted major depression disorder could have a trait character (Paelecke-Habermann et al., 2005). During adolescence, no evidence has so far been observed for deficits in attention (see Baune et al. (2014), for a review). However, little is known how major depressive disorder during adolescence and early adulthood affects brain function later in life.

To summarize, previous studies have provided contrasting findings regarding voluntary and involuntary attention and major depression. At the same time, differing accounts exist on the state vs. trait dependency of attention deficits in major depressive disorder. Finally, it is unclear to what degree attentional abnormalities, if any, in individuals suffering from major depressive disorder reflect comorbid conditions including substance abuse. Therefore, we studied the association of past lifetime major depressive disorder with ERP indices of attention and other interrelated cognitive functions (associated with the P3a and P3b components) using data of young adult twins who had been followed since early adolescence with respect to depressive symptoms, alcohol use and abuse, and patterns of tobacco smoking. Here, we hypothesized that even when familial factors and comorbid factors like substance use are controlled, the correlation between major depressive disorder and P3 measures remains, consistent with observations made in previous studies. Due to the variability of designs and studied populations, previous studies have demonstrated differing types of correlations between depressive disorder and various P3 measures. Here, however, we hypothesized that particularly in individuals without current depression, a history of major depressive disorder correlates positively with novelty-related distractibility (enhanced P3a to novel sounds) and negatively with indices of voluntary target detection (reduced P3b to target sounds).

2. Methods

2.1. Participants

Twin pairs were recruited from *FinnTwin16*, which is a longitudinal study of five subsequent birth cohorts of Finnish twins born in 1975–1979 (see Kaidesoja et. al, 2019, for a review). All study protocols were approved by the IRB at Indiana University and by the Ethics Committee of the Helsinki and Uusimaa metropolitan hospital district, and participants signed a written informed consent. The selection of the final sample for the ERP protocol was based on patterns of alcohol use of the participants, including 177 twin pairs from whom 150 pairs were selected for intrapair concordance or discordance for problems related to alcohol use at age 18½. For a more detailed description of the participants and the sample selection procedure, see Koskinen et al. (2011). Here, we are interested in studying these participants in order to determine the association between attentive functions, as reflected by P3, and depression.

2.2. Procedure

Participants filled out extensive health questionnaires at the ages of 16, 17, 18½, and 23–25 years, assessing drinking patterns and drinking-related problems with a 22-item Rutgers Alcohol Problem Index (RAPI) (for more detailed descriptions, see Koskinen et al. (2011)). RAPI is a self-report measure of alcohol-related problems in adolescence (White & Labouvie, 1989); with good internal consistency (Cronbach's alpha=0.92), and has become one of the most widely used assessment measures in the alcohol literature.

The ERP measures were recorded at the mean age of 25.8 years. These laboratory-studied participants were administered the Semi-Structured Assessment for Genetics of Alcoholism (SSAGA) interview during the same research day, yielding, including diagnostic content (Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised, DSM-III-R) for alcohol dependence and for depressive disorders; major depressive disorder currently and major depressive disorder lifetime (most severe). This SSAGA interview was administered by SSAGA-trained nurses and Masters of Health Science graduates. Although SSAGA is designed to provide for broad phenotyping of alcoholism, it is suitable psychiatric interview for a variety of family studies (Bucholz et al., 1994); reliability of depression has been good in both

within- and cross-center test-retest studies. Smoking was classified into 2 classes, smoking currently (at least once a week) and not smoking currently (smoking less often or not at all), from the questionnaire administered at ages 23–25 (typically within a half year before the laboratory study and the interview).

For our multilevel model, variables with nominal scaling, such as diagnosis, were centered, and alcohol variables were recoded as continuous measures, and to better meet assumptions of normality, a logarithm transformation was applied to alcohol variables. See Table 1 (Koskinen et al., 2011) for distributions of demographic characteristics, diagnosis and covariates, by zygosity. In addition, 30.3% (N = 107 individual twins) of the final sample had lifetime major depressive disorder (DSM-III-R), and 3.1% (N = 11 individual twins) had major depressive disorder (DSM-III-R) at the time of ERP data collection. Psychotropic medication use was inquired in the SSAGA interview, and 4.0% (N = 14 individual twins) of the final sample reported that they had used antidepressants during the past 30 days.

