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Virtual Reality Frontiers in Bipolar Disorders: A Recovery Oriented Cognitive Rehabilitation tool.

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Ph.D. Student: ***Dr. Alessandra Perra***

Supervisor ***Prof. Mauro Giovanni Carta***

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To my family and my friends

Contents

Introduction

"Disease occurs not only in the body –
in the sense of an ontological order in the great
chain of being – but in time, in place, in history,
and in the context of lived experience and the social world.
Its effect is on the body in the world"
Byron J. Good. Medicine, Rationality and Experience:
An Anthropological Perspective, 1994.

Being a mental healthcare professional means working with people, their experiences and their needs. Mental health represents a resource for individual in daily life, it allows to lead a productive life in social, economic and individual terms. To ensure an adequate and high-quality response to health needs it is necessary a good analysis of needs "Needs Assessment" [WHO, 2006]. At that same time means to wonder what is a normal and/or pathological experience? In a society where the gap and social conflicts are increasing there is a natural link with mental disorders experiences [Foucault, 2003]. To manage these complex needs is required a multiprofessional and transversal approach that take into account human evolutionary changes. In line with the bio-psycho-social model, this prospective seeks to enhance and improve social and personal resources. And in line with the global technology digitalization promote innovative rehabilitation setting is an important objective for the health services. Exploiting the potential of new technologies this creates a stimulating rehabilitation

context that facilitates the improvements of life skills. For these reasons in the *section 1* there is an explanation about what are the mental health needs object of the present thesis. The focus is on the field of psychiatric rehabilitation. Especially about the impact of the cognitive deficit in mental disorders and specifically in bipolar disorder, the main rehabilitation treatments like cognitive remediation program and the use of technology for the rehabilitation of cognitive deficits in mental health disorders.

The objective of medical and rehabilitation research is to promote health and well-being. To achieve this goal, before researchers analyze the current literature and then they develop a research hypotheses and project. Analyzing the scientific literature make possible understanding why it is crucial create new and specific sector of technological application in mental health rehabilitation. For this reason, in the *section 2,* there is an exploration of the current state of art about the application of virtual reality used for the cognitive remediation program. In particular was conducted a preliminary research project with a systematic scoping review and meta-analysis method that underlined why is important implementing studies in the field explained before.

In line with the results of the preliminary project, in the present research project object of this thesis it is hypnotized that the implementation of a fully immersive virtual reality cognitive remediation program could improve cognitive deficits in bipolar disorders. It was conducted an experimental clinical trial that involved different phases: the creation of the research protocol, the training of the professionals and the conduct of a randomized clinical trials. In *section 3* there is the explanation how was conducted the research general project.

In *section 4-5* there are the results and the discussion about the implications of this research.

The human rights approach, according to the United Nations Convention on the rights of person with disabilities [MacKay, 2006], is the value followed in all part of the present work results of three years of research experiences and the longest years of clinical experience and research in different topic.

1. Cognitive Impairment in Bipolar Disorder and Digital Innovation in Mental Health

"But it must be said from the outset that
a disease is never a mere loss or excess—
that there is always a reaction,
on the part of the affected organism or individual,
to restore, to replace, to compensate
for and to preserve its identity,
however strange the means may be"

Oliver Sacks. The man who mistook his wife

for a hat and other clinical tales, 1985.

"One day the machines will be able
to solve all the problems,
but none of them will ever be able to solve one"
Albert Einstein

1.1. Mental health, bipolar disorders and cognitive impairment

The mental health is a fundamental resource that allow people to achieve daily goals life and exercise the role of citizen of a community. Despite this information the economic and health impact of mental diseases represent a worldwide problem of public health [World Health Organization, 2001; Saxena & Setoya, 2014]. According with the Global Burden of Mental Disease, it is estimated that 13% (approximately 971 million people) of the global population has experienced an episode of a mental disorder [Vigo,

Thornicroft & Atun 2016; Global Burden Disease, 2018]. Depression in 2030 will be the disorder that will most affect the world of employment and the leading cause of absence at work. This pathological condition currently belongs to about 300 million people [Global Burden Disease, 2018]. The bipolar disorder affects about 45 million people; schizophrenia is a severe mental disorder, affecting 20 million people [Wang et al., 2007]. In particular, the WHO underline that, in the world, 10-20% of children and adolescents suffer from mental disorders. In low- and middle-income countries, 76-85% of people with mental disorders do not receive any treatment while in high-income countries it falls to values ranging between 35-50% [Saxena & Setoya, 2014; Patel et al., 2007]. Pervasive stigma and discrimination contribute, at least in part, to the imbalance between the global burden of disease attributable to mental disorders, and the attention these conditions receive [Lasalvia et all., 2013; Thornicroft et al., 2009].

Bipolar disorder is a range of chronic disease characterized by recurrent episodes of mania/hypomania, depression and periods of euthymia (mood dysregulation); dysregulation in sleep/wake rhythm and medical and psychiatric comorbidities [Balanzá-Martínez et al., 2010]. The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-5) define bipolar disorders as a group of mental disorders that cause extreme fluctuation in a person's mood, energy and ability to function. Community surveys found that the lifetime prevalence of Bipolar disorder ranges between 1% to 2.4%, although the methodology of published studies may underestimate its prevalence [Carta & Angst, 2016]. The disease is highly disabling due to its early onset, severity and chronicity: it is considered one of the leading causes of disabilities in the world [Carta et al., 2021], accounting for 7.0% of all DALY's due to mental and substance use disorders [Ferrari et al., 2016; Merikangas et

al., 2011; Whiteford, 2013]. Bipolar disorders are a category that includes: bipolar I disorder that is a manic-depressive disorder; bipolar II disorder consist of a manic-depressive disorder typically less severe; and cyclothymic disorder that is a cyclic disorder that causes brief episodes of hypomania and depression. Alongside effective symptoms, cognitive impairment is believed to be a core component of bipolar disorder [Rampino et al., 2021], and in the long-term bipolar disorder was found to be associated with a high risk of dementia [da Silva et al., 2013; Musat et al., 2021]. Another central element in BD is the alteration of the circadian rhythm including social and behavior rhythms present from the genesis of the illness [Carta et al., 2021; Steardo et al., 2019] and the comorbidity with anxiety symptoms [Cullen et al., 2021; Albert et al., 2008].

Cognitive impairment is a fundamental component of mental disorders that contribute to psychosocial disabilities and limits the recovery process in psychiatric rehabilitation [Harvey, 2014; Vita et al., 2021]. Cognitive deficits are present in most disorders like psychosis, mood, anxiety, personality and eating disorders [Sharma & Antonoya, 2003; Gold et al.2016; Tchanturia, Davies & Campbell 2007; Douglas et al., 2018; Vita et al., 2018], but in schizophrenia is a core symptom [Peyroux & Franck, 2014] and also approximately 60% of people with bipolar disorder have neurocognitive impairment [Solé et al., 2017; Carta et al., 2021]. In general, cognitive deficits negatively impact personal, social and work occupational functioning [Douglas et al., 2018; Schaefer et al., 2013; Keefe et al., 2011; Shamsi et al., 2011] and they are a barrier to achieve a good quality of life and an independent living [Brissos, Dias & Kapczinski 2008; McGurk et al., 2007; Piras et al., 2022]. CI could be defined as a complex relationship of selective hypo and hyperactivity networks linked to attention, verbal fluency, memory and executive function [Thorsen, Johansson & Loberg 2014; Li

et al., 2020]. The principle neuropsychological deficits in BD are in attention, processing speed verbal learning/memory, memory and executive functions including cognitive flexibility, inhibitory control and working memory [Musat et al., 2021; Kurtz & Gerraty, 2009; Torres et al., 2010].

Overall, approximately 40% to 60% of people that experienced one or more episodes of bipolar disorder have neurocognitive impairment [Solé et al., 2017]. Neurocognitive dysfunctions may be found in premorbid stages, before the disease onset [Martino et al., 2015], in the early course of the illness [Lee et al., 2014], and during the euthymia phase [Bortolato et al., 2015]. Poor cognitive performance impacts negatively on occupational and social functioning [Douglas et al., 2018], increases the hospital admissions, affects direct/indirect healthcare related costs [Keefe et al., 2012], hinder the benefits of psychotherapy [Martinez-Aran & Vieta, 2015], and represent a barrier to achieve an adequate social and occupational functioning and a good quality of life [Brissos, Dias & Kapczinski 2008]. Despite the grown attention paid to identify and treat cognitive impairment in bipolar disorder, evidence is still lacking on effective interventions aiming to minimize cognitive symptoms in these patients [Ott et al., 2021]. Others core symptoms of BD like depressive/maniac symptoms improve thanks to psychopharmacological treatments and in add-on with psychosocial interventions [American Psychiatric Association, 2002; Goodwin et al., 2016]. Cognitive deficits do not improve with psychopharmacological treatments and get worse over time [Martinez-Aran & Vieta, 2015]. Only Lithium was deemed to have an indirect positive effect on cognition in bipolar disorder, but other drugs used in the treatment of bipolar disorder entail cognitive side-effects related to extrapyramidal, sedative, anticholinergic, and blunting mechanisms [Vieta, 2009].

