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Can Virtual Reality Cognitive Remediation in Bipolar Disorder Enhance Specific Skills in Young Adults through Mirror Neuron Activity?—A Secondary Analysis of a Randomized Controlled Trial

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Abstract: Introduction: Impairments in social cognition and cognitive deficits in bipolar disorder (BD) offer insights into the disorder's progression. Understanding how interventions impact both cognitive and emotional aspects of social cognition is essential. This study examines the effects of virtual reality (VR) cognitive remediation on cognitive skills, stratified by age, in the early stages of the disorder. Methods: A secondary analysis of a randomized controlled trial (RCT) compared the efficacy of VR cognitive remediation on cognitive skills between young adults ($\leq$58 years) and older adults ($\geq$59 years) in the experimental group with BD. Results: The experimental group included 39 participants: 24 $\leq$ 58 years and 15 $\geq$ 59 years. Young adults showed greater improvement in the Digit Span Backward (0.37 $\pm$ 0.35 vs. 0.07 $\pm$ 0.26, F = 9.882, p = 0.020) and Digit Symbol tests (3.84 $\pm$ 3.05 vs. 1.16 $\pm$ 3.8, F = 5.895, p = 0.020). Older adults improved more in the Frontal Assessment Battery (1.00 $\pm$ 0.95 vs. 0.54 $\pm$ 0.21, F = 5.295, p = 0.027), Matrix test (0.58 $\pm$ 0.35 vs. 0.37 $\pm$ 0.26, F = 4.606, p = 0.038), and Test of Tale (0.81 $\pm$ 0.36 vs. 0.42 $\pm$ 0.38, F = 10.115, p = 0.003). Conclusions: Young adults improved more in complex cognitive tasks, while older adults showed better results in simpler tasks. The effectiveness of VR may be due to hyperstimulation of mirror neurons. Further studies are needed to confirm these findings.

Keywords: cognitive impairment; bipolar disorder; cognitive remediation; virtual reality; advanced technology laboratory

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1. Introduction

The study of rehabilitative approaches to manage cognitive impairment (CI) in bipolar disorder (BD) is currently a significant topic of research [1,2]. Scientific evidence indicates that a significant proportion of individuals with BD exhibit neurocognitive dysfunction, even in periods of euthymia [3–6]. The most impaired domains in BD are verbal learning and memory, executive functions, and attention [1,5]. Premorbid intelligence appears to remain preserved [7]. However, over the past decade, increasing evidence suggests impairments in social cognition, influenced by CI [8,9]. CI specifically affects social competence tasks that involve "social intelligence" [10–13]. Social cognition and social intelligence encompass complex cognitive and affective skills [11–13]. Specifically, individuals with BD demonstrate difficulties in mentalizing, i.e., understanding and discriminating emotions and intentions [11,13]. It has been hypothesized that when facing emotional problems requiring complex responses, people with BD exhibit low activation of the "mirror neuron system" (right inferior frontal cortex, premotor cortex, insula) [4]. Consequently, they may struggle to effectively integrate and compare their own memories and others' experiences/emotions with daily experiences requiring understanding [4]. In this context, studying interventions that can positively impact not only CI but also the emotional aspects related to social cognition becomes essential.

