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Article

Differences in Children and Adolescents with Depression before and after a Remediation Program: An Event Related Potentials Study

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Abstract: Depression is diagnosed when a specific set of symptoms appear over a defined period with a certain intensity. According to the DSM-5, Major Depressive Disorder (MDD) is diagnosed when five or more symptoms are present over a two-week period. Depression, a debilitating mental health disorder affecting millions worldwide, poses a complex challenge for researchers and clinicians. In children and adolescents, depression can result in negative outcomes such as substance abuse, academic problems, risky sexual behavior, physical health issues, impaired social relationships, and a thirty-fold increased risk of suicide. This paper presents the findings of a study that evaluated the effectiveness of Cognitive Behavioral Therapy (CBT) alone and CBT combined with selective serotonin reuptake inhibitors (SSRIs) in a remediation program. The study included 16 children and adolescents with depression (8 males and 8 females) and 16 typically developing peers (8 males and 8 females) aged 9 to 15 years ($M = 11.94$, $SD = 2.02$). Baseline evaluations using Event-Related Potentials (ERPs), the Children Depression Inventory (CDI), and reaction time tests showed that participants with depression had cognitive deficits in attention and memory, indicated by longer P300 latencies. After undergoing remediation with either CBT alone or CBT combined with medication, the children and adolescents with depression exhibited lower CDI scores and shorter P300 latencies and reaction times compared to before remediation and relative to the control group.

Keywords: children and adolescent depression; cognitive behavioral therapy; event related potentials; remediation depression; P300 latency

1. Introduction

Major Depressive Disorder (MDD) is one of the most prevalent mental disorders among children and adolescents. The 3-month rates of prevalence for children and adolescents aged 9-16 are 2.2% overall, 2.8% for males, and 1.6% for females. By the age of 16, the cumulative prevalence rate is expected to reach 9.5% in the overall population, 11.7% in females, and 7.3% in males [1]. A meta-analysis estimated the prevalence of depression among young children (under 13) is 2.8%. Furthermore, 5.6% of all adolescents (aged 13 to 18) suffer from depression, including more female patients (5.9%) than male patients (4.6%) [2]. Another study found that the onset of mental health disorders (such as depression) peaks about 14 years of age [3]. According to the World Health Organization, depression and anxiety disorders are among the top five causes of psychopathologies in European children and adolescents [4].

According to the DSM-5, cognitive impairments are one of the primary symptoms of depression. It is defined as a reduction in the ability to think, focus, or make judgments. The cognitive level of performance in patients with major depressive disorder (MDD) is extremely important because cognitive impairments correlate with impaired ability to function in daily life [5]. Previous study has found executive function, memory, psychomotor speed, and attention problems in MDD patients

compared to healthy controls [6]. Such deficits range from mild to severe and may persist even after depression has been treated [7]. These studies also describe impairments in attention, executive function, and memory after remission. They note that reducing depression symptoms does not necessarily result in cognitive enhancement. This could be because cognitive impairments are trait markers, not condition signals, for depression [8]. So far, research on the association between symptom severity and cognitive impairment has yielded ambiguous results, while a positive correlation is suggested [9].

Neural and psychological assessments can provide relatively objective measures of emotional processing, offer insight into the brain circuitry underpinning susceptibility, and contribute to levels of analysis of elements of the study domain criterion [10]. The application of neuroimaging techniques has significantly advanced our understanding of the neural underpinnings of depression. According to Mclean's description [11], the brain is divided into three parts: the prefrontal neocortex (involved in higher cognitive processes as well as emotion regulation via connections to the limbic region), the limbic brain (involved in emotions that guide self-preservation and species procreation), and the reptilian complex, which includes the basal ganglia and brain stem structures and is involved in routine motor function and reflexes, as well as social communication achievement.

In vivo neuroimaging studies have revealed depression-related correlations in brain structure and function. Discoveries connecting amygdala-medial prefrontal cortex circuitry to emotional [12] and social processing [13] led to the concept that dysfunctional interactions of cortical and subcortical systems cause depression [14]. Disrupted metabolism and changed gray matter volume in patients' prefrontal cortex are other important features of depression which may track illness duration [15]. Furthermore, neuroimaging studies have revealed minor patterns of cortical thinning in the medial prefrontal cortex, subgenual anterior cingulate cortex, and ventral temporal lobes that correlate with illness severity [16]. Depression is related with reductions in global brain connectivity in medial prefrontal cortex and subgenual anterior cingulate cortex, which extend to dispersed portions of the multimodal association cortex [17]. Additionally, in people with depression, the salience network (cortical and limbic brain areas, such as the amygdala-hippocampal complex), which is activated by emotional salient stimuli, tends to perpetuate negative affect, and the amygdala is hyperactive during negative stimuli but hypoactive during positive ones. Adolescents with severe depressive disorders showed reduced activity in the amygdala-hippocampal complex during positive self-processing compared to neutral processing tasks. [18]. The biological causes of these changes are unclear, but they may be related to GABAergic changes [19] or decreased size and density of neurons and glia, particularly astrocytes [20].

Event-related potentials (ERPs) are a non-invasive electrophysiological technique that can lead to the acquisition of information about brain activity associated with cognitive information processing. ERPs have been proposed as the most investigated tool for determining correlations between brain electrical activity and the dynamic processes of cognitive stimuli [21]. The P300 is a well-studied ERP component that has been proposed to represent higher-order cognitive information processing and attentional tasks linked with contextual evaluation when attending to a given stimuli [22]. P300 latency of ERPs is proposed to reflect higher-order cognitive processes such as classification and stimulus appraisal. As a result, it has been claimed that P300 latency may serve as a temporal signal of brain activity, supporting the speed of attention allocation and memory processes [23].