1.2. Psychiatric rehabilitation interventions for cognitive impairment

Among others, cognitive remediation programs (CR) and the physical activity are psychiatric and neurological rehabilitation interventions that showed to be effective in improving cognition, as the main outcome [Vita et al., 2021; Thérond et al., 2021; Dandil et al., 2020; Firth et al., 2017; Brasure et al., 2018], as well as to improve social and personal functioning outcome [Montemagni et al., 2021; Sancassiani et al., 2017]. At the same time, physical activity and CR were proven to be effective to prevent cognitive decline in healthy populations [Carta et al., 2021 (2); Young et al., 2015]. Cognitive, social and personal functions are important mental health outcomes to achieve a real impact in daily life. Indeed, CR programs are interventions based on a behavioral training that aims to improve cognitive domains (memory, attention, executive functions, social cognition and metacognition) with the goal of obtaining the persistence of the cognitive strategies and their generalization in daily life [Wykes & Spaulding, 2011]. CR was found to be effective in the treatment of cognitive deficit in people with psycho-social disorders such as psychosis, mood disorders, anxiety disorders, personality and eating disorders [Elgamal et al., 2007; Bellani et al., 2019; Choi & Medalia, 2005; Tchanturia, Davies & Campbell 2007; Gold et al., 2016; Vita et al., 2018; Cella et al., 2017; Grynszpan et al., 2011]. There is also evidence of its effectiveness in neuropsychological disorders such as dementia, MCI, behavioral disorders [Alves et al., 2013; Rodakowski et al., 2015]. Currently the application methods of CR include a set of heterogeneous interventions: computerized, paper, in individual or group set [Velligan, Kern & Gold 2006].

Synthesizing to prevent and treat cognitive decline there are initial evidence suggests that CR and physical activity may exert protective effects [Carta et al., 2021 (2)],

and to treat CR has been found to be effective in the treatment of various psychosocial disorders (including bipolar disorder) to improve the cognitive and social-occupational domains, although the evidence base is still inconclusive [Choi & Medalia, 2005; Ott et al., 2021; Tsapekos et al., 2020]. Indeed The CR traditional methods for BD has poor quality preliminary evidence due to the high risk of bias precisely for the sample size and drop outs rate [Tsapekos et al., 2020].

1. 3. Digital innovation and virtual reality technology in health services

In the Digital Era, the mental health care system is exposed to a technological revolution [Freeman et al., 2017]. The high request for health care services, the decreasing costs and increasing convenience and power of digital media and new technologies are affecting how we provide and access care [Valmaggia et al., 2016]. The artificial intelligences are used for different health services, in prevention activities including screening instruments and health monitoring, in treatment activities including training and triage activities [Milne-Ives et al., 2020].

One of the increasing technological instruments are an extension of games like Virtual Reality (VR). Virtual reality is an important tool that facilitates learning and / or the enhancement of different skills, thanks to the ability to make learning experiences real and ecological compared to traditional intervention techniques [Freeman D. et al., 2017]. VR includes some interactive video gaming, virtual environments, and, commonly, a multisensory experience to merge real and virtual worlds [Mesa-Gresa et al., 2018]. VR environments elicit sense of presence and stimulates real time cognitive, emotional, behavioral, and physiological responses to real time situations [Parsons et al., 2011]. This sense of being there like in a real-life situation has led researcher to describe VR environments as ecologically valid [Seidel & Chatelier, 1997]. For this

reason, researchers and clinician try to design realistic scenarios that can be used to assess and improve the individual daily skills in order to respond to health needs of people who have experienced with psychosocial disabilities [Slater, 2004; Skivington et al., 2021]. Current research on the clinical use of VR software has led to positive results in cardiovascular, neurological and musculoskeletal rehabilitation [Bird et al., 2017; Albiol-Pérez et al., 2017].

1.4. Virtual reality instruments in mental health

In line with the WHO innovation objective in mental health and the global digitalization [World Health Organization, 2014] are increasing the use of technologies for the assessment and treatment mental and neurodegenerative disorders [Freeman et al., 2017; Park et al., 2019]. Virtual Reality (VR) due to the fact that engage people in a playful and ecological scenario facilitates the generalization of the trained skills [Costa et al., 2019; Tsapekos et al., 2020; Lima et al., 2020; Robert et al., 2014; Manera et al., 2016]. VR has garnered significant attention as a cost-effective tool for the treatment of mental health problems [Freeman et al., 2017; Riva, Wiederhold & Mantovani 2019]. It is currently used for the assessment of cognitive and motor deficits, for the psychotherapy of anxiety and phobia disorders and for social skill improvement in psychosis disorders [Adams et al., 2009; Elkind et al., 2021; Iriarte et al., 2016; Liu et al., 2019]. VR is actually considered effectiveness like add-on intervention in psychosocial rehabilitation [Park et al., 2019]. In particular for social cognition training like social/occupational skill training in people with schizophrenia or autism [Liu et al., 2019]; in add-on to psychotherapy of anxiety, phobia and post-traumatic syndrome disorders [Powers & Emmel Kamn, 2008; Maples-Keller et al., 2017; Norr, Smovenski & Roger 2018]; for the assessment and treatment of cognitive deficits in people with

Mild Cognitive Impairment (MCI), Alzheimer's disease and dementia [Lasaponara et al., 2021; García-Betances et al., 2015; Zakzanis et al., 2009; Cotelli et al., 2019]. The CR interventions in full immersive VR program are increasingly used and to date in the scientific literature there are preliminary evidence for CR program with fully immersive VR used in the treatment of mental disorders [Jahn et al., 2021; Riva et al., 2020; Qian, McDonough & Goa 2020].

2. Preliminary research project: virtual reality and cognitive remediation state of art

2.1. Background and aims

The CR programs in fully immersive VR are still increasing, they are focused only on MCI and schizophrenia and to data there are preliminary evidence with poor methodological quality [Jahn et al., 2021; Riva et al., 2020; Qian, McDonough & Gao 2020]. Although there is some preliminary evidence, the quality of the studies is still low and there are also many points of uncertainty. Source of concerns are the variability of the methods (duration and frequency) [Jahn et al., 2021], the variability in the level of virtual immersion [Sayma et al., 2020] and the reference framework for the development of complex intervention [Skivington et al., 2021]. The last one it is a very important aspect in the development of rehabilitative interventions in order to achieve a real impact in daily life [Jahn et al., 2021; Skivingstone et al., 2021].

The first aim of this study is to scope the published literature of the fully immersive VR used for the CR program in psychiatric rehabilitation treatments in adult in order to describe the different methods intervention components. Furthermore, highlighting gaps in the framework of the development intervention of CR in fully immersive VR, in order to understand if there is the explanation of the hypothesis/outcomes/methods and coherence with the games used and cognitive domains. In general, our goal is to map the current state of knowledge and to identify gaps in the existing literature that merit further research [Rotenberg, Anderson & McKenzie 2020]. To our knowledge, in the literature there are three systematic review [Jahn et al., 2021; Riva et al., 2020; Qian et al., 2020] that assessed the effectiveness of randomized clinical trials, and no meta-analysis has been carry out. For this reason, the

second aim is to evaluate the effectiveness of the current evidence on the effect of clinical outcomes of CR program with fully immersive VR in people with psycho-social disabilities with a meta-analysis.

2.2. Methods

Search strategy

This study used an established scoping review methodology [Arksey & O'Malley, 2005] and followed the reporting guidelines outlined in the PRISMA reporting guidelines [Page et al., 2021] and its extension for Scoping Reviews [Tricco et al., 2018]. The articles to be included were identified through the keys words "Virtual Reality"[All Fields] AND "Mental Health"[All Fields]; "Virtual Reality" [All Fields] AND "Cognitive Remediation" [All Fields], "Virtual Reality" [All Fields] AND "Cognitive training" [All Fields] searched in the electronic databases PubMed and Embase and in the Cochrane Library, with temporal limit (from January 1, 2010 until April 30, 2022). The search was updated on September 30, 2022. Two independent reviewers extracted data, screened the articles for title/abstract and full-text, removed the duplicates, and screened the reference lists of eligible articles and relevant systematic reviews published on the topic, the grey literature was searched on ClinicalTrials.gov. The authors of the primary studies were contacted in case of unavailability of the studies. In case of disagreements in the steps elicited above, those were solved by a third author. Each step of this systematic review was discussed and peer-reviewed by two researchers. As this is a scoping review, its protocol was not eligible for the registration in PROSPERO. All the authors (psychiatrists, medical doctors and psychiatric rehabilitation technicians) are expert in the field of the contents and/or methods of the review.

