Journal of Neural Transmission (2021) 128:371–380
https://doi.org/10.1007/s00702-021-02321-3

PSYCHIATRY AND PRECLINICAL PSYCHIATRIC STUDIES - ORIGINAL ARTICLE

Improvement of brain functional connectivity in autism spectrum disorder: an exploratory study on the potential use of virtual reality

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Received: 25 October 2020 / Accepted: 26 February 2021 / Published online: 6 March 2021

Abstract

Patients with Autism Spectrum Disorder (ASD) need to be provided with behavioral, psychological, educational, or skill-building interventions as early as possible. Cognitive Behavior Therapy has proven useful to manage such problems. There is also growing evidence on the usefulness of Virtual Reality Therapy (VRT) in treating various functional deficits in ASD. This exploratory study is aimed at assessing the changes in cognitive functions in children with ASD, and the putative subtending neurophysiological mechanisms, following the provision of rehab training using an innovative VRT system. Twenty patients with ASD, aged 6–15 years, were provided with 24 sessions of VRT by using the pediatric module of the BTS NIRVANA System. Neuropsychological and EEG evaluations were carried out before and at the end of the training. After VRT, all patients showed a significant improvement in their cognitive-behavioral problems concerning attention processes, visuospatial cognition, and anxiety. These findings were paralleled by an evident reshape of frontoparietal connectivity in the alpha and theta frequency range. Our study suggests that VRT could be a useful and promising tool to improve ASD neurorehabilitation outcomes. This improvement is likely to occur through changes in frontoparietal network connectivity following VRT.

Keywords Virtual Reality Therapy (VRT) · Autism Spectrum Disorder (ASD) · Frontoparietal connectivity · Anxiety

Introduction

Autism spectrum disorder (ASD) (including Autistic disorder, Asperger's syndrome, and Pervasive developmental disorder not otherwise specified) is a neurodevelopmental disorder characterized by a variety of symptoms with differing severity, such as difficulties in joint attention and visual contact, fascination with sensorial stimuli, lack of social intent to communicate, and imitative social play (Toth et al. 2006; Brentani et al. 2013; Fuentes et al. 2014; Ogundele 2018). All these symptoms account for the limited capacity in communicating and interacting with other people, restricted interests, and repetitive behaviors, thus negatively affecting functional activities, including school, work, and other areas of life (Park et al. 2019; Diagnostic and Statistical Manual of Mental Disorders 5).

Patients with ASD show often-high levels of anxiety and cognitive deficits, mainly involving attention, executive function, and praxis, negatively affecting their quality of life (Zwick 2017). Consistent with the wide range of cognitive impairments related to the disease (Toth et al. 2006; Brentani et al. 2013; Fuentes et al. 2014; Ogundele 2018), patients with ASD need to receive behavioral, psychological, educational, or skill-building interventions. These interventions include the following: (i) learning life-skills necessary to live independently; (ii) reducing challenging behaviors; (iii) increasing or building upon strengths, and (iv) learning/potentiating social, communication, and language skills.

Cognitive Behavior Therapy (CBT) is a valid strategy to mitigate mood-related symptoms and potentiate cognitive, communicative, sensorimotor, adaptive behavior, and socio-emotional reciprocity abilities (Gaus and Attwood 2018; Ben-Sasson et al. 2009; Edgington et al. 2016; Douglas 2019; Werchan et al. 2018; Sukhodolsky et al. 2013;

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Wood et al. 2015; Kose et al. 2018). However, there is no clear evidence of CBT's effectiveness in cognitive domains for young ASD patients, whereas some evidence is available for anxiety reduction following CBT (Leichsenring and Steinert 2017; Hofmann et al. 2012; Walters et al. 2016; Spain et al. 2017). Therefore, innovative and multidisciplinary approaches aimed at targeting cognitive dysfunction in ASD should be welcomed.