There have been studies that have used ERPs as a method of assessing depression suggesting inconsistent results. More specifically, a previous study found no significant difference in the latency of the P300 waveform [24]. These findings have been attributed to the wide variety of methodological interventions and the utilization of varied research groups that included both patients receiving pharmacological and psychotherapy interventions as well as patients receiving neither. Nevertheless, the P300 component has garnered particular interest in the study of depression.

Numerous studies have reported alterations in P300 amplitude and latency in individuals with depression, suggesting disruptions in cognitive processing and attentional mechanisms [25]. It is now understood that patients suffering from depressive disorder have a significant difference in latency of P300 waveform. In various cross-sectional studies, P300 in individuals with depression presents

lower amplitudes and prolonged latencies compared to healthy controls [26–32]. This result is proposed to be indicative of the severity and pathogenesis of depression combined with cognitive deficits that face participants with depression [33]. In general, electrophysiological studies provide knowledge on the neural mechanisms following depression, revealing abnormalities in brain activity that contribute to the disorder's cognitive, affective, and behavioral indicators.

Leveraging neuroscience to explore cognition, behavior, and the impact of the environment greatly contributes to developing and accessing personalized treatments and clinical methodologies [34]. Brain plasticity, characterized by rapid and reversible alterations in brain function and structure, manifests in learning, memory, and perception. Changes in synaptic plasticity signify learning and memory on a cellular level, indicating that neurons have the ability to adjust the strength and arrangement of their synapses based on experience [35].

Cognitive behavioral therapy (CBT) is one of the empirically supported psychological methods for the treatment of a variety of psychological disorders, including depression [36,37]. CBT is a group of methods that includes cognitive reconstruction, behavioral change, and social support, with the goal of assisting individuals in identifying stress levels and modifying negative cognitive beliefs and behaviors, reducing or eliminating symptoms of psychological distress, and resuming normal psychological and social functions [38]. Group CBT and individual CBT treatment options have the same content. Group CBT uses the group format to encourage peer modelling, practice interpersonal and communication skills, provide feedback, use positive reinforcement, and examine social comparisons [39]. Numerous studies have been conducted suggesting the efficacy of CBT in depressive disorders. A review and meta-analysis of studies [40] found that CBT is an effective treatment strategy for depression, and that combining it with medication is much more beneficial than pharmacotherapy on its own. Evidence also suggests that patients treated with CBT had a reduced relapse rate than those treated with medication alone [41–43].

The main aim of this research was to contrast the electrophysiological brain responses of children and adolescents diagnosed with depression for the first time, at a state child and adolescent psychiatric hospital, with those of their typical peers using Event-Related Potentials (ERPs). Specifically, the ERP component investigated was the P300 latency. Subsequently, the group of depressed children and adolescents engaged in a remedial program based on Cognitive Behavioral Therapy (CBT) intervention or a combination of CBT and psychopharmacological support, as recommended by their children and adolescent psychiatrist. Their brain activity was recorded upon completion of the program. Additionally, both the depressed group and the control group underwent two behavioral assessments. The first assessment involved all participants completing the Greek version of the Children Depression Inventory (CDI) [44], while reaction times were measured by instructing all participants to press a button on a joystick when the oddball stimuli presented.

Along the lines of previous studies, the first hypothesis of the current study was that children and adolescents with depression would have higher P300 latency, reaction times, and CDI scores than the control group. The second hypothesis of the current study was that after conducting the remediation program, individuals with depression would have decreased P300 latency, response time, and CDI scores than before remediation [45,46]. The current study's third hypothesis was that following administration, participants with depression would have differential P300 latency and reaction time according to the remediation program used.

2. Materials and Methods

2.1. Participants

Sixteen right-handed children and adolescents (8 males and 8 females) aged 9 to 15 years old ($M = 11.94$ $SD = 2.02$) who had been diagnosed with depression by the Athens Children and Adolescent Psychiatric Hospital participated in this study. It is important to note that none of the participating in the depression group had previously completed any therapeutic program as they received assessment and diagnosis for the first time. The control group consisted of sixteen right-handed children and adolescents of the same age ($mean = 11.74$, $SD = 3.10$) and gender (8 males and 8 females) as the depression participants. No one in the control group had any psychopathological difficulties.

According to school medical records, no one of the control or depressed children and adolescents' group had learning difficulties, developmental disorders, or significant visual or hearing impairments. All volunteers were recruited after reading informative newspaper articles, receiving study notifications from the hospital, and attending informative school sessions. Participants with depression were diagnosed using standard and typical assessment protocols, such as a clinical interview using the Greek version of K-SADS-PL DSM-5 [47] administered by a child and adolescent psychiatrist in accordance with DSM-5, as well as their responses to the Greek version of Children Depression Inventory (CDI) [44] a widely used and well-studied scale for depressive symptoms in children [48,49]. It is worth noting that all participants' parents/guardians were required to sign the consent form allowing their child to participate in the research. Finally, all human data included in this manuscript were obtained in compliance with the Helsinki Declaration and the guidelines of the Ethics and Deontology Committee of the University of Thessaly.

2.2. Electrophysiological Assessment

A paradigm involving auditory oddballs was employed in the study. Participants received 200 auditory stimuli through headphones while seated comfortably in a reclining armchair with their eyes closed. These stimuli consisted of tones at 85 dB intensity and 40 milliseconds duration (with 10 milliseconds rise and fall times), separated by an interstimulus interval (ISI) of 1500 milliseconds. The non-target stimuli had a frequency of 1000 Hz, whereas the target stimuli had a frequency of 2000 Hz. Participants were instructed to press a button quickly and accurately upon detecting the oddball (target) stimulus using their right hand, with their reaction time being recorded [50].