Eligibility criteria and data extraction

We included only randomized controlled clinical trials that met PICO model identified for this study and the eligibility criteria: studies had to be (1) randomized controlled clinical trials; (2) conducted from 2010 onwards; (3) reported in English languages, and (4) focused on the use of the cognitive remediation in fully immersive VR program for the treatment of psychosocial disabilities (mental disorders). The data extraction form included: author, location; sample size/type of study, type of sample, control, type of intervention, measurement, fully immersive VR, duration of the intervention, drop outs, main findings. Were excluded: (1) duplicates; (2) argument not relevant (not mental disorders, not cognitive remediation program, not fully immersive virtual reality program); (3) not available after that we contact the author for the study request; (4) not RCT. A summary of the search strategy is shown in Table 1.

Database searched	Pubmed Embase Cochrane	
Limits	Languagge: english only. Years: last 12 years (2022-2010) Geographic: no limits	
PICOS	**Population**	People (adult, any gender) with psychosocial disabilities included mild cognitive impairment/alzheimer and dementia
	Intervention	Studies that used cognitive remediation program in fully immersive virtual reality
	Comparison	No restrictions
	Outcome	Cognitive and clinical effectiveness, methods used
	Study Type	Only randomized clinical trials
Exclusion	Duplicates, not rct, articles not in english or not available, not cognitive remediation in fully immersive virtual reality program and not adult population with mental diseases	

Table 1. Search strategy

Quality assessment of the studies

To assess the risk of bias in the studies, we used the checklist for quality assessment of controlled intervention studies that was validated by the US National Heart Lung and Blood Institute [Goff et al., 2014]. For each item, a low risk of bias was assigned when the study met the expected criterion; a high risk of bias was assigned when the study did not meet the expected criterion; some concerns of bias were rated when the study did not report information about the criterion or we cannot determine whether the criterion was met. Overall, a high quality of the study means that the majority of criteria met little or no risk of bias; an acceptable quality means that some criteria had some flaws in the study with some concerns for risk of bias; a low-quality means that most criteria had significant flaws relating to key aspects of study design. The graphic presentation of the risk-of-bias assessment summary plot was created with the "robvis" package running in R [McGuinnes & Robyis, 2019].

Meta Analysis

Studies that were enough homogeneous in design were included in a meta-analysis. Overall, 8 studies on fully immersive VR for CR in subjects with MCI were surveyed. Effectiveness was estimated by comparing baseline data with data at the end of treatment [Morris, 2008]. The effect size was expressed as the bias-corrected standardized mean change score (Hedges' g) and computed so that a positive value indicated a favorable outcome (e.g. improvement in cognition) (Hedges & Olkin, 1985). More specifically, a positive effect size implicated that change in scores was greater in the treated than in the control condition. According to Cohen’s rule-of-thumb, effect size was interpreted as small when around 0.20; moderate when around 0.50; and large when ≥ 0.80 [Cohen, 1988].

When a study included more than one measure for the same outcome, all relevant measures' effect sizes were aggregated in a single score considering the measures correlations. If this information was not reported, a default correlation between measures was set at 0.5 and dependent effect sizes were aggregated [Cooper, Hedges, & Valentine, 2009].

Heterogeneity was assessed with Cochran's Q and I2 statistics (Huedo-Medina et al., 2006). Heterogeneity was deemed negligible when I2 < 30%; moderate for values between 30 and 60%; substantial for 75–100% values (Higgins et al., 2003). Egger's regression test could not be used because studies were less than ten (Egger et al., 1997). Thus, publication bias was evaluated by using the trim-and-fill procedure (Duval & Tweedie, 2000). The trim-and-fill method assumes that the most extreme results are not published and recalculates the effect size by the imputation of missing studies to produce a symmetrical funnel plot.

The radial plot was used to assess model adequacy (Galbraith, 1994). For each study, the observation of a large standardized residual (above 2, as a rule of thumb) suggests that the study does not fit the assumed model (i.e., it may be an outlier).

The results of both fixed- and random-effects models were reported. Between studies variance and variance of the effect size parameters across the population were estimated with the $\tau 2$ statistics using the Empirical Bayes estimator, with Knapp and Hartung adjustment for random-effects model. We calculated the 95% CI for the heterogeneity using the Q-Profile method, to assess the extent and relevance of heterogeneity (Viechtbauer, 2010). The significance level threshold was set at $p < 0.05$.

Meta-analysis was carried out with R (version 4.2.2) (R_Core_Team, 2022) using the following packages: 'metafor' (version 3.8-1), 'meta' (version 6.0-0) and 'MAd' (version 0.8-3).

2.3. Results and discussion

Search results and study selection

The flow diagram (Fig. 1) shows the selection and screening process of the included articles. The initial studied screened included 4905 from database and 7 from manual/citation searching articles. Of these, 1834 duplicates as well as 553 articles from database searches and 6 articles from manual/citations searching were excluded because of they did not match with the inclusion criteria. After title, abstract screening and eligibility assessment, 11 studies that met the inclusion criteria were included.