2.3. Stimuli and tasks

The ERP paradigm was adapted from Knight et al. (1984, 1989, 1996). A quasi-random sequence of 1000-Hz standard ($P = 0.68$) and 1500-Hz target pure tones ($P = 0.16$), and acoustically complex unique novel sounds ($P = 0.16$) were binaurally presented. The volume was 60 dB over the subjective hearing threshold, and inter-stimulus interval 1.2-s (NeuroStim, Neuro Scan Inc., USA). The duration of standard and target tones was 40 ms (with a 10 ms rise/fall time) and that of novel sounds 75-358 ms. Before the main experiment, there was a session including 50,1500-Hz target tones only, in which participants were instructed to press a button every time when a tone was presented. This session was conducted to control for the activity elicited by motor responses in the main experiment. The main experiment contained 600 stimuli presented in three blocks with each block including 200 stimuli. When a target was heard, participants were instructed to press a button, but not to respond to standard tones or novel sounds. The recordings took time on average 20 min including instructions.

2.4. EEG recordings and analysis

In an electrically shielded room, EEG was recorded using a 64-channel electrode cap (Virtanen, et al., 1996) with nose-reference, and 100 Hz low pass and 500 Hz sampling rate. EEG epochs were stimulus-locked and the duration was 900-ms (including 100-ms pre-stimulus baseline). Epochs were filtered off-line at 0.01–24 Hz. Eye movements (horizontal and vertical) were monitored with electro-oculogram (EOG) electrodes, which were placed below and lateral to the left eye. If an epoch contained deflections > 150 μV (at any of the EOG or EEG channels) it was rejected. Separate averaged ERPs were obtained to the 1500-Hz tones in the training session, to the 1500-Hz target tones in the oddball paradigm, to the novel sounds and to the standard tones after artifact rejections.

Difference novel-minus-standard ERPs were calculated to quantify the novelty-related P3. The target-related P3 was quantified from target-minus-training difference ERP to control for electrophysiological activity produced a motor response. Amplitude averages were calculated at the frontal (F1, Fz, F2), central (C1, Cz, CPz, C2), and parietal region (P1, Pz, P2) electrodes at the peak latency. These procedures reduced the number of statistical comparisons, as well as improved the signal/noise ratio (SNR) reducing the account of uncorrelated noise across the individual electrodes. The peak latency was determined at the electrode location where each component was expected to be maximal: The novelty-related P3 latency was determined at 200–550 ms from the most positive peak at electrode Cz, and the target-related P3 latency at 200–550 ms from the most positive peak at electrode CPz (an electrode between Cz and Pz lines). See Table 2 (Koskinen et al., 2011) for the mean latencies and amplitudes of novelty- and target-related P3s. Intraclass Correlation Coefficients (ICC) for the latencies and amplitudes of novelty- and target-related P3s in MZ and DZ twins are presented in Supplementary Table 1.

Table 1
The depression variable results of the dyadic LMEM, which best explained ERP values data according to our automatic backward-stepwise elimination procedure. The statistical significance was determined using the FDR procedure of Benjamini and Hochberg (1995).

	Novelty-related P3 amplitude	Novelty-related P3 latency	Target-related P3 amplitude	Target-related P3 latency
β	59.0 ***	138.3	110.9	-658.1 **

FDR corrected $p < 0.01$, ***FDR corrected $p < 0.001$. **Abbreviations: Parameter estimate, β.