Event-related potentials were recorded using a Medtronic device. The P300 latency was measured from 15 electrode sites based on the 10–20 International System [51] using Ag-AgCl electrodes (FP1, FPz, FP2, F3, Fz, F4, F7, F8, C3, Cz, C4, P3, Pz, P4, Oz). All channels were referenced to linked mastoids, and the ground electrode was positioned at the nasion. Electrode impedance was maintained below 10 k Ω . Recordings were sampled at 256 Hz with bandpass filters ranging from 0.16 to 70 Hz. EEG data were segmented into epochs spanning from 200 milliseconds pre-stimulus to 800 milliseconds post-stimulus. P300 latency was assessed across all derivations for both standard and target stimuli. The P300 component, identified as the longest positive peak following the N200 waveform with a delay of 250–450 milliseconds, was analyzed. Trials were excluded if voltage exceeded 70 μ V in any of the 15 channels (excluding EOG) or if incorrect responses were given. Separate period averaging was conducted for target and non-target stimuli, with baseline correction applied to the 200 milliseconds pre-stimulus period. Only children with a minimum of 30 artifact-free sessions for both non-target and target stimuli were included in the analysis, ensuring consistency across participants in the post-remediation program. Recordings were conducted in a distraction-free, soundproof room [52–54].

2.3. Remediation Program

All sixteen children diagnosed with depression participated in the four-month remediation program (16 sessions), which included two additional sessions held one and three months later. Children's sessions were held once a week for 45 minutes to an hour. The general terms of the CBT program include activities in order to inform the child/adolescent about depression, according to their cognitive and emotional development, and establish a good therapeutic association. Also, activities were included in order to establish the structure and content for the remediation, set an agenda and agree upon the goals of the CBT intervention. Additionally, CBT included: (a) Exposure techniques and guided discovery; (b) Cognitive restructuring techniques and behavioral experiments; (c) Self-talk and a combination of thought interruption and positive imagery; (d) Communication skills and scheduling interesting and pleasant events with peers in order to build friendship relations; (e) Strengthening problem solving abilities and relaxing techniques. Furthermore: Self-help sessions in order to recognize and dealing appropriately with their depression symptoms, and also training in reinforcement strategies, including logical rewards for gradually facing depressive situations.

The CBT program also encompasses family interventions. All parents of depressive children formed a group and attended 10 sessions, one day each week, isolated from their children and lasting 45 minutes to an hour. The parent sessions aimed at dealing appropriately with their own anxiety and/or depression, and also included: (a) Strengthening family communication in order to solve possible tensions in an intelligible approach; (b) Informative sessions about depression and expectations; (c) Role play strategies with examples of their child’s fearful behaviors, including cognitive techniques and problem-solving skills. Lastly, parents were instructed in order to form a support group.

It should be noted that 8 children (4 males and 4 females) were only engaged in the CBT program, whereas another 8 children (4 male and 4 female) participated in both the CBT program and psycho-pharmacological support. The child and adolescent psychiatrist who diagnosed them suggested SSRIs.

3. Statistical Analysis

The following statistical tests were performed: series of one-way ANOVAs comparing pre-remediation P300 latency in children and adolescents with depression against control group, post-remediation P300 latency results in children and adolescents with depression against their average peers. Furthermore, non-parametric statistical analysis was used to compare children and adolescent P300 latency who participated in the CBT program against those who used CBT in conjunction with medication. In addition, effect sizes using Cohen’s d were calculated and reported alongside the ANOVA findings. Cohen categorizes effect sizes as small (less than 0.20), medium (0.20–0.50), and big (more than 0.50) [55]. Moreover, series of one-way ANOVAs was used to compare the differences in reaction time before and after remediation against the control group. Lastly, descriptive statistics were conducted to present the results in CDI test in children and adolescents with depression before and after remediation in comparison to control group.

4. Results

Prior to commencing the remediation program, we performed a series of one-way analyses of variance (ANOVAs) to compare the results of children with depression against their typically achieving peers. Descriptive statistics have been utilized to analyze mean scores and standard deviations of P300 latency (in milliseconds) measured at 15 scalp sites. The same procedure was followed for the reaction time measurement. Additionally, Cohen’s d effect sizes were calculated. Table 1 presents the mean scores, standard deviations, statistical significance and effect size of P300 latency from all recorded brain areas.

Table 1. Mean scores, standard deviations, significance and effect size of P300 latency for children and adolescents that participated in the control group and children and adolescents with depression pre-remediation.

Electro/ encephalographic sites	Control group		Depression pre- remediation		F	Cohen’s d
	M	SD	M	SD		
FP ₁	304.28	13.74	377.11	13.64	64.247**	5.32
FP _z	306.67	13.72	381.20	16.57	58.237**	4.89
FP ₂	313.02	8.22	373.95	10.66	58.936**	6.40
F ₃	310.41	10.64	365.28	9.98	75.102**	5.32
F _z	316.24	11.12	372.01	19.41	99.454**	3.55
F ₄	320.20	10.31	363.96	14.10	100.391**	3.54
F ₇	311.97	10.47	375.57	15.31	86.294**	4.85

F ₈	318.99	9.03	364.65	14.71	48.201**	3.74
C ₃	319.50	12.28	351.15	15.23	41.882**	2.29
C _Z	325.58	7.38	346.56	16.01	22.684**	1.68
C ₄	328.36	14.25	347.65	17.99	11.316*	1.19
P ₃	314.30	15.34	352.15	18.68	21.659**	2.21
P _Z	321.88	12.87	349.90	11.36	20.211**	2.31
P ₄	326.06	8.72	346.48	17.67	17.283**	1.46
O _Z	321.36	9.05	336.56	14.44	5.436*	1.26

Note: * p<0.05 ** p<0.01.