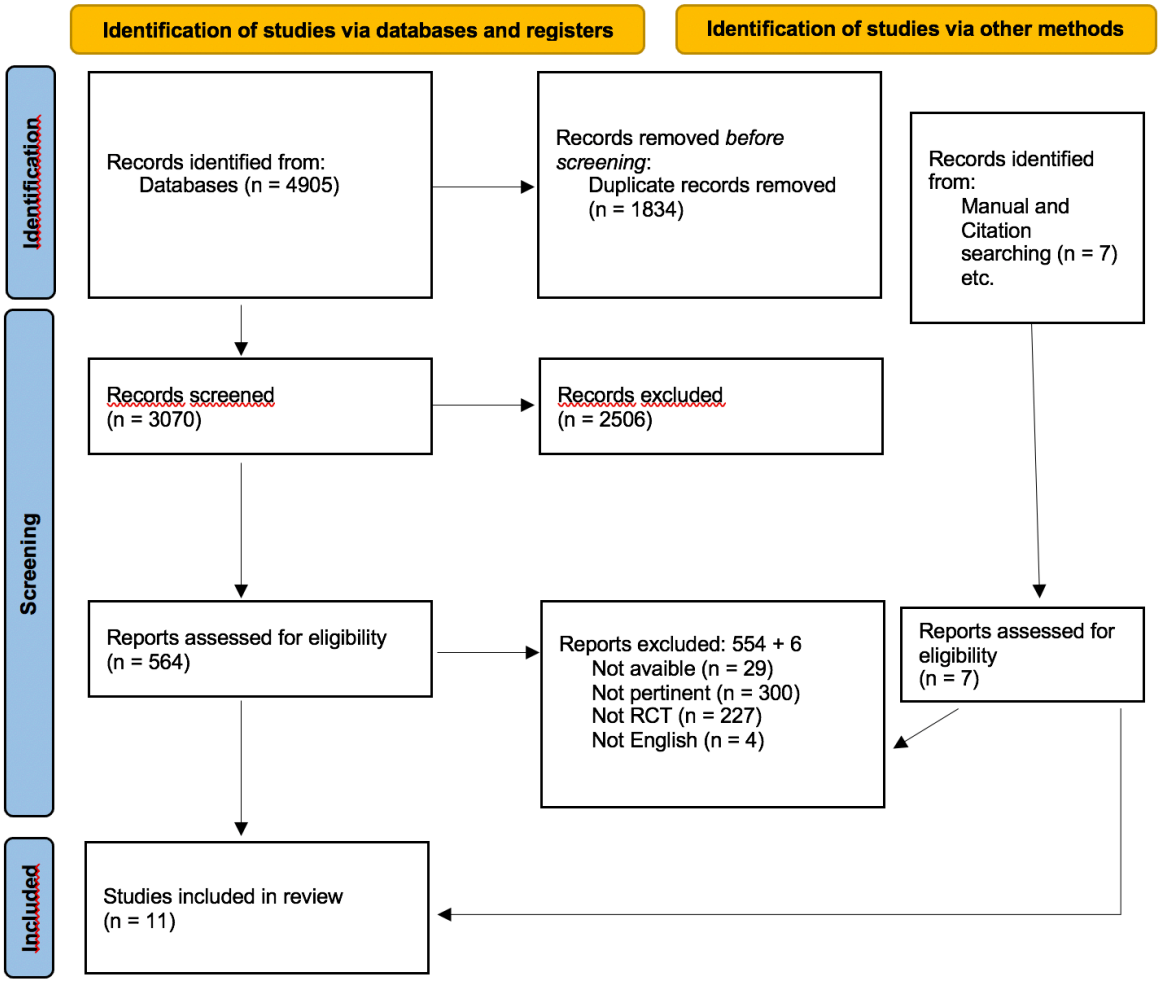


Fig. 1 PRISMA 2020 flow- diagram

Descriptions of studies

Among the selected articles all involved fully immersive VR-CR program. Nine studies included people with Mild Cognitive Impairment (MCI), seven of this were defined as Randomized Clinical trial [Kim et al., 2021; Kang et al., 2021; Maeng et al., 2021; Liao et al., 2019; Thapa et al., 2020; Liao et al., 2020; Hwang et al., 2017] and two of this as pilot study [Kwan et al., 2021; Park et al., 2020]. One included people with Mild Dementia [Zając-Lamparska et al., 2019] and it is a pilot study; and one included people with Schizophrenic Disorder defines as Controlled Clinical Trial [La Paglia et al., 2016]. Six study showed statistical difference in clinical outcomes between experimental and control group. Specifically Kang et al. 2021 for quality of life outcomes, for cognitive outcomes (attention, memory and executive function, global cognition); Maeng et al., 2021 for depressive symptoms, for cognitive outcomes (languages, memory, executive function); Liao et al., 2019 and Thapa et al., 2020 for cognitive outcome (executive function); Liao et al., 2020 for daily functioning outcome; and Hwang et al., 2017 for cognitive outcomes (memory). Two studies showed a statistically significant difference before and post treatment for the experimental group but not between groups on global cognition [Kwan et al., 2021; La Paglia et al., 2016] and on attention [La Paglia et al., 2016]. Three studies didn't show any difference between time and/or groups, two of this involved people with MCI [Kim et al., 2021; Park et al., 2020] and one people with Mild dementia [Zając-Lamparska et al., 2019]. The majority of the studies used a VR-CR program that trained all cognitive domains in a mixed ecological scenario (house room and open space city) [Kang et al., 2021; Thapa et al., 2020; Liao et al., 2020; Kwan et al., 2021; Park et al. 2020]; two studies that trained all cognitive domains in an unique ecological scenario (supermarket) [Kim et al., 2021; Maeng et al., 2021]; one used trained executive function in a shop scenario [Liao et al., 2019]; one that trained attention function in an open space scenario (park,

lake, valley) [La Paglia et al., 2016]; and two did not specify the cognitive domains trained and the type of scenario [Hwang et al., 2017; Zając-Lamparska et al., 2019].

Among the six studies, that showed statistically differences between experimental and control group after treatment [Kang et al., 2021; Maeng et al., 2021; Liao et al., 2019; Thapa et al., 2020; Liao et al., 2020; Hwang et al., 2017], the intervention method used was an overage of 60 minutes session and an average of 7 weeks with 3 sessions per week.

Among the other five studies the intervention method used was an overage of 50 minutes session and an average of 6 weeks with almost 2 session per week [Kim et al., 2021; Kwan et al., 2021; Park et al., 2020; Zając-Lamparska et al., 2019; La Paglia et al., 2016]. Only Kwan et al., 2021specifies the framework for the development intervention. Table 2 show a synthesis of the characteristics of the included studies.

Study	**Location**	**Sample size/ Type of study**	**Type of sample**	**Control**	**Measurement**	**Fully Immersive VR**
Kim et al., 2021 (1)	South Korea	31 EG 25 CG; RCT	MCI/Cognitively normal individuals	Cognitive training sessions using VR	CRI; CERAD-NB	YES
Kang et al., 2021 (2)	South Korea	25 EG 20 CG; RCT	MCI both EG and CG	Usual therapy such as pharmacotherapy	MMSE; DST; TMT A-B; K-BNT; SVLT; COWAT; SCWT; GDS; AES; PANAS-P/N; QoL-AD; ROCFT; VRSQ	YES
Zając-*Lamparska et al., 2019 (3)*	Poland	75 EG 75 CG; Pilot Study	Mild dementia/Healthy older adults (age 60–89)	VR-based cognitive training using the GRADYS game	DSST; DS; BDT; CTT; TA (d2); BVRT; AVLT; ROCFT; ACE-III; BNT	YES
Maeng et al. 2020 (4)	South Korea	31 EG 25 CG; RCT	MCI/Cognitively normal individuals	Virtual reality-based cognitive therapy program	CERED; KQOL-AD; GDS	YES
Liao et al., 2019 (5)	Taipei (Taiwan)	21 EG 21 CG; RCT	MCI; both EG and CG	Combined Physical (resistance, aerobic and balance exercises) and Cognitive Training (different tasks in ecological scenarios)	TMT; SCWT	YES

Kwan et al., 2021 (6)	Hong Kong (China)	9 EG 8 CG; Pilot Study	MCI and physical frailty	Non-VR motor-cognitive training program: Physical task: cycle on the ergometer; Cognitive training: four cognitive games on a tablet computer	MoCA; VRSQ	YES
Park et al., 2020 (7)	South Korea	12 EG 12 CG; Pilot Study	amnestic MCI (aMCI), both EG and CG	Waiting list	K-MMSE; SGDS-K; SNSB-D; DST; SCWT; WFT	YES
Thapa et al., 2020 (8)	Busan (South Korea)	34 EG 34 CG; RCT	MCI; both EG and CG	Educational program on general health care (8 sessions - 30/50min)	MMSE-DS; NCGG-FAT; TMT A & B; DSST	YES
Liao et al., 2020 (9)	Taipai (Taiwan)	21 EG 21 CG; RCT	MCI, both EG and CG	Combined physical and cognitive training: -physical exercises included resistance, aerobic and balance task; -cognitive task were trained during the physical exercises	MoCA; EXIT-25; AVLT; IADL	YES
La Paglia et al., 2016 (10)	Palermo (Italy)	9 EG 6 CG; RCT	Schizophrenic disorders, both EG and CG	Integrated Psychological Therapy (IPT)	MMSE; FAB; TMT A/B/B-A; ToL; WCST	YES
Hwang et al., 2017 (11)	Daegu (South Corea)	12 EG 12 CG; RCT	MCI, both EG and CG	Traditional occupational therapy for memory and balance ability	VST; WCT	Not specified

Study	**Type of intervention**	**Duration**	**Drop out**	**Main results**
Kim et al., 2021 (1)	VR cognitive training program: train memory, attention and executive functions. Supermarket scenario..	50–60 min; 2 times a week for 4 weeks	EG 9/31 (29%); CG 3/25 (12%)	No statistically significant differences between groups after intervention
Kang et al., 2021 (2)	VR cognitive training: train multi domain cognitive (attention, executive function and memory, working memory; mathematical calculations, visuospatial function,verbal memory, visual memory, processing speed and working memory). Multiple games.	20-30 min; 2 times a week for 4 weeks	EG 2/25 (8%); CG 2/20 (10%)	Statistically significant difference between groups in improving quality of life (QoLAD), attention, memory and executive function (DST; SVLT; TMT:SCWT)
Zając-*Lamparska et al., 2019 (3)*	VR-based cognitive training: divided in four modules (attention, memory, language, and visuospatial processing). The storyline of each module scenario consists of tasks inspired by daily life. Each module has three difficulty levels. GRADYS game.	45-60 min; 2 times a week for 4 weeks	ES 48/75 (64%); CG 3/75 (4%)	Statistically significant only for the control group in improving cognitive function
Maeng et al. 2020 (4)	VR-based cognitive therapy program: train multi domain cognitive (memory, attention and executive function). In each session, items were evenly and randomly selected. There were four levels of	50-60 min; 2 times a week for 4 weeks	EG 7/31 (22%); CG 2/25 (8%)	Statistically significant difference between groups in improving depressive symptoms (GDS), memory, language and