2.5. Statistical analysis

We tested for an association of P3 variables with lifetime major depression via between-family dyadic and backward-stepwise Linear Mixed Effects Models (LMEM). The fixed-effect variables of interest included lifetime major depression diagnosis (yes/no; *"Depression"*), alcohol use / problem drinking (RAPI at the age of 18; RAPI18), *Gender*, the twin pairs' *Zygosity*, currently *Smoking* tobacco (yes/no), the twin-pairs' *Birth Order*, and the EEG *Electrode Set* (frontal, central, or parietal). To control the effects of alcohol, we used RAPI18 (RAPI at age 18 ½), because this sample was initially selected according to intra-pair RAPI scores. In addition, RAPI predicts alcohol use disorder diagnosis over a 7-year follow-up (Dick et al., 2011). The factor Electrode Set was not considered in the ERP latency models, because the peak latency for each component was determined at a single electrode site for each component. The correlation within pairs was controlled for by treating twin pair (i.e., the family number) as a random variable. The optimal number of terms in the LMEMs was determined using a backward stepwise procedure, which started from a full model that included all possible main effects and interactions, and which eliminated variables from the LMEM in a stepwise fashion for finding the model that best explained the data. The LMEM analyses were conducted using R, by using the functions "lmer" (lme4 module), "step" (lmerTest module), "anova" (lmerTest module), and "summary" (Bates and Mächler, 2009; Bates et al., 2015). To control for the multiple comparisons problem, all p-values were corrected for the false discovery rate (FDR) by using the method of Benjamini and Hochberg (1995), as implemented in the p. adjust-function of R. Since some participants (3.1%) in the sample had major depressive disorder at the time of ERP recordings, we calculated the same LMEM analyses also without these participants, to see the possible effects of the current depression. Finally, for the visualization of the main ERP result only, we selected two subsets of subjects that represented the two extremes of lifetime major depression symptoms (Fig. 2). Note that the displayed average ERP time courses show subaverages of actual data. Unlike predicted values from the model (such as, e.g., "estimated marginal means"), this data display does not control for familial factors and other covariates like substance use variables. Therefore, subaverages are shown here to visualize the results of our statistical analysis, which would have been obscured in a larger sample due to the effects of aforementioned nuisance effects.

3. Results

The main results from the LMEM analyses are presented in Table 1 and Fig. 1. P3a amplitude was significantly increased and P3b latency decreased, in individuals with a past lifetime major depression, when the fixed effects of alcohol problem drinking, tobacco smoking, gender, birth order, and zygosity, and the random effect of twin pair membership, were controlled. These main results remained when we did the same LMEM analyses without the small number of participants (N = 11)

Table 2
The results of the dyadic LMEM, which best explained the Novelty-related P3 amplitude and latency data according to our automatic backward-stepwise elimination procedure. The statistical significance was determined using the FDR procedure of Benjamini and Hochberg (1995).

LMEM predictor term	*SS*	*MS*	*Df*		*F*	*β*	*p*	
For amplitude								
Depression	534.4	534.4	1	879	24.6	59.0	< 0.0001	***
RAPI18	189.9	189.9	1	873	8.7	0.8	0.0046	**
Smoking	654.5	654.5	1	882	30.1	-4.8	< 0.0001	***
For latency								
Depression	127.7	127.7	1	882	0.2	138.3	0.7094	
RAPI18	330.6	330.6	1	878	0.5	23.9	0.6643	
Smoking	2376.6	2376.6	1	881	3.6	-12.4	0.1118	

*FDR corrected $p < 0.05$, **FDR corrected $p < 0.01$, ***FDR corrected $p < 0.001$. **Abbreviations**: Sums of Squares, SS; Mean Squares, MS; Degrees of freedom, Df; Parameter estimate, β.

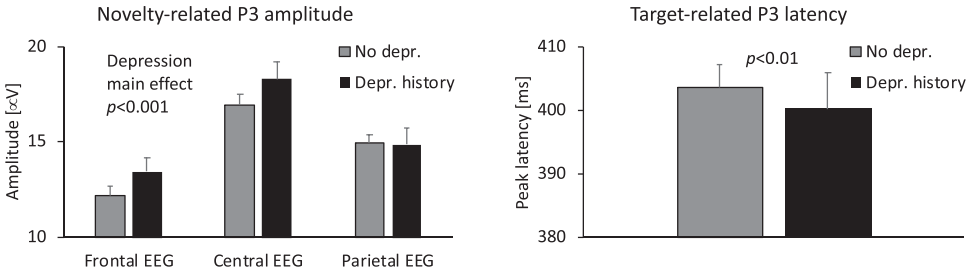

Fig. 1. EEG results. (**Left**) Group averages and standard errors of the mean (SEM) of Novelty-related P3 amplitude in the three EEG electrode set locations. The data show the enhancement of Novelty-related P3 in individuals with a history of depression diagnosis. (**Right**) Group averages of Target-related P3 latencies. The data show the acceleration of Target-related P3 processing in individuals with a history of depression diagnosis. The statistical significance was determined using the FDR procedure of Benjamini and Hochberg (1995).

with major depressive disorder at the time of the ERP recordings.