Virtual Reality Therapy (VRT) is a new way to deliver a wide range of treatments within a multimodal approach, thus representing a tool that can be implemented within CBT. It consists of a VR environment (VRE), such as computer-based simulations of reality, designed to comprehensively or selectively stimulate different motor and cognitive domains in patients with neurologic (e.g., stroke) or psychiatric disorders, including ASD. There is some evidence of the usefulness of VRT in the treatment of both adults and children with ASD (Bernard-Opitz et al. 2001, Mitchell et al. 2007a, b; Ozonoff and Miller 1995; Wainer and Ingersoll 2011; Mesa-Gresa et al. 2018; De Luca et al. 2018, 2019; Didehbani et al. 2016; Wang and Reid 2013; Rizzo and Buckwater 2004; Kandalaft et al. 2013). The advantage of adopting VRT lies in the fact that an individual can practice difficult or personally challenging social interactions in a less-anxiety-producing platform, i.e., in a VRE (Kandalaft et al. 2013; Maskey et al. 2014; Parsons and Mitchell 2002; Wainer and Ingersoll 2011). Furthermore, VRE can offer patients simple emotion recognition tasks or role-playing scenarios. VRT can provide patients with safe, unlimited, and commonly encountered day-to-day contexts to practice social and or interactive scenarios, allowing for repeated practice in a dynamic, continually changing social context, such as identifying/finding objects, counting, and describing, chasing, or moving items (Kandalaft et al. 2013; Parsons et al. 2005; Wallace et al. 2010). Lastly, VRT is often experienced by children as highly engaging, interactive, motivating, and rewarding (Parsons and Mitchell 2002). One important detail is that the motor, cognitive, and social skills learned in the VRE can be transferred to everyday life interactions by intensive, repetitive, and task-oriented VRT practice (Bellani et al. 2011, Parsons and Cobb 2011; Tzanavari et al. 2015). This practice is also thought to cognitively rehearse the learned motor schemas to enhance motor performance beyond cognitive processes (Kitago and Krakauer 2013).

Despite these premises, there are only a few VRT-based studies focused on reducing anxiety symptoms (Conaughton et al. 2017), improving sensory processing difficulties (Edgington et al. 2016), and ameliorating cognition, affective communication, social skills, and facial emotion perception in young patients with ASD (Weston et al. 2016). Furthermore, the neurophysiological underpinnings of VRT remain only partially elucidated, although a selective effect of VRT has been hypothesized on the brain network activity sustaining cognitive processes (Faria et al. 2016; Petzinger et al. 2013; Fan et al. 2005; Doniger et al. 2018; Wang et al. 2013; Boutros et al. 2015; De Luca et al. 2019).

The present pilot study was aimed at assessing the changes in some aspects of cognitive functioning (including non-verbal fluid intelligence, attention processes, and sensorimotor integration) and anxiety symptoms in children with ASD following a rehab training using an innovative VRT system, i.e., the pediatric module of the BTS NIRVANA System v.2.0 (BTSN) (BTS Bioengineering; Garbagnate Milanese, Italy). Using this device, we provided patients with a semi-immersive VRE in which children had to carry out different motor exercises involving their trunks and limbs and stimulating different cognitive domains.

Furthermore, we aimed at assessing the putative neurophysiological mechanisms subtending the abovementioned changes. We hypothesized that BTSN might target the detrimental long-range networks that are strategic to sustain the above-mentioned cognitive functions.

Materials and methods

Study population and setting

Forty-seven school-aged children affected by ASD and attending the child neuropsychiatry outpatient ambulatory of the IRCCS Centro Neurolesi (Messina, Italy) were screened for study inclusion from January to June 2018.

The inclusion criteria were (i) diagnosis of ASD, according to the DSM-V (American Psychological Association 2015); (ii) age range 5–18 years; and (iii) no cognitive therapy within the last six months before enrollment. Exclusion criteria included: (i) severe aggressive, self-directed, and/or hetero-directed behaviors; (ii) severe intellectual disability according to the IQ score ranges on the Wechsler Abbreviated Scale of Intelligence (WASI), so that only children with ASD having a mild to moderate intellectual disability were included in the study; (iii) acute psychiatric condition or a history of neurologic disorders; and (iv) epileptic seizure induced by light stimuli.

Thirty patients met the inclusion/exclusion criteria, and 20 of them (aged 6–15 years; mean ± sd 11 ± 3 years; 13 females and seven males) received the experimental protocol. Indeed, parents of ten children with ASD refused to give informed consent for different personal and work-related reasons.

The local Ethics Committee approved the study (IRCCSME 39/2017), and all patients' caregivers provided their written informed consent to study participation and data publication.

Outcome measures

All patients were assessed before (baseline, T0), immediately after (T1), and one month after (T2) the completion of the VRT training using a specific psychometric battery. This included the Raven's Colored (RSPM) and Standard Progressive Matrices (RSPM) (Raven et al. 1998) to measure the non-verbal fluid intelligence; the Modified little bell test (MTCM) (Biancardi 1997) to evaluate the attention processes; the Developmental Test of Visual-Motor Integration (VMI) (Beery and Beery 2004) to assess the visual-spatial functions; and the Beck Anxiety Inventory for Youth (BAI-Y), which belongs to the self-report multi-assessment instrument Beck Youth Inventories (Beck et al. 2005) to rate anxiety symptoms. EEG recording in resting conditions at T0 and T1 was also carried out to investigate the neurophysiological changes following the training.