	difficulty from level 1 (four items to buy) to level 4 (seven items to buy); participants chose the difficulty level according to their performance in each session. Supermarket scenario.			executive function (CERED)
Liao et al., 2019 (5)	VR based Physical and Cognitive training: Physical tasks: simplified 24-form Yang-style Tai Chi, resistance exercise, aerobic exercise, other functional VR daily activities; Cognitive tasks: IADL based scenarios involving orientation, working memory, attention, planning and task switching	60 min; 3times per week for 12 weeks	EG 3/21 (14,28%); CG 5/21 (23,81%)	No statistically significant differences between groups after intervention cognitive function like executive function (TMT)
Kwan et al., 2021 (6)	VR simultaneous motor-cognitive training: Cognitive tasks: 8 tasks in ecological virtual scenarios involving visuospatial, calculation, memory, reaction time and attention; 2 difficulty levels. Motor training: traveling through the virtual world cycling on the ergometer	30 min; 2 times a week for 8 weeks	EG 1/9 (11,11%); CG 2/8 (25%)	No statistically significant differences between groups after intervention. Positive change in global cognition in the experimental group (MOCA)
Park et al., 2020 (7)	VR cognitive tasks: 6 cognitive games that involved attention, perceptual space skills, numerical ability, perceptivity, logical ability and memory; different level difficulty (i.e., high, middle or low)	30 min; 2 times a week for 12 weeks	NO DROP OUT	No statistically significant differences between groups after intervention
Thapa et al., 2020 (8)	VR program: four series of games to aid different cognitive functions: memory, attention and processing speed. EG was also involved in an educational program on general health care	100 min; 3 times per week for 8 weeks	EG 1/34 (2,94%); CG 1/34 (2,94%).	Statistically significant differences between groups in improving executive function (TMT; DSST)
Liao et al., 2020 (9)	VR-based physical and cognitive training: -physical exercises included simplified 24-form Yang-style tai chi, resistance exercises, aerobic exercises and functionally oriented tasks (Kinect system, developed by Tano and Long-Good); -cognitive training included IADL activities (VIVE system, developed by the HTC company)	60 min (40 min of VR Cognitive training; 20 min of VR physical training); 3 times a week for 12 weeks	EG 3/21 (14,28%); CG 5/21 (23,8%)	Statistically significant differences between groups in improving daily functioning (IADL)
La Paglia et al., 2016 (10)	VR attention training: hierarchical sequences of tasks; settled in 3 ecological virtual environment, Park (sustained attention task), Valley (selective attention task), Beach (selective and divided attention task)	90 min; 1 time a week for 10 weeks	Not specified	No statistically significant differences between groups after intervention. Positive change in global cognition (MMSE) and attention (TMT) in the experimental group
Hwang et al., 2017 (11)	Not specified	30 min; 5 times a week for 4 weeks	Not specified	Statistically significant differences between groups in improving memory (VST)

Table 2. Synthesis of the characteristics of the included studies

Assessment of the risk of bias

Studies suffered from some bias in several key aspects of study design. In particular, quite never the statistical power was enough to detect the expected differences or assure replication of the study; randomization was often poor; problems were detected in the

percentage of dropouts at the end of the study and in the adherence to the treatment of participants. Overall, studies with a low risk of bias were about 25% of the total, all others were rated with some concerns of bias or of low quality (Fig. 2).

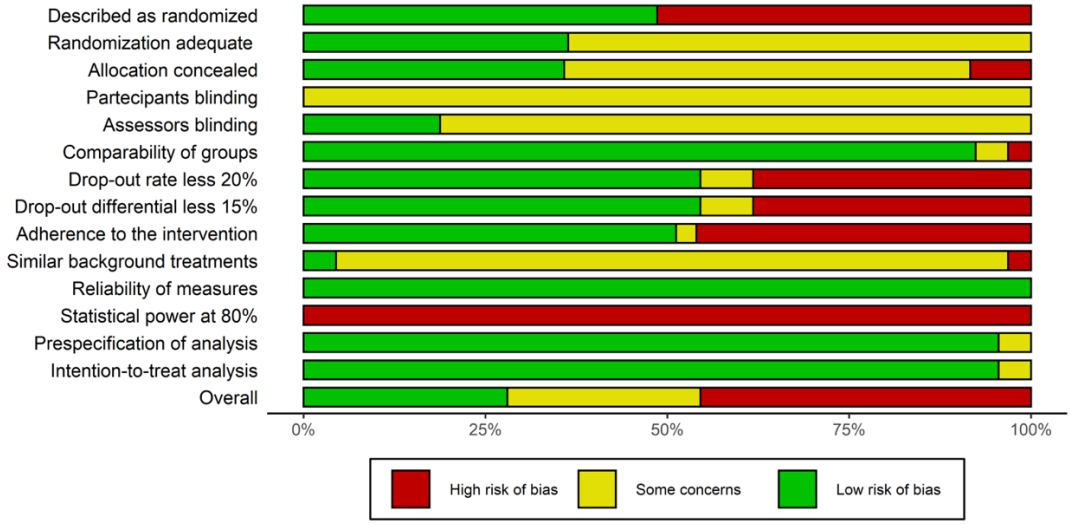


Fig. 2 Risk of bias summary plot according to the National Institutes of Health Quality Assessment of Controlled

Intervention Studies. Quality assessment of the included studies on cognitive remediation through fully immersive virtual reality in adults with psychosocial disabilities.

Synthesis of the Meta-Analysis

Five main outcomes were reconstructed by the studies: executive functions, measured with COWAT Test, Stroop Test, TMT, C-PRAXIS, SDST, EXIT-25; attention, measured with Digit Span Test, TMT, WCT; memory, measured with SVLT, WLM, Digit Span, CVVLT, VST; language, measured with K-BNT, VF, WFL, CVVLT; global cognition, measured with MOCA, MMSE, CERAD. The measures were assigned how declared the authors in the studies. Table 3 summarizes the results of the meta-analysis, which is further detailed hereafter.

Results of meta-analysis	Trim-and-Fill

Outcome	K	N	Model	Hedges'g	95% CI		z	p	Q	p	I^2	k added	New estimate	95% CI		p
Executive functions	6	252	FE RE	-0.13 -0.15	-0.34 -0.49	0.07 0.18	-1.30 -1.19	0.19 0.29	7.73	0.17	35 %	1	-0.11	-0.37	0.14	0.40
Attention	6	242	FE RE	-0.15 -0.15	-0.34 -0.32	0.04 0.02	-1.53 -2.24	0.12 0.07	2.33	0.80	0%	0				
Memory	5	176	FE RE	0.45 0.45	0.21 0.18	0.69 0.73	3.71 4.63	0.0002 0.001	2.58	0.63	0%	0				
Language	4	152	FE RE	0.46 0.48	0.20 -0.13	0.71 1.09	3.52 2.51	0.0004 0.087	5.80	0.12	48 %	0				
Global cognition	5	183	FE RE	0.36 0.41	0.14 -0.11	0.57 0.94	3.28 2.17	0.0011 0.096	11.02	0.03	64 %	1	0.41	-0.11	0.94	0.10

Table 3. Effects of fully immersive virtual reality for cognitive remediation in people with Mild Cognitive Impairment.

FE = Fixed-effects model; RE = Random-effects model.

Executive functions

Treatment did not improve executive functions (Figure 2). No outlier was detected based on the radial plot, and just one study was added by the Trim-and-Fill procedure, with no impact on the estimated effect (Table 2 and Figure A2). Cochran's Q test did not detect heterogeneity, however, heterogeneity was estimated negligible to moderate based on I2 (95%CI = 0% to 74%).