A recent randomized controlled trial conducted by our group demonstrated that a cognitive remediation intervention using virtual reality (VR) in individuals with BD improved cognitive performance, depressive symptoms, and levels of alexithymia [14]. The theoretical framework guiding the development of the trial and intervention methodology is the biopsychosocial model [15,16], viewed through an evolutionary lens of the disorder. Consequently, VR technology was chosen to train learning in a daily life context, offering more engaging experiences compared to traditional methods [17–19]. Additionally, the session methodology incorporates an integrated and recovery-oriented approach [20], encompassing relaxation techniques and psychoeducational strategies to generalize new skills within the individual's daily life context. The initial hypothesis was that using this device with such a methodology could enhance not only cognitive abilities but also other psychosocial well-being variables like clinical symptoms, quality of life, and alexithymia [21]. However, the measure of cognitive improvement, calculated as the number of total skills that reached the normative threshold at the end of the trial from below the threshold at the beginning, indicated that the improvement was more pronounced in younger participants compared to older adults [22]. To explain this difference, it was hypothesized that cognitive remediation might be particularly effective on cognitive social skills intrinsically linked to the cognitive dysfunction in BD but not on deficits secondary to neurovascular pathologies often comorbid with BD [23–26]. The significant results achieved by VR in addressing alexithymia (an ability fundamentally based on the recognition and communication of emotions) and cognitive performance suggest that these abilities may be intrinsic to the underlying profile of the disorder rather than arising from advanced stages of the disorder or being consequent to cardiovascular risk and associated diseases common in older adults [27,28]. These characteristics, hypothesized to predate the disorder, could also be typical of preclinical and at-risk conditions. According to the current classification by the American Psychiatric Association [29], which is widely used globally, depressive disorders and BD are separated based on their hypothesized different pathogenesis and genetic risk. This approach contrasts with the neo-Kraepelinian concept of the bipolar spectrum [30–32], which unifies several mood disorders into a pyramid. This pyramid predicts non-clinical conditions at the broad base, characterized by non-pathological hyper-energy and the search for energy and novelty [33–35], with bipolar type 1 disorder at the apex [36]. It has also been recently hypothesized that a non-specific syndrome characterized by dysfunctional social rhythms and hyperactivity could constitute an intermediate stage between pathology and well-being [37–39].

According to the neo-Kraepelinian approach, specific modes of cognitive functioning are present across the entire BD spectrum [40,41]. Given these premises, it is possible to highlight a specific effect of VR cognitive remediation with integrated approaches on skills that deteriorate within the intrinsic profile of the BD spectrum. This could have potential applications in preclinical or early clinical phases, providing significant benefits in both clinical and preventative fields. Therefore, the aims of this work are to conduct a secondary analysis, stratified by age, on specific cognitive skills before and after the VR cognitive remediation intervention to verify the presence of a specific effect in the early stages of the disorder.

2. Methods

2.1. Design

This study involves a secondary analysis of the data from a randomized controlled clinical trial (RCT) previously evaluating the feasibility and preliminary efficacy of a VR cognitive remediation intervention for individuals with BD [14,21]. The RCT protocol followed the CONSORT guidelines for feasibility studies [42] and was registered in ClinicalTrials.gov (NCT05070065, 2021). This analysis specifically compares the intervention's efficacy on distinct cognitive skills between young adults (≤58 years) and older adults (≥59 years).

2.2. Sample

Participants were recruited from individuals attending the Psychosomatic Psychiatry Unit at the University Hospital of Cagliari. Inclusion criteria comprised individuals aged between 18 and 75 years with a diagnosis of bipolar I or II disorder according to DSM-IV [43], without exclusion based on sex. Participants provided informed consent. Exclusion criteria included current severe episodes of depression or mania, as well as diagnoses of epilepsy or severe eye diseases (due to potential overstimulation from virtual reality). Participants were randomly assigned to one of two treatment arms. Randomization was conducted blindly by an operator who did not perform the evaluation or intervention, using online software. When stratifying the sample by age groups, it is not balanced for gender; thus, this limitation will be included in the discussion.

2.3. Intervention

The experimental group received VR remediation intervention (two sessions per week over three months) in addition to treatment as usual (pharmacotherapy, psychiatric visits, and psychotherapy sessions), whereas the control group received treatment as usual without any additional intervention. The software used for the VR cognitive remediation program has been previously described in published papers [14,21]. Briefly, it is the "CEREBRUM—Cognitive Rehabilitation" software (version 3.0.1), suitable for Oculus Go with 360° view for full immersion. It was designed and developed by mental health professionals, including psychiatric rehabilitation technicians and psychologists, with the support of computer engineers from the Cerebrum VR Society (Rome, Italy). It involves virtual scenarios simulating everyday issues and events (domestic and urban scenarios), consisting of 52 exercises each targeting specific cognitive tasks and skills. The intervention was designed so that exercises could be gradually presented with increasing levels of difficulty, while clinicians could adjust the difficulty based on the functional needs and abilities of each participant. Thus, exercises were selected to be sufficiently challenging to promote stimulating learning without being overly difficult or easy. In general, all participants completed the 52 exercises in the same order, with the level of difficulty of each exercise varying to make the intervention generalizable. In domestic and urban contexts, all cognitive strategies are trained, ranging from attentional and mnemonic to executive functions. An example of such an exercise, as illustrated in Figure 1, involves the user being exposed to four different scenarios: two in a bathroom/laundry room and bedroom setting and two in a living room. In each scenario, the user is required to identify, as quickly as possible, the intruding objects, those specific items that are generally not present or typically associated with that environment. All exercises are manualized, meaning that the operator follows the instructions provided in the manual.