3.1. Novelty-related P3 amplitude and lifetime major depression

Table 2 shows the LMEM main effects relevant to our *a priori* hypotheses, which best explained the Novelty-related P3 amplitude, as determined based on our Automatic Backward Stepwise procedure. This best-fitting LMEM revealed that Novelty-related P3 amplitude, a neuronal measure of involuntary shifting of auditory attention, was modulated by a history of major depression diagnosis (main effect of Depression, FDR corrected $p < 0.001$; see Table 2). According to the corresponding LMEM treatment contrast, the slope of this effect was positive ($\beta = 59$□0), which supports the interpretation that the amplitude of Novelty-related P3 is increased in individuals with a history of major depression diagnosis. The group averages of the P3 measures are shown in Fig. 1 (left panel). For details, see Supplementary Table 2, where all main effects and interactions of this best fitting LMEM are presented. A representative example of ERP responses in a subgroup of participants that reflect two extremes of lifetime major depression symptoms are shown in Fig. 2. In t-tests for these subgroup values, amplitudes differed statistically ($p < 0.05$), but latencies did not ($p = 0.50$).

3.2. Novelty-related P3 latency and lifetime major depression

Table 2 also shows the LMEM main effects designed to test our *a priori* hypotheses, which best explained the Novelty-related P3 latency data, as determined based on our automatic backward elimination

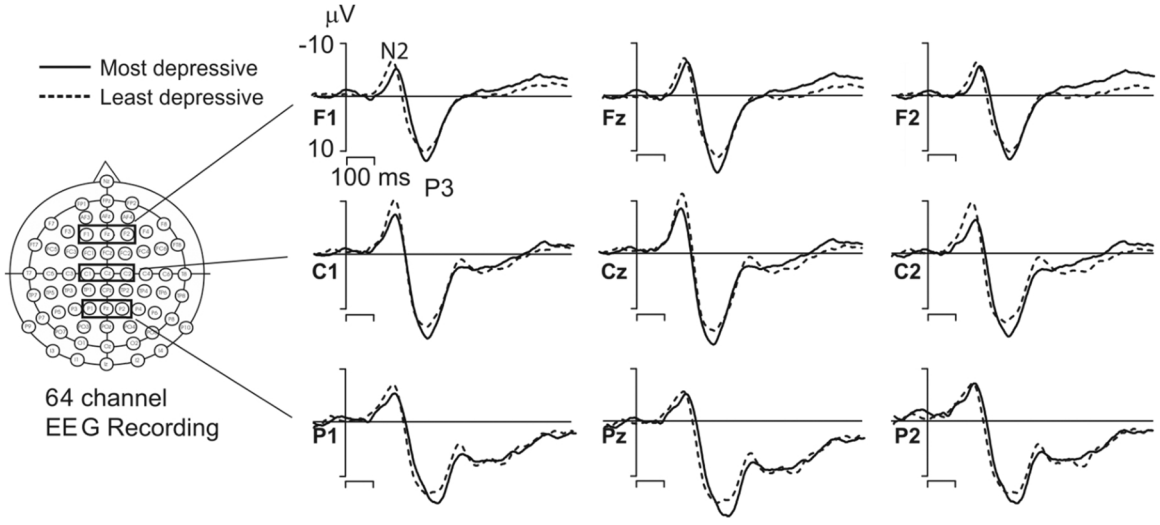

Fig. 2. Grand-average event-related potential (ERP) difference waves (novel minus standard) in "Most depressive" and "Least depressive" twins, indicating an increase of P3 amplitude for the novel sounds associated with lifetime major depression. "Most depressive" twins ($N = 9$) are those who have had all 9 depression symptoms and "Least depressive" twins ($N = 9$) are randomly selected from those who have had no symptoms. These subgroups are drawn from the total ERP twin sample.

procedure. This LMEM demonstrated no statistically significant P3 latency effects of Depression. However, the Novelty-related P3 latency was significantly modulated by some interactions; the significant interactions suggested by the LMEM are presented in Supplementary Table 3.

Target-related P3 Amplitude and Lifetime Major Depression.

Table 3 shows the *a priori* most relevant main effects of the output of the LMEM, which had the optimal level of complexity for explaining the Target-related P3 amplitude. This LMEM showed no significant effects of Depression on Target-related P3 amplitude. However, the optimal LMEM showed other significant interactions and one significant main effect (presented in Supplementary Table 4).