As shown in Table 1, all children and adolescents diagnosed with depression, presented longer latencies in P300 waveform in all topographic brain in comparison to the control group (p<0.05). The effect-sizes calculated in the fifteen brain areas were all large ranging from 1.19 to 6.40.

The reaction time was recorded as the participants with depression and their average peers had to push a button in joystick when the oddball stimuli was presented. The reaction time of children with depression was at 429.75 ms (SD 43.06 ms) and their average peers presented at 334.54ms (SD 23.55 ms). The ANOVA revealed that children with depression presented larger latencies in reaction time in comparison to children that participated in the control group (p<0.01). In CDI test all children and adolescents with depression recorded scores ≥ 22 in comparison to their typical achieving peers that scored ≤ 13.

Next, the analysis focused on children with depression post-remediation and children and adolescents that participated in the control group. It is worth to mention that for both groups electroencephalographic activity was reassessed following the same ERPs protocol. Table 2 presents mean scores and standard deviations of P300 latency (in milliseconds), one-way ANOVA results that was performed to compute the statistical significance and effect size.

Table 2. Mean scores, standard deviations, significance and effect size of children and adolescents that participated in the control group, and children and adolescents with depression post-remediation.

Electro/ encephalographic sites	Control group		Depression post- remediation		F	Cohen's d
	<u>M</u>	<u>SD</u>	<u>M</u>	<u>SD</u>		
F _{P1}	297.47	9.83	295.90	5.38	1.523	0.20
F _{PZ}	303.14	8.95	300.43	6.62	1.113	0.34
F _{P2}	307.21	8.22	303.26	6.33	1.417	0.54
F ₃	304.21	9.99	308.12	9.51	0.538	0.40
F _Z	307.77	9.66	311.26	7.94	0.424	0.39
F ₄	312.76	9.24	313.64	9.12	0.044	0.09
F ₇	306.72	11.47	303.80	8.09	1.029	0.29
F ₈	314.71	11.65	309.78	8.63	1.942	0.48
C ₃	319.41	6.50	317.02	7.31	0.654	0.34
C _Z	322.58	5.93	324.21	6.82	0.262	0.25
C ₄	326.28	6.58	326.11	7.53	0.014	0.02
P ₃	324.47	6.38	321.61	7.79	2.202	0.40
P _Z	323.18	7.08	323.46	6.17	1.303	0.04
P ₄	329.86	7.02	326.28	8.47	1.161	0.46
O _Z	323.48	6.19	325.94	12.82	0.584	0.24

Following the application of the remediation program, the same comparisons were performed between the two groups. As Table 2 indicates no statistically significant differences were detected in the P300 latency in these post remediation comparisons. The evidence suggests that the remediation program (CBT and combination of CBT with SSRIs) proved successful in improving the cognitive profile of children and adolescents with depression. A careful study of the calculated effect sizes reveals that in 12 out of 15 P300 waveforms, the differences between the two groups were small to medium, ranging from 0.02 to 0.40. It must be mentioned that only in Fp2, F8 and P4 brain regions the effect size was large ranging from 0.48 to 0.54.

The reaction time of children with depression was recorded at 325.09ms (SD 35.78 ms), and children that formed the control group pushed the bottom at the joystick when oddball stimuli was presented at 322.01ms (SD 28.22 ms). The ANOVA revealed no statistical difference ($p>0.05$) of the reaction time of both children with depression and the control group. In CDI test all children and adolescents with depression had a mean score of ≤ 15 , in comparison to their typical achieving peers that scored ≤ 13 .

Then the analysis concentrated exclusively on assessing any differentiations of the P300 latencies of children and adolescents with depression based on their participation in the remediation program, which consisted of either only CBT or both CBT and SSRIs. It should be noted that a Mann-Whitney non-parametric statistical analysis was performed, since 8 children and adolescents with depression participated in CBT, and 8 children and adolescents received both CBT and SSRIs medicine. The results are displayed in Table 3. Table 3 presents the mean scores, standard deviations, and statistical significance of the P300 latency of participants with depression based on the Remediation program they followed. It should be noted that because a non-parametric method of statistical analysis was implemented, the effect size was not computed.

Table 3. Mean scores, standard deviations and significance between children and adolescents with depression that followed CBT and SSRIs and children and adolescents that followed only CBT remediation program.

Electro/ encephalographic sites	Children and adolescents that followed CBT and medication		Children and adolescents that followed only CBT program		U
	<u>M</u>	<u>SD</u>	<u>M</u>	<u>SD</u>	
Fp1	291.36	3.07	295.90	5.37	0.071
FpZ	297.95	6.62	300.43	6.62	0.758
Fp2	301.65	7.55	303.25	6.33	1.000
F3	308.12	9.51	308.26	14.01	1.000
Fz	310.40	11.85	311.26	7.94	1.000
F4	313.64	9.12	314.04	11.05	1.000
F7	300.10	9.86	303.81	8.09	0.351
F8	305.69	9.63	309.78	8.63	0.351
C3	317.02	4.31	318.13	4.83	0.299
Cz	322.28	4.95	324.21	4.42	0.408
C4	326.09	4.09	326.11	4.72	1.000
P3	319.55	4.79	321.61	3.67	0.470
Pz	320.52	4.17	323.46	3.81	0.114

P ₄	325.64	7.07	326.28	7.44	1.000
O _z	321.29	5.19	323.50	4.34	0.299

As shown in Table 3, all children and adolescents with depression that followed CBT remediation program presented larger latencies of P300 waveform in comparison to participants that followed CBT and medication combined program. However, the analysis found no significant difference ($p>0.05$). Lastly, one-way ANOVA was implemented to measure the reaction time between the two groups. Children and adolescents with depression that followed a combined program using CBT and medication had a reaction time at 330.72 ms (SD 20.48ms) and children and adolescents that underwent only the CBT program reacted at the oddball stimulus at 338.84 ms (SD 22.81ms). These results were not statistically significant ($p>0.05$).