Integrated approaches were used in structuring the sessions; specifically, VR activities lasted a maximum of 15–20 min within each 50 min session. The remaining time was dedicated to relaxation techniques (as part of the introduction and welcoming at the beginning of the session), lasting a maximum of 10 min; psychoeducational strategies to understand the importance of the cognitive functions being trained with particular regard to their use in everyday life (post-welcoming phase), 10–15 min; feedback strategies (after each VR exercise and general feedback at the end of the session accompanied by homework assignments), 10 min; and everyday life generalization strategies through homework (at the end of the session), 5 min.

Figure 1. Fully immersive virtual scenarios.

2.4. Instruments

Cognitive performance was evaluated using a variety of standardized tools that assessed different aspects of cognitive functioning. For visuospatial functions, the Rey Figure Test was employed [44,45]. Immediate memory and verbal learning were measured using several tests: Rey's Words Test Delayed recall [46,47]; Babcock's Prose Memoir and Short Tale Test [48,49]; Backward Digit Span for memory [50–52]; Matrix test for immediate recall and attention [53]; and Words Test of Rey [47]. Simple attention function was assessed through the Forward Digit Span test [51,52] and Part A of the Trail Making Test (TMT) [53–56]. Language skills were evaluated using Phonological and Semantic Verbal Fluency Tests [49,56]. Executive functions were measured with the Stroop Test [57], the Digital Symbol Substitution Test (DSST) [55], the Frontal Assessment Battery (FAB) [58], and the Cognitive Estimates Test (CET) [59,60]. These assessments covered a broad range of cognitive domains, allowing for a comprehensive evaluation of cognitive performance in the study participants.

2.5. Statistical Analysis

The effect of the intervention across different age groups was assessed by measuring the specific improvements on each test administered within the experimental group of the trial. These improvements were compared between young and older adults from the start to the end of the trial (T0 to T1). To analyze the data, the following were conducted: between-group comparisons (young vs. older adults) at T0 and T1 were conducted using one-way ANOVA; within-group comparisons to calculate specific improvements over time utilized repeated measures ANOVA; and between-group comparisons of specific improvements in each test item were analyzed using one-way ANOVA. Only for variables that were not normally distributed, a non-parametric analysis was performed using the Kruskal–Wallis test. The normality test used for the distribution assumption was the Kolmogorov–Smirnov test. These statistical methods allowed for a comprehensive evaluation of how age influenced the efficacy of the intervention on cognitive performance.

3. Results

The final sample consisted of 39 individuals in the experimental group, divided into two subgroups for this secondary analysis. There were 24 individuals aged under 59 years and 15 individuals aged ≥59 years. Table 1 describes the two groups compared; they are balanced by sex, while, obviously, the group of young adults is younger (38.50 ± 9.38 years old vs. 61.53 ± 3.57; F = 82.261, 1.38 df; $p < 0.0001$).

Table 1. Characteristics of the sample.

	Old Adults (N = 15)	Young Adults (N = 24)	Statistics
Sex (Female)	11 (78.6%)	14 (58.3%)	Chi square 0.903, 1 df, $p = 0.342$
Age	61.53 ± 3.57	38.50 ± 9.38	F = 82.261, 1.38 df, $p < 0.0001$

The comparison of the effects of VR cognitive remediation by age on the skills measured by the specific tests is shown in Table 2. Young adults showed greater improvement in the Digit Span Backward test (score improvement of 0.37 ± 0.35 vs. 0.07 ± 0.26, F = 9.882, $p = 0.020$) and the DSST (score improvement of 3.84 ± 3.05 vs. 1.16 ± 3.8, F = 5.895, $p = 0.020$). Older adults showed statistically significant improvement compared to young adults in the FAB (score improvement of 1.00 ± 0.95 vs. 0.54 ± 0.21, F = 5.295, $p = 0.027$), Matrix test (score improvement of 0.58 ± 0.35 vs. 0.37 ± 0.26, F = 4.606, $p = 0.038$), and the Test of Tale (score improvement of 0.81 ± 0.36 vs. 0.42 ± 0.38, F = 10.115, $p = 0.003$).