VRT was delivered once daily, three times a week, for eight consecutive weeks (24 sessions, each session lasting about 30–45 min).

Device and procedures

BTSN is a VRE-based medical device specifically designed to rehabilitate patients with neurological disorders complaining of motor and cognitive difficulties. The tool is a movement-based system that provides the patients with interactive VRE, where different audio/video stimuli are presented in different parts of the screen. Indeed, the system is connected to a large projector or screen (i.e., a 2D flat-panel projection system), which reproduces an interactive series of exercises involving trunk and limbs and stimulating different cognitive domains. Moreover, an infrared video camera records the patient's movements, so he/she can interact with the screen on which a scenario is displayed and perform motor or cognitive activities (related to attention processes, memory, spatial cognition, equilibrium, and motor coordination functions), including identifying/finding objects, counting, and describing, chasing, or moving items.

Rehabilitation exercises with audiovisual stimuli and feedback involve the perceptual-cognitive abilities of patients, increasing motivation. Each activity has different modes and increasing levels of difficulty so that the therapist can use a predefined or new rehabilitation solution, depending on the patient's needs (Table 1). The data obtained after the training may be recorded and stored, allowing the therapist to evaluate the patient's progress and modify the rehabilitation program accordingly. The tool has six types of exercise concerning the patient's modality of interaction in different virtual tasks (Fig. 1): *sprites, follows me, hunts, motion, games, and virtual grasping*. *Sprites* allow exploring the available environment with a single or both upper limbs; this is a beneficial method to recover visual-spatial abilities and spatial cognition. *Follows me* is indicated to stimulate the upper or lower limb and to improve motor coordination. *Hunt* is meant to improve the attentional processes and ocular-manual coordination. *Motion* aims to control movement within fixed positions to improve limb and trunk control. *Games* allow the interaction of multiple patients in a session and a strategy of taking the turn. *Grasping* permits stimulating the attention processes, motility, and coordination. Other scenarios were designed to reduce the patient's anxiety, with the therapist's support to practice specific techniques (supplementary Table 1).

The participant was invited to interact with various scenarios to perform motor and cognitive tasks and improve the attention processes and spatial cognition. Moreover, we used specific scenarios with three hierarchically graded levels of exposure. We started from the lowest level without direct therapist assistance (i.e., a quiet dog at a distance and/or water that moves with the participant's movement). In the next levels, the therapist supported the participants in practicing techniques and reducing anxiety (including relaxation exercises, breathing exercises, and stimulating thoughts). If the anxiety increased as the scene became demanding,

Table 1 The virtual reality training (VRT) by BTS-NIRVANA used in the patient with ASD

DOMAIN		VRT
Cognitive	Visuo-Spatial Cognition (15-min)	In this session, we used virtual scenarios with low-immersion (Cooking; Basket Case, Billiards. Dog, Find the Apple, Goal, Tape the Mole, The four Seasons) to improve the spatial cognition through the engines that triggered scenario sequences receiving a video-sound feedback. After reaching a single target, the difficulty of the task and the motor sequences were increased
	Attention Process (15-min)	In this session, we used virtual scenarios to increase the attention process (Farm's Sounds, Find the Apple and Tape the Mole). Upon indication of the therapist, the patient interacted with the virtual system at a fixed time, producing a visual and sound change (positive reinforcement). In case of error, the element disappears (negative reinforcement). After reaching the single target, the difficulty level was increased by introducing a greater number of distractors and reducing the execution time
Behavioral	Anxiety (15-min)	In this session, we used some virtual task (Storm; Freshness; Water Classic; Mood) to reduce the anxiety symptoms, to recognizing and managing the emotions, using the same emotional awareness training and the psychoeducational to use a diaphragmatic breathing technique

Fig. 1 A subject with ASD while performing cognitive and behavioral exercises in a virtual reality environment in double modality: on the wall and flooring. In particular, the subject can interact with different virtual scenarios to increase specific cognitive abilities and reduce anxiety symptoms. BTS Nirvana screen allows to work on various domains based on attention and sensorimotor processes (including to indicate the objects, naming's image, colors, fruits, left–right–center spatial exploration with the visual-spatial scanner, the animal's position in the virtual space, and so on) and to control emotion and anxiety (recognition of emotion and the use of peculiar diaphragmatic breathing techniques)

the therapist suggested relaxation and breathing exercises or moving to relaxation scenes, whichever was necessary. Each level was customized to the participant's needs. After the participant was exposed to the third level, the therapist met the participant and his/her caregivers, giving them indications on managing a more stressful situation resembling real life.