3.3. Target-related P3 latency and lifetime major depression

The *a priori* most relevant main effects of the best-fitting LMEM, which optimally explained the Target-related P3 latency data is shown also in Table 3**.** According to this LMEM, the Target-related P3 latency is significantly modulated by a history of major depression diagnosis (FDR corrected $p < 0.01$). The slope of this effect was negative ($\beta = -658$□1), which supports the interpretation that the latency of Target-related P3 is decreased in individuals with a major depression diagnosis, consistent with the group average data in Fig. 1 (right panel). In addition, the optimally-fitting LMEM of Target-related P3 latency suggested many significant interactions and some other significant main effects presented in Supplementary Table 5.

3.4. Behavioral task performance

In the main experiment, the average reaction time to targets was 457 ms (SD = 80 ms) and the proportion of correct responses was 95.6% (SD = 6.1%). We compared average reaction times to targets between those who had a history of major depression diagnosis (470 ms) and those who had not (451 ms) with a t-test, finding no statistically significant differences. We also compared the average hit rates between those with major depression diagnosis (94.8%) and those without it (96.1%), finding no significant differences either.

4. Discussion

We studied the novel and target elicited P3 components associated with MDD experienced earlier in life in a population-based twin sample of young adults. The longitudinal health information available of these twins enabled us to attempt to control for genetic and common environmental factors, and the comorbidity issues such as alcohol abuse and tobacco smoking. The results show that past lifetime MDD is associated with enhancement of novelty-related P3 component and acceleration of target-related P3 component in early adulthood. Previous studies suggest that enhanced novelty-related P3 amplitude, in particular, reflects hyperactivity of involuntary auditory attention that leads to elevated distractibility (see Escera et al., 2000), whereas decreased latency of target-related P3 is a widely accepted measure of the sensitivity of voluntary auditory attention, amongst a collection of other functions proposed to be associated with this component. The present findings could thus reflect MDD related alterations in brain mechanisms that control orienting of attention to auditory stimulus changes (see Escera et al., 2000, for a review).

Our ERP results are consistent with earlier reports of enhanced novelty-related P3 in children with MDD (Lepistö et al., 2004), as well as with studies showing enhanced responses to task-irrelevant stimulus changes in adults suffering from MDD (Kähkönen et al., 2007). Enhanced novelty-related P3 amplitudes similar to the present observations have also been reported in depressive patients that are anxious-agitated-impulsive (Pierson et al., 1996). At the same time, a previous study also found reduced latency of the target-related P3 in individuals with a history of MDD (Bange and Bathien, 1998). However, our results differ from a few previous findings in MDD P3a studies that reported amplitude reductions (for reviews, see Bruder et al., 2012 and Justo-Guillen et al., 2019). One of the major reasons for these differing results could be that instead of the effects of currently ongoing depression, our sample focused primarily on young adults who had depression earlier in their lives. It is also worth noting that our study includes a larger population-based sample than most of the previous ERP studies, which makes it possible to control for the effects of co-morbid conditions and genetics, especially since our sample consists of twins, which is exceptional. The present findings, which suggest elevated sensitivity of attentional orienting to stimulus changes in individuals with a history of MDD, are also broadly consistent with evidence that adolescents with MDD show abnormal fMRI activations in frontocingulate regions (Colich et al., 2017), which regulate involuntary attention shifting (Crottaz-Herbette and Menon, 2006). Further studies are needed to elucidate the underlying neurobiological mechanisms. One possibility could be disrupted maturation of long-range axonal connections in frontolimbic regions critical for the control of attention, which has been reported to follow from depression experienced early in life (Ellis et al., 2017).

We used a twin data set which provides broad and longitudinal information regarding the variables of interest. Our earlier study that used this same twin sample showed decreased novelty-related P3 amplitude associated with, and perhaps caused by, adolescent alcohol abuse (Koskinen et al., 2011). It is, however, worth noting that based on our previous analysis of the same participant sample, the effect of alcohol use on novelty-related P3 should be opposite to the MDD-related effects observed here. The same is true for the latency of target-related P3 activity, which is typically delayed after long-term alcohol use (Carlson et al., 2002; Hada, Porjesz et al., 2000; see Porjesz and Begleiter, 1997, for a review). It is therefore unlikely that biases caused by past alcohol use, which were controlled in our dyadic linear mixed model, explains the present P3 results related to MDD history.