Table 2. Cognitive functions before (T0) and after (T1) VR cognitive remediation in younger sample (n = 24) vs. older sample (n = 15).

	T0 (Mean ± SD)	T1 (Mean ± SD)	Improvement (Mean ± SD)	ANOVA 1wy 1; 38 df or No Parametric Test
Rey Immediate (Cut off = 6.44) Old	10.02 ± 7.06	13.66 ± 7.51	3.64 ± 2.55	F = 3.073
Rey Immediate (Cut off = 6.44) Young	13.47 ± 7.51	18.28 ± 7.76	4.81 ± 1.63	$p = 0.088$
Rey's Words Immediate (Cut off = 0) Old	2.06 ± 1.69	2.75 ± 1.56	0.69 ± 0.34	F = 0.067
Rey's Words Immediate (Cut off = 0) Young	2.50 ± 1.44	3.16 ± 1.34	0.66 ± 0.36	$p = 0.797$
Ray's Words Delayed (Cut off = 0) Old	2.10 ± 1.45	2.81 ± 1.46	0.71 ± 0.48	F = 1.651
Ray's Words Delayed (Cut off = 0) Young	2.00 ± 1.58	2.87 ± 1.45	0.87 ± 0.30	$p = 0.207$
Stroop Test Time (Cut off = 0) Old	2.40 ± 1.66	2.81 ± 1.37	0.41 ± 0.38	F = 0.001
Stroop Test Time (Cut off = 0) Young	2.75 ± 1.42	3.16 ± 1.37	0.41 ± 0.32	$p = 0.999$
FAB (Cut off = 15.7) Old	14.06 ± 3.35	15.06 ± 2.51	1.00 ± 0.95	F = 5.295
FAB (Cut off = 15.7) Young	15.70 ± 2.71	16.16 ± 2.46	0.54 ± 0.21	$p = 0.027$ *
Digit Span Direct (Cut off = 0) Old	2.26 ± 1.43	2.37 ± 1.36	0.26 ± 1.88	H = 3.360
Digit Span Direct (Cut off = 0) Young	3.08 ± 1.46	3.04 ± 11.45	−0.04 ± 1.48	$p = 0.066$
Digit Span Backward (Cut off = 0) Old	1.80 ± 1.37	1.87 ± 1.57	0.07 ± 0.26	F = 9.882
Digit Span Backward (Cut off = 0) Young	2.00 ± 1.73	2.37 ± 1.65	0.37 ± 0.35	$p = 0.003$ *
Verbal Phonological Test (Cut off = 0) Old	2.50 ± 1.35	3.00 ± 1.32	0.50 ± 0.44	F = 1.590
Verbal Phonological Test (Cut off = 0) Young	2.79 ± 1.44	3.16 ± 1.17	0.37 ± 0.20	$p = 0.215$
Verbal Semantic Test (Cut off = 0) Old	2.33 ± 1.44	3.06 ± 0.96	0.73 ± 0.31	F = 2.441
Verbal Semantic Test (Cut off = 0) Young	2.79 ± 1.22	3.37 ± 1.18	0.58 ± 0.28	$p = 0.127$
Matrix (Cut off = 0) Old	1.73 ± 1.43	2.31 ± 1.57	0.58 ± 0.35	F = 4.606
Matrix (Cut off = 0) Young	2.08 ± 1.28	2.45 ± 1.32	0.37 ± 0.26	$p = 0.038$ *
Substit. Digit Symbol (Cut off = 34.2) Old	36.23 ± 14.30	37.39 ± 8.46	1.16 ± 3.8	F = 5.895
Substit. Digit Symbol (Cut off = 34.2) Young	36.44 ± 14.59	40.28 ± 13.48	3.84 ± 3.05	$p = 0.020$ *