EEG processing and analysis

EEG was recorded for at least 10 min in a resting state (to produce a sufficiently long recording and obtain intervals free from artifacts) while the patient was sitting on a comfortable chair in a silent room with a controlled temperature. A standard EEG headset with 19 channels (placed according to the International 10–20 System) wired to a BrainQuick device (Micromed; Mogliano Veneto, Italy) was used. EEG was sampled at 256 Hz, filtered at 1–60 Hz (by Butterworth filters), and referenced to both mastoids. The EEG segments without eye blink and other gross artifacts were subjected to ICA to be further cleaned of artifacts. Then, the pruned data were subjected to wavelet decomposition using Synchronization Likelihood (SL) as a nonlinear measure of interdependence between EEG signals. This allowed for evidencing abnormalities in functional connectivity of brain networks in all EEG sub-bands and full-band EEG (Stam and Dijk 2002; Zou et al. 2008; Rizzi et al. 2009). We adopted such an approach to identify neuronal-network connectivity changes in specific loci and sub-bands, which may not have been detectable in the full-band EEG.

Briefly, we carried out a 4-level wavelet decomposition on each EEG channel in the following frequency bands (Adeli et al. 2007): gamma (30–60 Hz), beta (15–30 Hz), alpha (8–15 Hz), theta (4–8 Hz), and delta (0–4 Hz); omega frequency rage (full range) was also considered. Then, signals were reconstructed in keeping with the Takens theorem (Chan and Tong 2001). Finally, the Fuzzy Synchronization Likelihood (FSL) within and between EEG signals (i.e., EEG signals Xx and Xy obtained from electrodes x and y) from specific regions of interest (ROIs) was computed through averaging the bivariate FSLs (according to FSL-wavelet methodology for the diagnosis of ADHD) (Ahmadlou and Adeli, 2010, 2011; Ahmadlou et al. 2010, 2012). ROIs were categorized into six conventional regions: frontal (F) (Fp1/2, Fz, F3/4, and F7/8), right temporal (rT) (T4/6), left temporal (lT) (T3/5), central (C) (C3/4 and Cz), parietal (P) (P3/P4 and Pz), and occipital (O) (O1/2). Then, 100 EEG signals (20 patients × 5 EEG bands) were obtained and used to extrapolate FSL within and between ROIs in each EEG sub-bands and the whole-band. A 6 × 6 functional connectivity matrix (between all ROIs) in each of the EEG sub-bands was obtained by averaging the bivariate FSL values. Five functional connectivity matrices (one for each of the four sub-bands and the whole-band) for each of the six ROIs (30 functional connectivity matrices overall) were thus obtained.

Statistical analysis

The Kolmogorov–Smirnov test was used to assess the clinical data's normal distribution (all $p > 0.2$). Repeated measures ANOVA was calculated to evaluate the significance of clinical outcome changes using the factor *time* (three levels: T0, T1, and T2). When appropriate, post hoc *t* tests were applied with Bonferroni correction for multiple comparisons.

The significance of the changes in functional connectivity within each of the EEG bands and the whole EEG frequency range (based on the FSL values) was assessed using repeated-measures ANOVA employing the factors *time* (two levels: T0 and T1) and *ROI* (six levels). The connections were more detrimental whether multivariate SLs were lower in the pre- than post-treatment. Finally, we computed the Pearson correlation coefficient as the linear bivariate correlation between the overall clinical improvement and the changes in functional connectivity according to the FSL values within each EEG band and ROI pair. The overall clinical improvement was calculated by adapting the win ratio method on pooled together clinical outcome measures (Pocock et al. 2012). The win ratio was the total number of wins (i.e., improvements in any outcome measure) divided by the total number of losses (i.e., non-improvements in any outcome measure) for each patient.

Results

All patients showed a marked degree of impairment in each administered cognitive test, as indicated by the deviation from the mean normal value for age and gender (n.v. ± SD) in each test. In particular, RCPM showed a decrease of 21% from the n.v. (33 ± 3), RSPM a decrease of 33% from the n.v. (46 ± 5), MTCM rapidity a decrease of 53% from the n.v. (3.2 ± 0.1), MTCM accuracy a decrease of 58% from the n.v. (4.5 ± 0.2), and VMI a decrease of 29% from the n.v. (102 ± 10). Furthermore, all patients showed a marked degree of anxiety as the BAI-Y score was 2% lower than the maximum value (63, n.v. ≤ 7) (Table 2). Two children were on paroxetine for anxiety.