In summary, the results of the study, taken collectively, suggest positive outcomes for both the remediation programs. The implications of this study are discussed in the next section.

5. Discussion

The present study was designed in order to evaluate the electrophysiological brain activity of children and adolescents with depression utilizing the latency of P300 waveform of ERPs, against those of typically developing counterparts. The first hypothesis, which was based on earlier studies [eg. 31] compared the P300 latencies and reaction times of children and adolescents with depression against those obtained from a control group. The expected longer latencies in the P300 component in individuals with depression were verified within the present study.

The statistically significant ($p<0.05$) longer latency of P300 waveform that is presented for children and adolescents with depression in this and other studies probably explains the cognitive deficits that depressed children exhibit. It is suggested that the longer latency of P300 reflects cognitive impairments of children and adolescent participants with depression [56]. In a meta-analytic level, the study of Marchetti et al. [57] found a strong association between depression and memory. Moreover, the same study suggested that preferential recall of depressotypic information is already present in individuals who are at-risk to develop major depression. Furthermore, cognitive disorders such as attention deficit, memory and executive function impairments are commonly suggested by studies in depressed individuals [30,32]. Effect sizes that have been found large in this study were ranging from 1.19 to 6.40. This result suggests that the differences in P300 latencies between the two groups were large and clinically important [55]. Reaction time was found statistically significant between children and adolescents with depression and their typically developing peers, in the same line of other studies [58,59]. Delays in reaction time can be seen as a result of poor attention to and interest in the activity, particularly in depressives, where this theory appears to correspond to their clinical picture [60]. Children and adolescents with depression scored higher at Children Depression Inventory in comparison to the control group. These results verify our first hypothesis.

The present study’s second hypothesis stemmed from research on brain plasticity and neural cortex activation, which demonstrated variations in P300 latencies and reaction times after administering CBT and/or SSRIs to children, adolescents, and adults with depression. In the present study, children and adolescents with depression presented shorter latencies in the P300 component and reaction times after the implementation of the remediation program. There were no statistical differences in P300 latency and reaction time ($p>0.05$) in comparison to their typically developed peers. Also, effect size revealed that in 12 out of 15 brain sites P300 waveforms, the differences between the two groups were small to medium, ranging from 0.02 to 0.40. This finding suggests small variations between the two groups of children and adolescents. Shorter P300 latency and reaction time is possibly reflecting better memory and attentional functions, as it is proposed that the ability of children and adolescents with depression post remediation to inhibit responses, improves sufficiently as they answer with more confidence [61]. According to a number of studies, CBT

intervention program and family CBT programs are suggested to have significant and clinically relevant results in remediation of adult and children depression [36,62–65].

The third hypothesis of the present study concentrated only on depressed children according to their remediation program. It is worth to keep in mind that children and adolescents with depression followed only a CBT remediation program or a combination of CBT and SSRIs. The analysis revealed that depressed children that implemented the combined program exhibited better P300 latency and better reaction time in comparison to depressed children that were treated only with a CBT program. This might reflect that neurotransmitter such as serotonin play an important role in both depression and P300 waveform. However, results presented no statistically significant differences ($p>0.05$). Consequently, the third hypothesis of the present study was partly verified.

SSRIs are a well-established, evidence-based intervention method that can significantly improve symptoms and functioning [66]. Sufficient data supports their safety and tolerability in children and adolescents, and they have the added benefit of being widely available in most communities. While SSRIs are beneficial as a monotherapy, when paired with CBT, they consistently produce the most positive benefits for children and adolescents with depression [67]. The American Psychiatric Association practice guidelines for the treatment of patients with major depressive disorder suggests the combination of CBT with SSRIs [42].

The reader should bear in mind various limitations of the current research protocol. Not all ERP waveforms mentioned in the literature were used in the present investigation. Only P300 was chosen since it is the most typically used when dealing with higher mental ability concerns. Another limitation is the small sample size, which may have lowered statistical analysis power. Our study's strength is determined by the vast number of statistically meaningful results presented. Furthermore, the researcher tried to find children and adolescents who were drug free and never followed any psychotherapeutic protocol, as all participants received the diagnosis of depression for their first time.

Behaviorally the current protocol found that children and adolescents with depression have longer latencies than the control group, indicating that they have attentional and memory deficits, which may explain their poor academic performance. Research data suggests that increased P300 latency is associated with attention [68]. and memory deficits [25]. The shorter P300 latency, demonstrated in the current research protocol, indicates an improvement in the higher cognitive functions. Furthermore, the reduction in reaction times observed in children with depression following the remediation program may reflect a change in cognitive behavior, as well as advanced organization. These findings can be used to inform the development of intervention programs in schools.