Table 2. *Cont.*

	T0 (Mean ± SD)	T1 (Mean ± SD)	Improvement (Mean ± SD)	ANOVA 1wy 1; 38 df or No Parametric Test
CET (Cut off = 0) Old CET (Cut off = 0) Young	1.93 ± 1.34 1.95 ± 1.51	2.81 ± 0.88 2.75 ± 1.25	0.88 ± 034 0.80 ± 0.40	F = 0.413 *p* = 0.525
Test of Tale (Cut off = 0) Old Test of Tale (Cut off = 0) Young	2.00 ± 1.26 2.20 ± 1.44	2.81 ± 1.13 2.62 ± 1.11	0.81 ± 0.36 0.42 ± 0.38	F = 10.115 *p* = 0.003 *
TMT A (Cut off = 0) Old TMT A (Cut off = 0) Young	2.66 ± 1.39 3.00 ± 1.15	2.81 ± 1.55 3.20 ± 1.25	0.15 ± 037 0.20 ± 0.38	F = 0.163 *p* = 0.689

* Significant with $p < 0.05$.

No statistically significant differences were detected between the two groups in the following tests: Rey Immediate Score, Rey's Words Immediate Score, Rey's Words Delayed, Stroop Test Time, Digit Span Direct, Verbal Phonological Test, Verbal Semantic Test, CET, and the TMT A.

4. Discussion

This study demonstrates that cognitive remediation using virtual reality impacts specific areas of cognitive functioning differently in older and younger adults. The FAB score increased more in old adults; however, the increase was not sufficient to surpass the performance of younger adults, who evidently started with a higher baseline score. Thus, the intervention appears to restore previously lost skills rather than enhance them from a new baseline. The FAB measures executive functions, which involve a set of operations coordinated by various processes to perform actions flexibly in non-routine contexts. These complex and heterogeneous abilities are predominantly regulated by neuronal mechanisms localized in prefrontal regions [58,61,62]. Given the complexity of the subcortical coordination required by these operations, the results should be interpreted from a rehabilitative perspective. Similarly, the Matrix test, despite showing a greater increase in scores among older adults, did not result in older adults achieving better scores than younger adults by the end of the trial. This test assesses different aspects of visual attention, such as speed, detection capacity, and interaction between working memory and visuo-attentive processes [53]. While performance on this test is affected by visual impairment and motor weakness, the role of "social intelligence" is minimal; the test tends to deteriorate significantly with age [53]. Therefore, the results are likely influenced by these factors rather than reflecting the specific characteristics of BD related to the impairment of cognitive and affective intelligence. It is important to consider that impairments, which can be exacerbated by microvascular issues common in aging and BD, may contribute to the observed results [27,28]. Thus, the findings are notable from a rehabilitation perspective. The Babcock Story Recall Test, a neuropsychological measure of episodic memory for immediate and delayed recall [49], revealed that older adults with BD showed nearly double the improvement in scores compared to younger adults. However, this test measures more than just memory performance; it is strongly correlated with movement velocity and both cerebellar and non-cerebellar motor control functions [63]. Once again, the interactions between social intelligence and cognitive intelligence appear marginal. A significant heterogeneity in clinical cognitive aging has been observed among individuals with BD. Researchers have proposed three hypotheses to explain these variations in aging [64]. The first hypothesis suggests that different endophenotypes interact with the cognitive aging process in distinct ways, leading to a decline in certain cognitive domains while others remain relatively stable over time. The second hypothesis posits that BD undergoes intrinsic neuroprogression, evolving naturally and progressively toward a state characterized by cognitive impairment. According to this hypothesis, BD would evolve "naturally" and progressively towards a disorder characterized by cognitive impairment. According to this view, a severe manic or depressive episode could induce a systemic response that results in a loss of brain connectivity. The third hypothesis considers the risk of vascular dementia, given the documented increase in vascular disorders associated with the progression of BD.

These hypotheses are not mutually exclusive; the predominance of any one hypothesis may depend on additional factors such as the effects of medication and overall health conditions, particularly dysmetabolic syndromes [64].