All patients completed the VRT training without reporting any adverse event or side effects. They were provided with just VRT, so they did not practice physiotherapy, counseling, or other individualized approaches. We found a significant *time* effect concerning anxiety (BAI-Y; reduced) ($F_{(2,38)} = 43$, $p < 0.001$, $\eta^2 = 0.99$), non-verbal fluid intelligence (RCPM, improved, $F_{(2,38)} = 29$, $p < 0.001$, $\eta^2 = 0.99$; RSPM, improved, $F_{(2,38)} = 20$, $p < 0.001$, $\eta^2 = 0.99$) and visuospatial cognition (VMI; improved) ($F_{(2,38)} = 26$, $p < 0.001$, $\eta^2 = 0.99$). All such changes were maintained up to T2, as revealed by the paired *t*-tests comparing pre and post differences for the total sample (Table 2). Concerning attention, there was a significant *time* effect for the accuracy score of MTCM ($F_{(2,38)} = 7$, $p = 0.002$, $\eta^2 = 0.92$), which increased. However, this improvement was not maintained at T2. Conversely, the rapidity scores of MTCM improved only at T1, but there was a significant *time* effect ($F_{(2,38)} = 4$, $p = 0.02$, $\eta^2 = 0.683$) (Table 2).

Electrophysiological data

Patients showed a decreased functional connectivity, especially in the theta and alpha bands at baseline, as suggested by the significantly lower global (i.e., across all pair-wise channels) mean functional connectivity values ($t_{(19)} = 3.2$,

Table 2 Neuropsychological scores data before (T0), immediately after (T1), and one month after (T2) the intervention.

Domain		Cognitive tests	Time				
			T0	T1	T1–T0	T2	T2–T0
Non-verbal fluid intelligence	RCPM raw score *0–36	Median (IQR)	26 (23–29)	29 (25–34)	− 6.7	29 (25–34)	− 3.7
		Mean (SD)	26 ± 1.7	29 ± 2.6	< 0.001	29 ± 2.6	002
	RSPM raw score *0–60	Median (IQR)	31 (28–34)	34 (31–35)	− 5.4	34 (31–36)	− 3.2
		Mean (SD)	31 ± 1.7	33 ± 1.1	< 0.001	34 ± 1.4	0.004
Attention processes	MTCM rapidity scores SD *0–10	SD	1.5	1	− 2.2 0.04	0.9	− 2 0.05
	MTCM accuracy scores SD *0–5	SD	1.9	0.2	− 2.7 0.01	0.2	0.7
Anxiety symptoms	BAI-Y raw score *0–63	Median (IQR)	60 (58–62)	49 (38–55)	7.5	55 (43–61)	4.4
		Mean (SD)	60 ± 2.3	48 ± 4.9	< 0.001	55 ± 6.6	< 0.001
Visuo-spatial cognition	VMI raw score *70–118	Median (IQR)	72 (71–74)	80 (76–85)	5.9	80 (74–87)	4.1
		Mean (SD)	72 ± 1.5	80 ± 2.3	< 0.001	80 ± 3.8	0.001

Bonferroni corrected post hoc comparisons ($t_{(1,19)}$, p) at T1–T0 and T2–T0 are also reported

RCPM Raven's Colored Progressive Matrices, *RSPM* Raven's Standard Progressive Matrices, *MTCM* Modified little bell test, *BAI-Y* Beck Anxiety Inventory-Youth, *VMI* Visual-Motor Integration, *IQR* interquartile range, *SD* standard deviation

*Absolute range of scoring

$p=0.02$ and, respectively $t_{(19)}=3.4$, $p=0.02$) as compared to the entire frequency range (Fig. 2).

We found a significant *time* × *ROI* main interaction concerning omega (*time* × *ROI* $F_{(5,95)}=22$, $p<0.001$), alpha (*time* × *ROI* $F_{(5,95)}=5.7$, $p<0.001$), and theta (*time* × *ROI* $F_{(5,95)}=7$, $p<0.001$) frequency band. Specifically, there were various changes in FLS values following the intervention, which were significant within the fronto-parietal, centro-parietal, and temporo-occipital connectivity paths and within the abovementioned frequency bands (Fig. 3; Table 3). There were also other, specific-ROI differences in frequency ranges, but these were not significant (*time* × *ROI* interaction; Table 3).