Despite the limitations of the present study, the findings are positive, not only for the assessment of children with depression, but also for the scientific community's continued efforts to develop and implement better therapeutic programs for children and adolescents with that kind of diagnosis. The current research is based on the outcomes of a remediation program on a rather small sample size, and additional research is necessary. Future study efforts could focus on repeating this intervention in more participants and implementing more ERPs waveforms, allowing for more accurate generalization. Notably, such research will be more important to be longitudinal in nature, comprising follow-up assessments of remediated children over extended time periods.

Institutional Review Board Statement: Ethics and Deontology Committee of the University of Thessaly.

Informed Consent Statement: all participants' parents/guardians were required to sign the consent form allowing their child to participate in the research.

Conflicts of Interest: The author declare no conflicts of interest.

References

1. Wagner, S., Müller, C., Helmreich, I., Huss, M., & Tadić, A. (2015). A meta-analysis of cognitive functions in children and adolescents with major depressive disorder. *European child & adolescent psychiatry*, 24, 5-19.

2. Jane Costello, E., Erkanli, A., & Angold, A. (2006). Is there an epidemic of child or adolescent depression? *Journal of child psychology and psychiatry*, 47(12), 1263-1271
3. Paus, T., Keshavan, M., & Giedd, J. N. (2008). Why do many psychiatric disorders emerge during adolescence?. *Nature reviews neuroscience*, 9(12), 947-957
4. World Health Organization. (2018). Adolescent mental health in the European Region: Factsheet for World Mental Health Day 2018. In *Adolescent mental health in the European Region: factsheet for World Mental Health Day 2018*.
5. American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5* (Vol. 5, No. 5). Washington, DC: American psychiatric association.
6. Vives, M., López-Navarro, E., García-Campayo, J., & Gili, M. (2015). Cognitive impairments and depression: a critical review. *Actas Esp Psiquiatr*, 43(5), 187-193.
7. Hasselbalch, B. J., Knorr, U., & Kessing, L. V. (2011). Cognitive impairment in the remitted state of unipolar depressive disorder: a systematic review. *Journal of affective disorders*, 134(1-3), 20-31.
8. Bora, E., Harrison, B. J., Yücel, M., & Pantelis, C. (2013). Cognitive impairment in euthymic major depressive disorder: a meta-analysis. *Psychological medicine*, 43(10), 2017-2026.
9. Kriesche, D., Woll, C. F., Tschentscher, N., Engel, R. R., & Karch, S. (2023). Neurocognitive deficits in depression: A systematic review of cognitive impairment in the acute and remitted state. *European archives of psychiatry and clinical neuroscience*, 273(5), 1105-1128.
10. Kujawa, A., & Burkhouse, K. L. (2017). Vulnerability to depression in youth: Advances from affective neuroscience. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, 2(1), 28-37.
11. MacLean, P. D. (1985). Evolutionary psychiatry and the triune brain1. *Psychological Medicine*, 15(2), 219-221.
12. Phelps, E. A., & LeDoux, J. E. (2005). Contributions of the amygdala to emotion processing: from animal models to human behavior. *Neuron*, 48(2), 175-187.
13. Beaudoin, C., & Beauchamp, M. H. (2020). Social cognition. In *Handbook of clinical neurology* (Vol. 173, pp. 255-264). Elsevier.)
14. Price, J. L., & Drevets, W. C. (2010). Neurocircuitry of mood disorders. *Neuropsychopharmacology*, 35(1), 192-216.
15. Anderson, K. M., Collins, M. A., Kong, R., Fang, K., Li, J., He, T., et al., (2020). Convergent molecular, cellular, and cortical neuroimaging signatures of major depressive disorder. *Proceedings of the National Academy of Sciences*, 117(40), 25138-25149
16. Treadway, M. T., Waskom, M. L., Dillon, D. G., Holmes, A. J., Park, M. T. M., Chakravarty, M. M., et al., (2015). Illness progression, recent stress, and morphometry of hippocampal subfields and medial prefrontal cortex in major depression. *Biological psychiatry*, 77(3), 285-294.
17. Ahrweiler, N., Santana-Gonzalez, C., Zhang, N., Quandt, G., Ashtiani, N., Liu, G., et al., (2022). Neural activity associated with symptoms change in depressed adolescents following self-processing neurofeedback. *Brain sciences*, 12(9), 1128.
18. Schultz, D. H., Ito, T., Solomyak, L. I., Chen, R. H., Mill, R. D., Anticevic, A., & Cole, M. W. (2018). Global connectivity of the fronto-parietal cognitive control network is related to depression symptoms in the general population. *Network Neuroscience*, 3(1), 107-123.)
19. Hasler, G., & Northoff, G. (2011). Discovering imaging endophenotypes for major depression. *Molecular psychiatry*, 16(6), 604-619.)
20. Wartchow, K. M., Scaini, G., & Quevedo, J. (2023). Glial-Neuronal Interaction in Synapses: A Possible Mechanism of the Pathophysiology of Bipolar Disorder. In *Neuroinflammation, Gut-Brain Axis and Immunity in Neuropsychiatric Disorders* (pp. 191-208). Singapore: Springer Nature Singapore
21. Karapetsas, A. V., & Zygouris, N. C. (2011). Event Related Potentials (ERPs) in prognosis, diagnosis and rehabilitation of children with dyslexia. *Encephalos*, 48(3), 118-127.
22. Howe, A. S., Bani-Fatemi, A., & De Luca, V. (2014). The clinical utility of the auditory P300 latency subcomponent event-related potential in preclinical diagnosis of patients with mild cognitive impairment and Alzheimer's disease. *Brain and cognition*, 86, 64-74.
23. Demirayak, P., Kıyı, İ., İşbitiren, Y. Ö., & Yener, G. (2023). Cognitive load associates prolonged P300 latency during target stimulus processing in individuals with mild cognitive impairment. *Scientific Reports*, 13(1), 15956.)
24. Sara, G., Gordon, E., Kraiuhin, C., Coyle, S., Howson, A., & Meares, R. (1994). The P300 ERP component: an index of cognitive dysfunction in depression?. *Journal of affective disorders*, 31(1), 29-38.
25. Polich, J. (2007). Updating P300: an integrative theory of P3a and P3b. *Clinical neurophysiology*, 118(10), 2128-2148.
26. Vandoolaeghe, E., van Hunsel, F., Nuyten, D., & Maes, M. (1998). Auditory event related potentials in major depression: prolonged P300 latency and increased P200 amplitude. *Journal of affective disorders*, 48(2-3), 105-113.