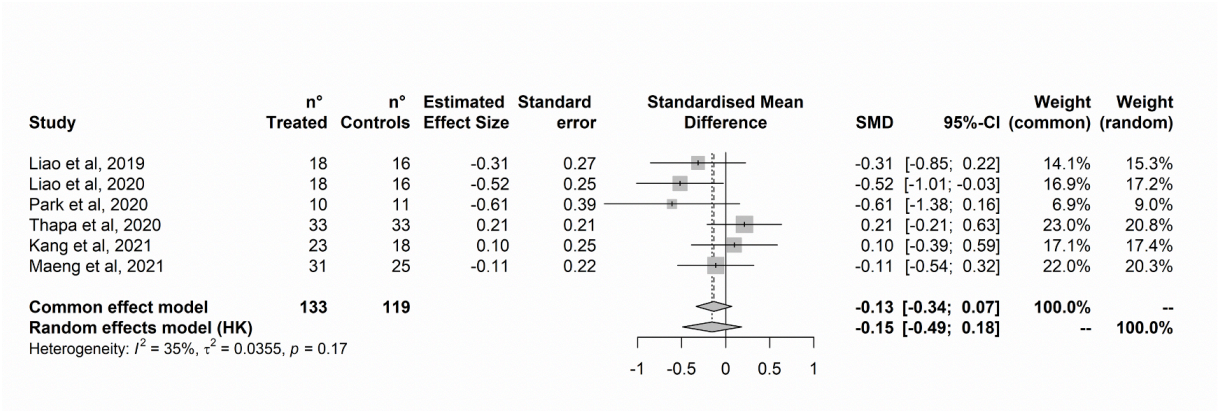
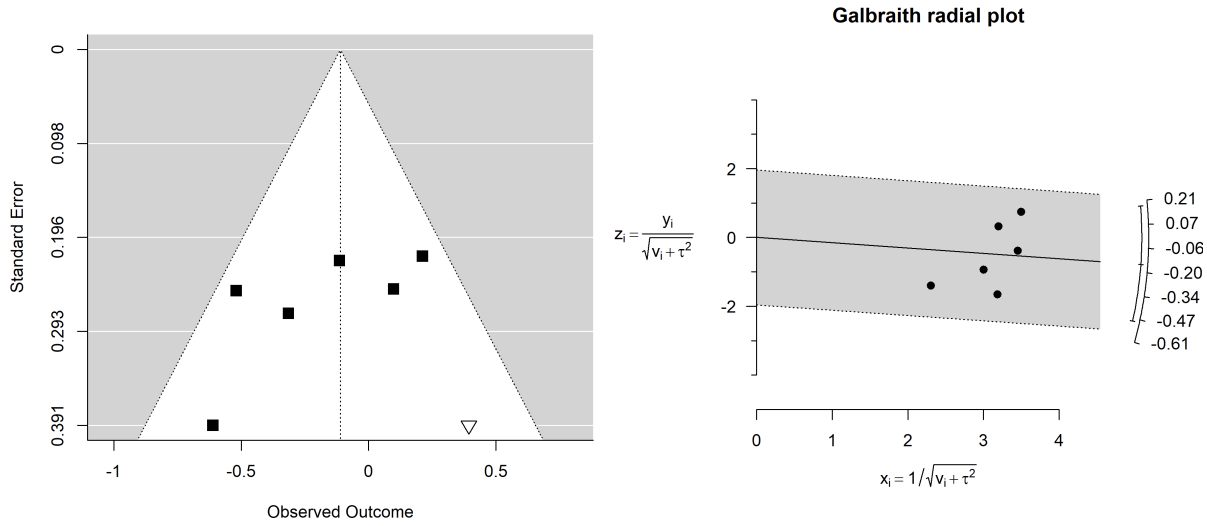


Fig. 2 Executive Function



Fig_A2_EX

Attention

Treatment did not improve attention (Figure 3). No outlier was detected based on the radial plot and no study was added by the Trim-and-Fill procedure (Table 2 and Figure A3). Cochran's Q test did not detect heterogeneity, however, heterogeneity was estimated negligible to moderate based on I2 (95%CI = 0% to 74%).

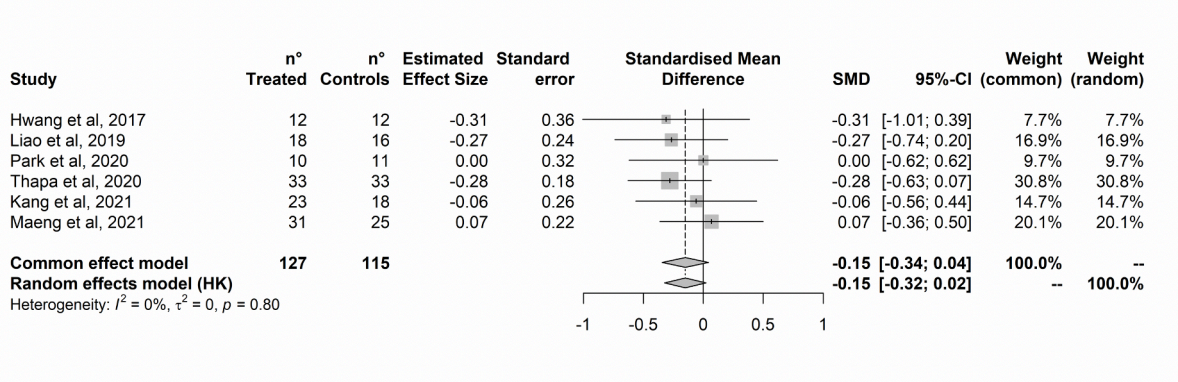
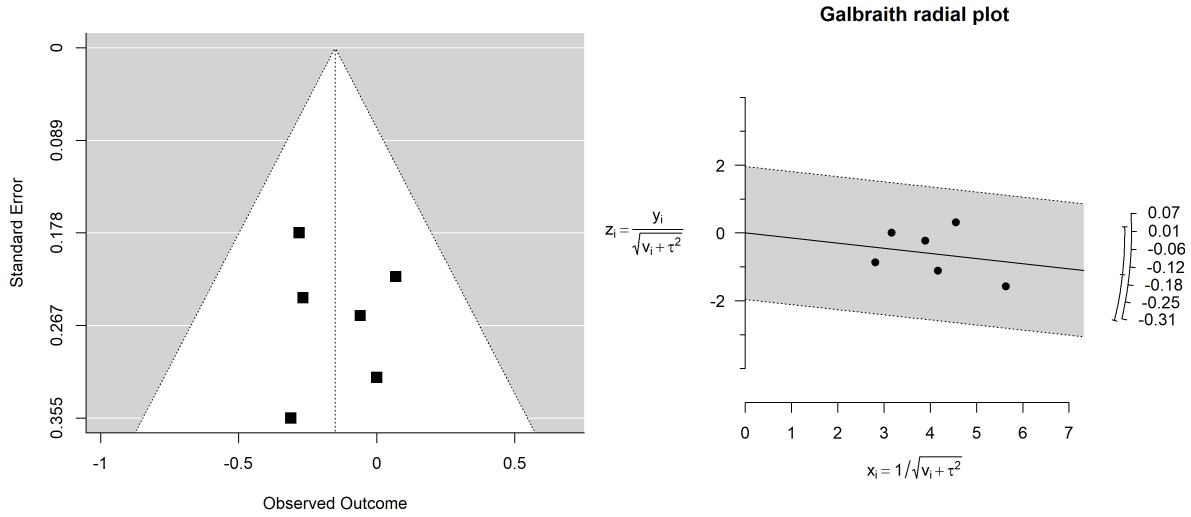


Fig. 3 Attention



Fig_A3_ATT

Memory

Treatment improved memory in both the fixed-effects and the random-effects model (Figure 4).

Effect size ranged from small to moderate. No outlier was detected based on the radial plot and no study was added by the Trim-and-Fill procedure (Table 2 and Figure A4). Cochran's Q test did not detect heterogeneity, however, heterogeneity was estimated negligible to substantial based on I2 (95%CI = 0% to 79%).

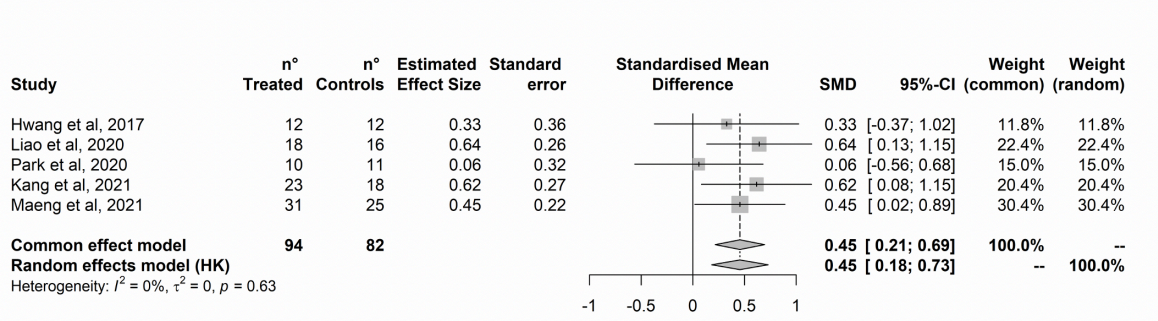
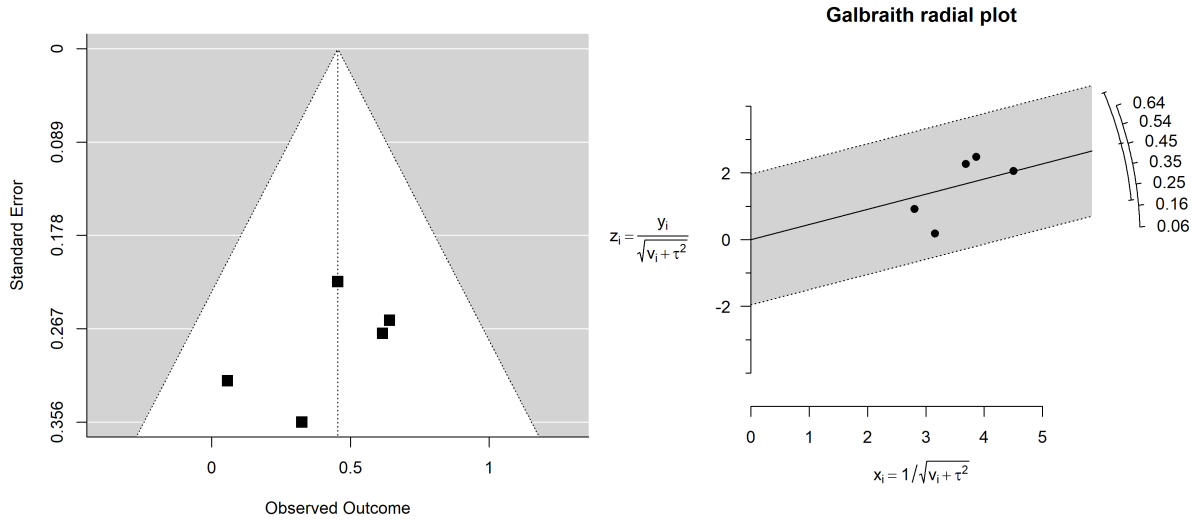