Only the fronto-parietal connectivity changes in the theta range were significantly correlated with the overall clinical improvement ($r=0.759$, $p=0.0001$) (Fig. 4). Furthermore, the anxiety changes significantly correlated with fronto-parietal connectivity changes ($r=0.512$, $p=0.02$) (Fig. 4).

Table 3 Summary of *time* effect ($F_{(1,19)}$, p) for each ROI pair (those not reported were not significant) and frequency range (gamma frequency range was not significant)

	Delta	Theta	Alpha	Beta
F-P	>0.1	13, <0.001	6, 0.04	6.5, 0.04
C-P	10, 0.02	9.9, 0.02	9, 0.02	8.8, 0.02
lT-O	15, <0.001	14, <0.001	7, 0.03	>0.1
F-rT	>0.1	13, <0.001	12, <0.001	>0.1
lT-P	>0.1	13, <0.001	11, <0.001	>0.1
C-rT	12, <0.001	>0.1	11, <0.001	10, <0.001

F frontal, *rT* right temporal, *lT* left temporal, *C* central, *P* parietal, and *O* occipital

Discussion

Patients showed functional improvements in anxiety and some cognitive domains, including selective attention, visual research, visuospatial integration, after the provision of semi-immersive VRT. Given that this was a pilot, exploratory, and uncontrolled study, our results can, at most, be interpreted as hinting at a possible utility of VR for the rehabilitation of children with ASD. Despite these limitations, our data offer some innovative and promising information concerning additional ASD management strategies. Only some studies examined VRT as a treatment option for individuals with ASD, focusing on teaching emotion recognition, simple language skills (including learning vocabulary words and receptive language), training social skills, awareness, understanding, and teaching problem solving (Bernard-Opitz et al. 2001; Mitchell et al. 2007a, b; Ozonoff and Miller 1995; Herrera et al. 2008; Beaumont and Sofronoff 2008; Wainer and Ingersoll 2011). Conversely, as far as we know, this is the first study addressing cognitive functions and anxiety in children with ASD. Specifically, our primary aim was to measure non-verbal fluid intelligence, attention processes, anxiety symptoms, and visuo-spatial cognition changes at post–pre training. Former studies evaluated the transfer effects from other and primarily targeted domains (e.g., social cognition) to non-trained domains (e.g., executive functions and anxiety) (Kandalaft et al. 2013). Instead, we hypothesized that stimulating problem solving and reasoning capacities could directly improve anxiety and specific areas of cognition (including non-verbal fluid intelligence, attention processes, and visuo-spatial cognition).

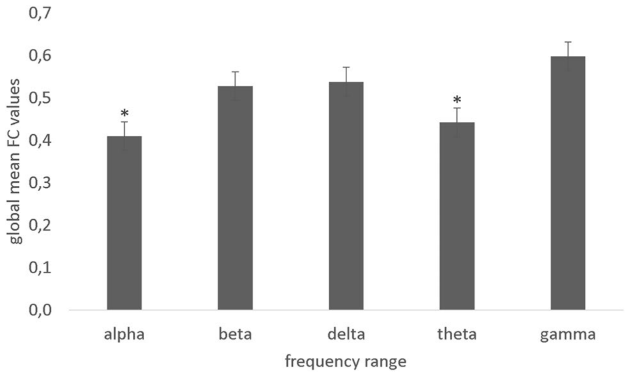
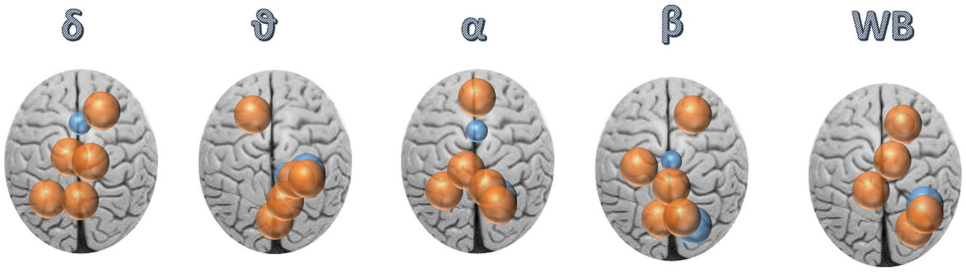


Fig. 2 Plot of the global mean functional connectivity (FC) values (i.e., across all pair-wise channels) in comparison to the whole frequency range. * denotes the significantly lower FC values for each of the frequency bands at the global level (i.e., across all pair-wise channels)