Given these factors, determining which specific intervention might better impact a particular cognitive ability in an older adult sample is challenging. However, if a specific cognitive ability that was deficient improves in younger individuals with bipolar disorder, this may provide more straightforward interpretative insights. In young adults, the intervention with virtual reality resulted in a greater improvement in certain tests compared to older adults, notably in the Digit Span Backward test. A recent study indicated that working memory performance, as measured by the Digit Span Backward, improves into young adulthood and declines with advancing age [65]. This finding may explain why cognitive remediation intervention had a more pronounced effect in younger adults, as it targets an ability that is still developing or has not yet begun to decline. Particularly noteworthy is the result for the Digit Symbol Substitution Test (DSST). At the start of the trial, both groups exhibited a relatively low and overlapping level of performance, with a broad distribution of scores. The cut-off for pathological performance (34.2) was well above one standard deviation from the mean in both groups. This low level of performance and the substantial overlap between young and older adults suggest that this may be a fundamental characteristic of bipolar disorder, unaffected by the disorder's progression. The DSST is a comprehensive measure of cognitive dysfunction across multiple domains [66], and its performance correlates with real-world functional skills and the ability to perform everyday tasks [66]. Notably, DSST performance has also been linked to social skills and negatively correlated with the misalignment of social rhythms [67]. The low interaction between cognitive and social intelligence, which involves the activity of mirror neurons, is considered a typical feature of BD [11], as is the misalignment of social rhythms [68], particularly in response to light stimuli [69]. The medium-low performance on the DSST compared to national normative data and its improvement, particularly in young adults, may further support its role in reflecting typical dysfunctions associated with bipolar spectrum disorders. It is important to note that the DSST has been shown to be sensitive to changes in cognitive performance in individuals with major depressive disorder and bipolar disorder, suggesting its utility in monitoring treatment efficacy for these conditions [66]. Individuals with BD exhibit low activations of the "mirror neuron system" [4], potentially relying on "fast" and "inefficient" response strategies that fail to adequately address complex emotional and cognitive demands. This issue persists even during euthymic phases [4], though it is exacerbated during hyperthymic episodes. The amplitude of the EEG gamma rhythm, which is associated with mirror neuron activity, has been found to increase during both real and imagined motor movements, with no significant differences between the two types of movements [70]. Given that virtual reality can strongly activate these rhythms through imagined movements, potentially more so than through real movements, it is plausible that VR cognitive remediation could significantly enhance functions related to cognitive recognition and mirror neuron activity in BD, including alexithymia [71] and complex tests such as the DSST. The improvement observed in the DSST among younger adults may be related to the fact that in this group, the "intrinsic" characteristics of the disorder are less compromised by additional deficits related to vascular issues. Despite being a feasibility study with primarily heuristic value and not aimed at establishing efficacy, the findings are interesting, albeit limited, and crucial for guiding future phase III studies. Another aspect is that omitting multiple testing corrections could inflate type one error; this could suggest that the results are only preliminary.

Limitations

This study represents a feasibility investigation with a small sample size due to the design used, which prioritizes feasibility outcomes as the primary objective. Consequently, this study is a secondary analysis of the secondary objectives of the original study (preliminary information on efficacy), which limits the generalizability of the results. The findings are preliminary and need to be validated through larger, confirmatory studies to establish broader applicability. Another limitation of the original study is the absence of an active control group. An influencing factor might also be the imbalance in the sample for sex after age stratification, which will need to be better balanced in phase III.

5. Conclusions

This study evaluated the impact of a cognitive remediation intervention using VR on a young adult cohort with BD. The intervention suggests enhancing cognitive performance in this population. The results indicated that deficits in complex cognitive tasks, which may require an integration of cognitive and social intelligence skills, were more markedly improved in young adults. Conversely, in less complex tasks where older adults initially exhibited greater deficits, the intervention produced less consistent improvements in young adults. The effectiveness of virtual reality may be attributed to the hyperstimulation of mirror neurons induced by simulated movements within the virtual environment. These findings warrant further validation through phase III studies to confirm the efficacy and generalizability of the intervention.

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Institutional Review Board Statement: This study received approval from the Local Independent Ethics Committee of the University Hospital of Cagliari, designated by protocol number PG/2020/21681, assigned on 22 December 2020. This study has been registered in September 2021 on ClinicalTrials.gov under reference number NCT05070065.

Informed Consent Statement: The trial conformed to the principles outlined in the Declaration of Helsinki. Prior to enrollment, all participants were thoroughly informed about this study's objectives and procedures. Informed written consent was obtained from each patient, or when necessary, from their legal guardians. To ensure confidentiality in compliance with European data protection regulations, study data were recorded in a secure database in an anonymized manner.

Data Availability Statement: Data are contained within this article.

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

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