27. Sumich, A. L., Kumari, V., Heasman, B. C., Gordon, E., & Brammer, M. (2006). Abnormal asymmetry of N200 and P300 event-related potentials in subclinical depression. *Journal of affective disorders*, 92(2-3), 171-183.
28. Zhao, L., Gong, J., Chen, C., & Miao, D. (2010). Event-related potential based evidence of cognitive dysfunction in patients during the first episode of depression using a novelty oddball task. *Psychiatry Research: Neuroimaging*, 182(1), 58-66.
29. Tripathi, S. M., Mishra, N., Tripathi, R. K., & Gurnani, K. C. (2015). P300 latency as an indicator of severity in major depressive disorder. *Industrial psychiatry journal*, 24(2), 163-167.
30. Zhou, L., Wang, G., Nan, C., Wang, H., Liu, Z., & Bai, H. (2019). Abnormalities in P300 components in depression: an ERP-sLORETA study. *Nordic journal of psychiatry*, 73(1), 1-8.
31. Wang, Y., Li, C., Peng, D., Wu, Y., & Fang, Y. (2023). P300 event-related potentials in patients with different subtypes of depressive disorders. *Frontiers in Psychiatry*, 13, 1021365.
32. Xue, Z., Zhu, X., Wu, W., Zhu, Y., Xu, Y., & Yu, M. (2024). Synapse-Related Serum and P300 Biomarkers Predict the Occurrence of Mild Cognitive Impairment in Depression. *Neuropsychiatric Disease and Treatment*, 493-503.
33. Wakode, S. L., Hulke, S. M., Sutar, R., & Thakare, A. E. (2022). Comparative change in P300 indices following antidepressant treatment in patients with major depressive disorder. *Industrial Psychiatry Journal*, 31(2), 243-247.
34. De Raedt, R. (2020). Contributions from neuroscience to the practice of Cognitive Behaviour Therapy: Translational psychological science in service of good practice. *Behaviour Research and Therapy*, 125, 103545.
35. Chen, Q., Bonduelle, S. L. B., Wu, G. R., Vanderhasselt, M. A., De Raedt, R., & Baeken, C. (2024). Unraveling how the adolescent brain deals with criticism using dynamic causal modeling. *NeuroImage*, 286, 120510.
36. Kunas, S. L., Lautenbacher, L. M., Lueken, U., & Hilbert, K. (2021). Psychological predictors of cognitive-behavioral therapy outcomes for anxiety and depressive disorders in children and adolescents: a systematic review and meta-analysis. *Journal of Affective Disorders*, 278, 614-626.
37. Hazell, P. (2021). Updates in treatment of depression in children and adolescents. *Current opinion in psychiatry*, 34(6), 593-599.
38. Beck, A. T. (Ed.). (1979). *Cognitive therapy of depression*. Guilford press
39. Nardi, B., Massei, M., Arimatea, E., & Moltedo-Perfetti, A. (2017). Effectiveness of group CBT in treating adolescents with depression symptoms: a critical review. *International journal of adolescent medicine and health*, 29(3), 20150080.
40. Reinecke, M. A., Ryan, N. E., & DuBOIS, D. L. (1998). Cognitive-behavioral therapy of depression and depressive symptoms during adolescence: A review and meta-analysis. *Journal of the American Academy of Child & Adolescent Psychiatry*, 37(1), 26-34
41. Lowry-Webster, H. M., Barrett, P. M., & Lock, S. (2003). A universal prevention trial of anxiety symptomology during childhood: Results at 1-year follow-up. *Behaviour change*, 20(1), 25-43.
42. Gelenberg, A. J., Freeman, M. P., Markowitz, J. C., Rosenbaum, J. F., Thase, M. E., Trivedi, M. H., & Van Rhoads, R. S. (2010). American Psychiatric Association practice guidelines for the treatment of patients with major depressive disorder. *Am J Psychiatry*, 167(Suppl 10), 9-118.
43. Zygouris, N. C., Vlachos, F., & Stamoulis, G. I. (2022). ERPs in Children and Adolescents with Generalized Anxiety Disorder: Before and after an Intervention Program. *Brain Sciences*, 12(9), 1174.
44. Giannakopoulos, G., Kazantzi, M., Dimitrakaki, C., Tsiantis, J., Kolaitis, G., & Tountas, Y. (2009). Screening for children's depression symptoms in Greece: the use of the Children's Depression Inventory in a nation-wide school-based sample. *European child & adolescent psychiatry*, 18, 485-492.
45. Karaaslan, F., Gonul, A. S., Oguz, A., Erdinc, E., & Esel, E. (2003). P300 changes in major depressive disorders with and without psychotic features. *Journal of affective disorders*, 73(3), 283-287.
46. Campanella, S. (2021). Use of cognitive event-related potentials in the management of psychiatric disorders: Towards an individual follow-up and multi-component clinical approach. *World journal of psychiatry*, 11(5), 153.
47. Kolaitis, G., Zaravinos-Tsakos, F., Rokas, I. M., Syros, I., Tsakali, A., Belivanaki, M., & Giannakopoulos, G. (2023). Navigating young minds: reliability and validity of the Greek version of kiddie-schedule for affective disorders and schizophrenia-present and lifetime DSM-5 version (K-SADS-PL-GR-5). *BMC psychiatry*, 23(1), 614.
48. Kovacs, M. (1992). *Children's Depression Inventory* Available from Multi-Health Systems Inc., 908 Niagara Falls Blvd. North Tonawanda, NY, 14120-2060.
49. Myers, K., & Winters, N. C. (2002). Ten-year review of rating scales. II: Scales for internalizing disorders. *Journal of the American Academy of Child & Adolescent Psychiatry*, 41(6), 634-659.
50. Luck, S. J., & Gaspelin, N. (2017). How to get statistically significant effects in any ERP experiment (and why you shouldn't). *Psychophysiology*, 54(1), 146-157.