Given that an uncontrolled, open, pre-post design cannot allow us interpreting any result in terms of causality (including correlations, which are not proof of causality), we have

Fig. 3 Plot of FSL changes with respect to VRT provision. Red spheres indicate an increase in FSL values, the blue ones a decrease. The size of the spheres indicates the magnitude of FLS changes



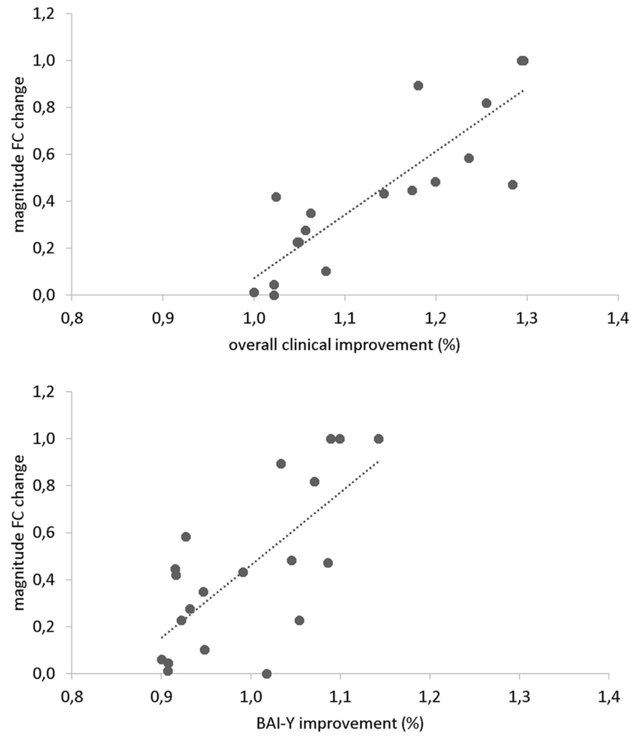


Fig. 4 The scatterplot for theta frequency connectivity changes within fronto-parietal ROI and the overall clinical improvement (as per the win ratio percentage) following VRT provision. FC functional connectivity, BAI-Y Beck Anxiety Inventory for Youth

to keep clear as hypothetical the discussion on the mechanisms subtending the changes we found. Consistently with these premises, the clinical and electrophysiological changes we found after VRT might benefit from the conjugation of complementary and ecologic virtual scenarios with repetitive, task-oriented exercises and augmented visual-audio feedback. This rehab approach permits addressing cognitive domains specifically and facilitating the dynamic of cognitive processes, such as concentration, abilities in recognition, analogic reasoning, and social skills to potentiate empathy and theory of mind (Wang et al. 2013; Mesa-Gresa et al. 2018). To this end, VRE works as a learning tool that can simulate real-life experiences safely and controllably, up to generalizing these virtual experiences to the real-world setting (Wang et al. 2013; Mesa-Gresa et al. 2018; de Moraes et al. 2020). It is noteworthy that VRE-based systems make cognitive tasks easily accessible to children with neurodevelopmental disorders, including ASD. This is due to the device's property maintaining patients' attention (providing structured and individualized activities) and addressing patients' weaknesses while potentiating patients' strengths (Mitchell et al. 2007a, b; Parsons et al. 2007). We observed that our patients were very motivated and engaged in the VRT, without significant interruptions during the rehabilitative sessions, which is an essential factor for successful cognitive rehabilitation. Another strength point of VRT is the capability to provide the patients with the knowledge of results (e.g., movement outcomes) and performance (e.g., quality of the movements), thus reinforcing the learning processes and positively impacting the cognitive outcomes (Grynszpan et al. 2014).

We also found a noticeable reduction of the anxiety levels. Addressing anxiety levels may be an important outcome in ASD management. A three-way interaction among cognitive functions, social understanding, and aggression exists with anxiety, and the association between cognition and anxiety is critically determined by social cognition ability development (Niditch et al. 2012). Therefore, anxiety reduction may strengthen the learning processes (as anxiety is known to negatively affect cognitive performance) (Wood et al. 2020), with positive results in task performance and, eventually, cognitive outcomes.