Fig. 4 Memory



Fig_A4_MEM

Language

Treatment improved language according to the results of the fixed-effects model but not based on the random-effects model (Figure 5).

No outlier was detected based on the radial plot and no study was added by the Trim-and-Fill procedure (Table 2 and Figure A5). Cochran's Q test did not detect heterogeneity, however, heterogeneity based on I2 was moderate (48%), ranging from negligible to substantial (95%CI = 0% to 83%).

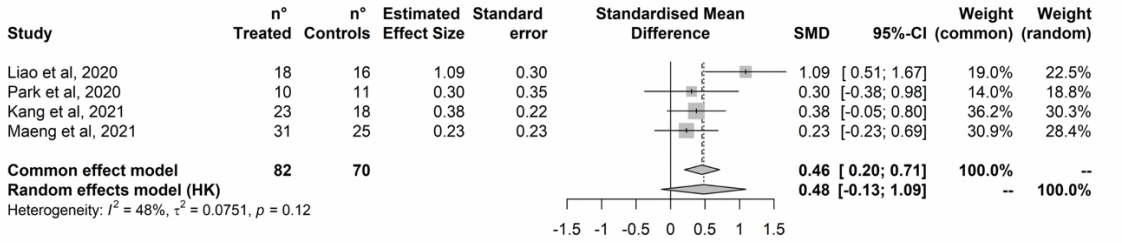
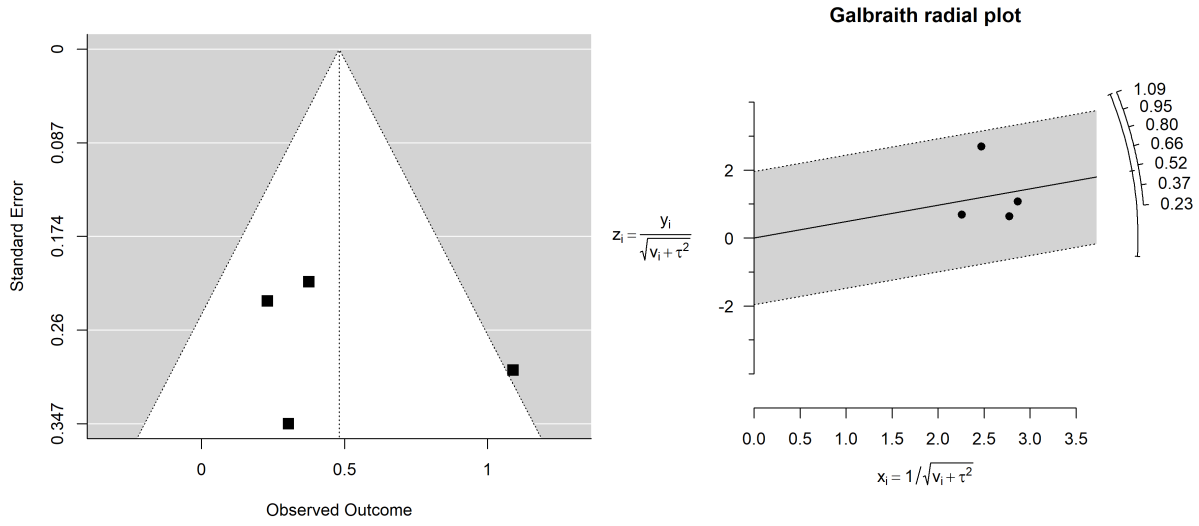


Fig. 5 Language



Fig_A5_LANG

Global cognition

For global cognition, too, treatment resulted effective according to the results of the fixed-effects model but not based on the random-effects model (Figure 6).

No outlier was detected based on the radial plot, and just one study was added by the Trim-and-Fill procedure, with no relevant impact on the estimated effect (Table 2 and Figure A6).

Cochran's Q test detected heterogeneity (Q = 11.02; df = 4; p = 0.03), and heterogeneity based on I2 was moderate (64%), ranging from negligible to substantial (95%CI = 4% to 86%).

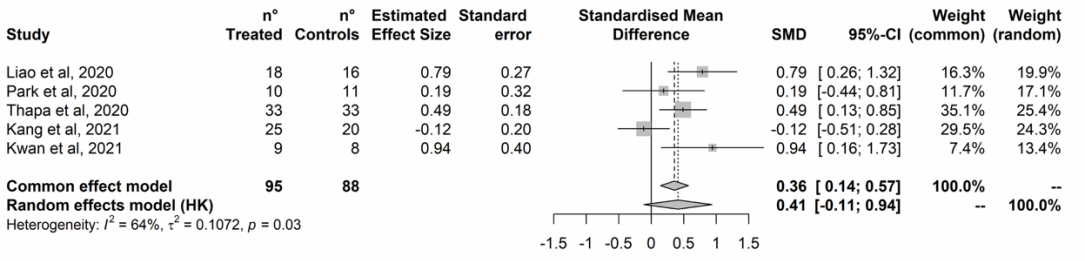
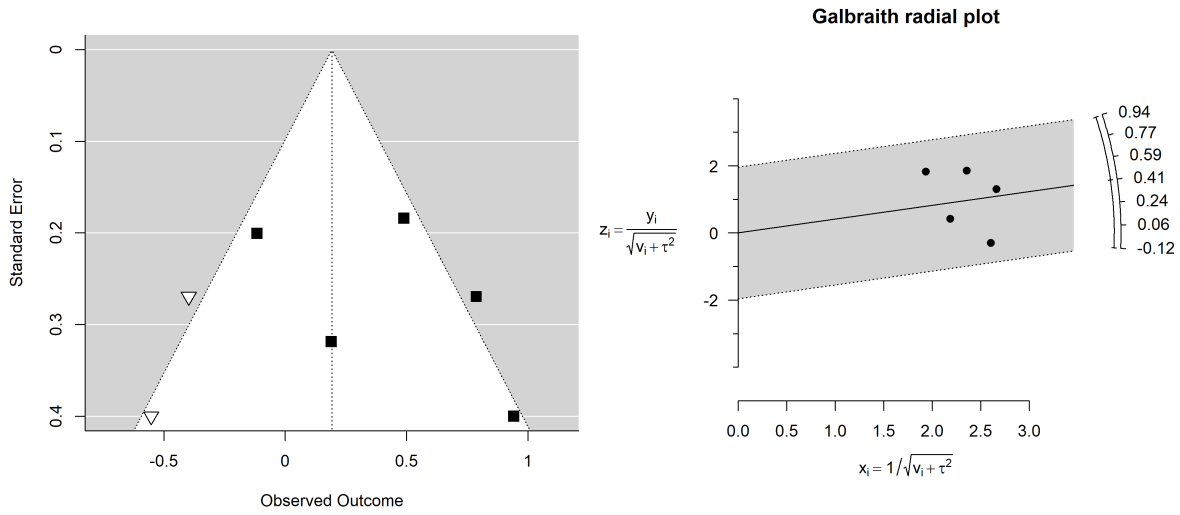