The present analyses also controlled for the effect of tobacco smoking, which was shown to be correlated negatively with P3 amplitude in our earlier study (Koskinen et al., 2011) and which has a strong association with depression (see Chaiton et al., 2009, for a review; see

Table 3
The results of the best-fitting LMEM of Target-related P3 amplitude and latency. The statistical significance was determined using the FDR procedure of Benjamini and Hochberg (1995).

LMEM predictor term	*SS*	*MS*	*Df*		*F*	*β*	*p*	
For amplitude								
Depression	101.4	101.4	1	577	3.1	110.9	0.1034	
RAPI18	26.9	26.9	1	636	0.8	11.3	0.3676	
Smoking	134.6	134.6	1	620	4.1	0.3	0.0793	
For latency								
Depression	21,742.4	21,742.4	1	620	9.9	-658.1	0.0051	**
RAPI18	15,179.7	15,179.7	1	608	6.9	-69.1	0.0141	*
Smoking	7308.2	7308.2	1	625	3.3	56.5	0.0766	

*FDR corrected $p < 0.05$, **FDR corrected $p < 0.01$, *** FDR corrected $p < 0.001$. **Abbreviations**: Sums of Squares, SS; Mean Squares, MS; Degrees of freedom, Df; Parameter estimate, β.

Mathew et al., 2017, for a review). In previous studies, tobacco smoking has been shown to correlate with diminished P3 amplitudes (Guney et al., 2009; Domino, 2003). P3 associations with smoking were detectable in the present sample as well, especially with novelty-related P3 amplitude, but the inclusion of the tobacco variable to the statistical model did not diminish the association between an MDD history and P3 variables.

4.1. Potential limitations

More than half of young adults suffering from depressive disorders have co-morbid conditions, such as substance abuse (Aalto-Setälä et al., 2001), which have detrimental effects on brain development (see Crews et al., 2007, for a review). For example, a potential limitation of the present study was that the sample was initially selected according to alcohol drinking-related problems. The potential limitations associated with comorbid alcohol use, as well as tobacco smoking, are discussed above. Furthermore, 3.1% (N = 11 individual twins) in our sample had major depressive disorder at the time of ERP recordings, but we wanted to keep them in the analysis to avoid tight exclusion criteria which can reduce the generalizability of the results. However, it should be noted that we did the same analyses without this small number of participants with current depression, and the main results remained the same. Some twins, that is, 4.0% (14 individuals; only three individuals with a depression diagnosis at the time of ERP recordings) of the final sample, reported that they had used antidepressants during the past 30 days. However, we decided to include these individuals in the analysis, to avoid excessively restrictive exclusion criteria. Notably, according our control analysis, our results remained the same when these three subjects were excluded from the analysis. Another modulating factor that is important to consider when studying depression and brain functions is the participants' gender. In our sample, depression history was emphasized somewhat more in females (38%) than in males (21%). The effect of gender was significant in many of our P3 analyses, but its inclusion to the linear mixed model did not change the main result. Finally, we attempted to control genetic influences with co-twin control comparisons. However, it should be noted that the sample of monozygotic pairs discordant (N = 10, and concordant pairs N = 28) for depression history constrained the statistical power of these comparisons. However, here, the main goal to use twin population was to control for the effects of familial factors in the data analysis, instead of investigating how genetic factors influence depression.

5. Conclusions

Enhanced novelty-related P3 amplitude and decreased target-related P3 peak latency were associated with past lifetime MDD in young adults. These results suggest that major depression experienced before young adulthood may lead to enhanced attentional sensitivity and distractibility in adulthood.

Acknowledgments

This work was supported by the National Institute on Alcohol Abuse and Alcoholism [grant numbers R37AA012502, R01AA08315]; the Academy of Finland [Center of Excellence in Complex Disease Genetics, and grant numbers 1211486, 118555, 100499]; Finnish Cultural Foundation; and NIDCD [grant numbers R01DC016765, R01DC016915, R01DC017991]. We thank Pasi Piiparinen for help with data acquisition.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopsycho.2022.108345.

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