At last, we observed a change in the baseline detrimental connectivity within several frontal-parietal connections, including the frontal–central–parietal, frontal–temporal, temporal–occipital, and central–temporal paths, with particular regard to the alpha and theta frequency ranges. This represents an original finding. Such functional connectivity triggering was markedly correlated with the changes observed in sensorimotor integration, visual-spatial cognition, attention abilities, and anxiety. Given the nature of the present study, we cannot be sure of a stringent causal link between cognitive, anxiety, and connectivity improvement. Notwithstanding, we observed a significant change in the most detrimental frequency ranges and connectivity paths in the baseline resting state (Kester and Lucyshyn 2018; Weiss et al. 2018; Uhlhaas and Singer 2007; Larrain-Valenzuela et al. 2017; Chou et al. 2012) after the VRT provision. Therefore, it is likely that theta frequency modulation within several large-scale brain networks may have a significant role concerning some cognitive domains in patients with ASD. Such a frequency modulation may be in keeping with the role of theta activity concerning cognitive performance and the importance of theta deterioration in patients with ASD concerning cognitive performance (Larrain-Valenzuela et al. 2017; Wang et al. 2013; Boutros et al. 2015; Sun et al. 2012; Gandal et al. 2010; Stroganova et al. 2012; Peiker et al. 2015). Furthermore, such a frequency modulation recalls a model of dysfunctional excitatory-inhibitory coordination mechanisms among neuronal assemblies in distinct frontoparietal areas as a putative neurobiological mechanism underlying ASD (Rubenstein and Merzenich 2003; Nelson and Valakh 2015), of which theta oscillation deterioration could be a marker (Buzsáki 2010). Therefore, a reshaping of the abovementioned excitatory-inhibitory coordination mechanisms could favor a better theta-frequency information flow that, in turn, allows for an improvement in cognitive and behavioral performance (Wang et al. 2013; Boutros et al.

2015; Rubenstein and Merzenich 2003; Nelson and Valakh 2015). All of the abovementioned modifications in connectivity patterns may be achieved through specific mechanisms involved in neuroplasticity and neural repair mechanisms, consistently with cognitive-motor learning principles (Ruggeri et al. 2020; Niederkofler et al. 2015).

Strengths, limitations, and conclusions

Compared to the other VRT-based approach in children with ASD reported in the literature, our approach was designed to train subskills of cognition specifically. Furthermore, the approach we adopted, i.e., with a "coach" who could provide immediate feedback (Schilbach et al. 2013), favored the practice of online cognitive tasks (that involves an integrative understanding of social perception and reciprocal communication) rather than offline cognitive tasks (i.e., passively observing an interaction). Finally, our protocol was specifically designed for children (as we used the pediatric module of BTSN). Therefore, VRT could be promising to safely practice and rehearse cognitive skills in children with ASD in an innovative and motivating manner (at least limitedly to the approach we adopted).

However, the evidence by our study is subject to some limitations. First, the present study was uncontrolled, as we did not compare CBT vs. VRT by either a parallel-group design or a randomized cross design). Second, the study focused on a limited number of trained skills and specific outcome measures that were relatively objective (instead of adopting more subjective rating scales). These two issues limit result interpretation, as they mean that the simple time effect cannot be ruled out to explain our findings as the study design was not experimental, and it did not even contain a simple waitlist control group. Therefore, it is necessary to rule out whether a concomitant CBT may equally sustain such broad and lasting changes. Third, the sample size and the follow-up period were limited but consistent with the pilot nature of the study. Fourth, this was a single-user VRT design, so the issues of social cognition and skills remain to be further assessed. Lastly, the magnitude of our EEG findings may depend on the specific analysis procedures we adopted. We applied a generalized measurement of synchronization with full-band EEG and EEG sub-bands (namely FSL) (Ahmadlou and Adeli 2010, 2011; Ahmadlou et al. 2010, 2012) to investigate the aberrant functional connectivity in ASD, instead of employing linear measurements of functional connectivity, as formerly carried out (Rippon et al. 2007; Coben et al. 2008; Chan et al. 2011). Further research is warranted to verify whether the detrimental theta range connectivity represents or not a specific target of VRT. Besides, the generalizability of the reshaping of frontoparietal connectivity in the alpha and theta range following VRT is limited somehow by the EEG approach's intrinsic spatial resolution.

In conclusion, our results hint at a possible utility of VR for the rehabilitation of children with ASD, given that we observed functional improvements in some cognitive domains (including selective attention, visual research, and visuospatial integration) and a reduction of anxiety after VRT, which could have actively contributed to cognitive improvement. However, it will be necessary for future studies to develop consistent validations confirming the hypothesis that VRT can represent a complementary treatment to ASD cognitive rehabilitation. Similarly, whether VRT may determine a large reshape of long-range connectivity patterns, mainly in the theta range, possibly mediating the ASD-related cognitive dysfunction recovery should be further ascertained.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00702-021-02321-3.

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