51. Jasper, H. H. (1958). Ten-twenty electrode system of the international federation. *Electroencephalogr Clin Neurophysiol*, 10, 371-375.
52. Picton, T. W., Bentin, S., Berg, P., Donchin, E., Hillyard, S. A., Johnson, R., et al., (2000). Guidelines for using human event-related potentials to study cognition: recording standards and publication criteria. *Psychophysiology*, 37(2), 127-152.
53. Zygouris, N. C., Dermitzaki, I., & Karapetsas, A. V. (2015). Differences in brain activity of children with higher mental abilities. An Event Related Potentials study using the latency of P300 and N100 waveforms. *International Journal of Developmental Neuroscience*, (47), 118-119.
54. Zygouris, N. C., Avramidis, E., Karapetsas, A. V., & Stamoulis, G. I. (2018). Differences in dyslexic students before and after a remediation program: A clinical neuropsychological and event related potential study. *Applied Neuropsychology: Child*, 7(3), 235-244.
55. Cohen, J. (1988). Set correlation and contingency tables. *Applied psychological measurement*, 12(4), 425-434.
56. Cao, P., Tan, J., Liao, X., Wang, J., Chen, L., Fang, Z., & Pan, N. (2024). Standardized Treatment and Shortened Depression Course can Reduce Cognitive Impairment in Adolescents With Depression. *Journal of the Korean Academy of Child and Adolescent Psychiatry*, 35(1), 90.
57. Marchetti, I., Everaert, J., Dainer-Best, J., Loeys, T., Beevers, C. G., & Koster, E. H. (2018). Specificity and overlap of attention and memory biases in depression. *Journal of affective disorders*, 225, 404-412.
58. Knott, V. J., & Lapierre, Y. D. (1987). Electrophysiological and behavioral correlates of psychomotor responsivity in depression. *Biological Psychiatry*, 22(3), 313-324.
59. Schrijvers, D., De Bruijn, E. R., Maas, Y., De Grave, C., Sabbe, B. G., & Hulstijn, W. (2008). Action monitoring in major depressive disorder with psychomotor retardation. *Cortex*, 44(5), 569-579.
60. Giedke, H., Thier, P., & Bolz, J. (1981). The relationship between P3-latency and reaction time in depression. *Biological psychology*, 13, 31-49.
61. Sanz, M., Molina, V., Martin-Loeches, M., Calcedo, A., & Rubia, F. J. (2001). Auditory P300 event related potential and serotonin reuptake inhibitor treatment in obsessive-compulsive disorder patients. *Psychiatry research*, 101(1), 75-81.
62. Baardseth, T. P., Goldberg, S. B., Pace, B. T., Wislocki, A. P., Frost, N. D., Siddiqui, J. R., et al., (2013). Cognitive-behavioral therapy versus other therapies: Redux. *Clinical psychology review*, 33(3), 395-405.
63. Honyashiki, M., Furukawa, T. A., Noma, H., Tanaka, S., Chen, P., Ichikawa, K., et al., (2014). Specificity of CBT for depression: a contribution from multiple treatments meta-analyses. *Cognitive therapy and research*, 38, 249-260.
64. Lepping, P., Whittington, R., Sambhi, R. S., Lane, S., Poole, R., Leucht, S., et al., (2017). Clinical relevance of findings in trials of CBT for depression. *European Psychiatry*, 45, 207-211.
65. Oud, M., De Winter, L., Vermeulen-Smit, E., Bodden, D., Nauta, M., Stone, L., et al., (2019). Effectiveness of CBT for children and adolescents with depression: A systematic review and meta-regression analysis. *European psychiatry*, 57, 33-45.
66. Treatment for Adolescents with Depression Study (TADS) Team. (2009). The Treatment for Adolescents With Depression Study (TADS): outcomes over 1 year of naturalistic follow-up. *American Journal of Psychiatry*, 166(10), 1141-1149.
67. Strawn, J. R., Mills, J. A., Suresh, V., Peris, T. S., Walkup, J. T., & Croarkin, P. E. (2022). Combining selective serotonin reuptake inhibitors and cognitive behavioral therapy in youth with depression and anxiety. *Journal of affective disorders*, 298, 292-300.
68. Kannen, K., Aslan, B., Boetzel, C., Herrmann, C. S., Lux, S., Rosen, H., ... & Braun, N. (2022). P300 modulation via transcranial alternating current stimulation in adult attention-deficit/hyperactivity disorder: a crossover study. *Frontiers in Psychiatry*, 13, 928145.

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