Fig. 6 Global Cognition



Fig_A6_GLOBAL COGNITION

Discussion

The present study, in our knowledge, is the first meta-analysis about the use of fully immersive VR-CR program for people with psycho-social disabilities. The systematic review suggested that VR has a positive impact on cognitive and functional outcomes in people with mental disorders and neurodegenerative disorders. The studies included in the systematic review involved people with MCI, one Mild Dementia and one Schizophrenic Disorders, in general there were fewer studies with fully immersive VR-CR program that involved people with different mental disorders not eligible. The studies reported a statistically significant difference between groups in cognitive functions (attention, memory, executive function, languages and global cognition) [Kang et al., 2021; Moeng et al., 2021; Liao et al., 2019; Thapa et al., 2020; Hwang et al., 2017], in daily functioning [Liao et al., 2020], in depressive symptoms outcome [Moeng et al., 2021], and in quality of life [Kang et al., 2021]. Compared with the previously systematic review and meta-analysis that used traditional CR methods and not fully immersive VR [Tulliani et al., 2022; Simon et al., 2012] our suggested not

only a cognitive functions improvement but also a general clinical improvement. The meta-analysis involved only people with MCI showed a positive effect in clinical cognitive outcomes specifically to memory, language and global cognition. It was not possible analyzed other general clinical outcomes due to their heterogeneity. In our study also we scope the gap between effectiveness on clinical outcomes and the methods used in CR program with fully immersive VR. Mainly, a higher weekly frequency with long term duration, an ecological scenario and multiple cognitive tasks trained are associated with a better clinical outcome, but often the instrument it is not clearly described. With short-term intervention the positive impact is related only to memory outcomes, with long-term interventions is related to different cognitive outcomes. The majority of the studies did not specify the framework for the development intervention that is the explanation of the coherence between the hypothesis/outcomes/methods and the games used in the VR program and the cognitive domains trained. In line with other review [Jahn et al., 2021; Riva et al., 2020; Qian et al., 2020] the results of these review showed a poor quality of the studies for instance, in terms of sample size and risk of bias, there are a large variability of the used methods like frequency and the type of cognitive tasks trained. In add on this study included only fully immersive VR, the precedent review included a range from not immersive to fully immersive.

Implication for research and clinics

Actually, it is necessary more RCT that study the effectiveness of fully immersive VR-CR program for people with different psycho-social disabilities; a better methodological quality; more details about the negative effect of the use of VR; and also more details for the reference framework for the development of a complex intervention. In particular the studies should better explain the hypothesis/outcomes/methods (for each

session) and coherence with the games used and cognitive domains for the repeatability of the intervention. Understanding effectiveness in relation to the methods used is an important aspect to create in the future a golden standard method of fully immersive VR-CR program for mental health rehabilitation. And a robust framework for the development of the intervention it is necessary in order to achieve rehabilitative goal as first the generalization in the daily life of the performed tasks and also to the reproducibility of the intervention in the clinical services.

Strengths and limitations

This study used a comprehensive search strategy that made possible the inclusion of several studies on CR in fully immersive VR. However, many studies had poor quality. In particular, the dropout rate is not often specified and there is a risk of bias for the statistical and sample power. More studies with adequate quality and including different clinical applications in different populations rather than only MCI, are needed.

3. The Research Project

3.1. Background and aims

To date, the methodological quality of preliminary evidence is poor [Jahn et al., 2021; Riva, Cavedoni & Stramba-Badiale 2020; Qian, McDonough & Gao 2020]. To our knowledge, no studies on the use of fully immersive VR as a CR intervention aiming to improve the cognitive and personal and social functioning processes of people with bipolar disorder, are available. Our hypothesis is that a fully immersive VR-based CR intervention could be feasible and clinically effective in people that have experienced BD.

Primary aim is to assess the feasibility of a confirmatory trial to evaluate the effectiveness of the use of a VR tool for a CR intervention for the treatment of cognitive deficits in people with bipolar disorder.

Secondary aim is to evaluate a preliminary effectiveness in terms of intervention's safety, participants' satisfaction, and clinical outcomes.

3.2. Methods

3.2.1. Study Design

This study is a randomized-controlled (two-arm) cross-over clinical feasibility trial. This study follows the reporting guidelines according to the CONSORT extension for feasibility studies [Eldridge et al., 2016]. After the experimental group (A) received the VR-based CR intervention and the control group (B) received conventional treatment for three months, group A underwent a one-month washout period, which was followed by a phase of conventional treatment, whereas group B received the VR-based CR intervention and became the experimental group.

50 people were randomized to assess the feasibility outcome, evaluating recruitment and retention rates. To date, an effective methodology in terms of sample size cannot be established yet, as the evidence in this field of research is limited [Ott et al., 2021; Bellani et al., 2019]. Therefore, the aim of this study is to verify the effectiveness of the use of a VR tool for a CR intervention for the treatment of cognitive deficits in people with bipolar disorder.

3.2.2. Participants, randomization, blinding and ethical aspects

This trial's target population included people with bipolar disorder recruited at the Consultation and Psychosomatic Psychiatry Center of the University Hospital of Cagliari (San Giovanni di Dio Civil Hospital), who met the following inclusion criteria: 1) age ranging from 18 to 75; 2) diagnosis of bipolar disorder according to DSM-IV [American Psychiatric Association, 2000]; 3) both sexes. The participants that met these inclusion criteria or their guardians were provided with an informed consent and signed it before the intervention started. Subjects that did not meet the inclusion criteria, or that were in manic/depressive phases, or had a diagnosis of epilepsy or serious eye diseases, were excluded due to the risk associated with the excessive stimulation of virtual reality.

Eligible participants were randomized into two groups. The experimental group received VR based CR program and. The control group consisted of patients put on a waiting list that received conventional treatment, consisting of a psychiatric consultation with or without psychotherapy. The random allocation sequence was generated using a computer-generated randomization list at the University of Cagliari. Randomization was carried out by a biometrician who was not aware of the participants' identities and was not involved neither in the assessment nor in the analysis process.

Neither the participants nor the mental health workers of the project could be blinded due to the nature of the intervention.

This study is registered on ClinicalTrials.gov (NCT05070065). The study was conducted in accordance with ethical principles of the Declaration of Helsinki [W Medical Association, 2013]. Before inclusion, written informed consent was obtained from all patients (or, alternatively) by their guardians. This protocol was approved by the Local Independent Ethics Committee with the number Prot. PG/2020/21681. Comprehensive information about the nature and purpose of the study was provided before participants accepted to participate. Participants were also provided with information about the possibility of interrupting the program at any time. The contact details of the coordinators were made available to participants who wished to have more information on the study. Subjects enrolled in the study were given information about data protection and privacy law. The data of the study was entered in a database to maintain confidentiality in accordance with local laws on Data Protection [Gazzetta Ufficiale, 2003; Reg UE, 2016]. An operator of the Psychiatry Center associated an alphanumeric code to the name before delivering the database to those involved in statistical analysis. The list of correspondences between individual names and alphanumeric code will remain in the exclusive availability of the guarantor (Psychiatry Center). This procedure will guarantee the complete anonymization of the data.

3.2.3. Technology device and intervention

The experimental group was involved in a fully immersive VR-based CR, recovery-oriented program. We used the “CEREBRUM” software, one of the most recent VR-implemented CR tools in psychiatric rehabilitation, conceived and designed by "PRoMIND - Services for mental health Srls" (Rome) in association with "IDEGO -

Virtual Psychology" (Rome). CEREBRUM is a fully immersive Virtual Reality software, created by clinicians and experts specialized in cognitive rehabilitation (psychiatric rehabilitation technicians and psychologists). It is compatible with the Oculus Go virtual reality viewer, a CE-marked device. The CEREBRUM App, which allows users to immerse themselves in virtual scenarios that simulate everyday reality (home and urban scenarios). Characteristics of the device: stereoscopic video production via GoPro Fusion camera 18 MP, 30 FPS; stereoscopic video made with 3K resolution mode and 60 FPS refresh rate; spherical photos taken with the 18 megapixel mode and 360 pixels of field of view; realization of software structure and user interface through Graphic Engine in real time, Unity 3D; logic programming in C; compatible with Stand Alone Virtual Reality Headset, Oculus Go; download via Store Oculus and activated by purchase of activation keys.

Offers 52 exercises of varying difficulty: 22 exercises are part of the Memory and Learning Module, 10 exercises are part of the Cognitive Estimates Module and 20 exercises are part of the Attention and Working Memory Module. During the VR exposure, while exploring the 360° scenario, the participants, who could not directly interact with the virtual environments, answered the health worker's questions. The increasing degrees of difficulty allowed the clinician to adapt the intervention to the

participants' functional diagnosis and to their residual abilities, creating a stimulating learning context in which the exercises were neither too easy nor too difficult.

The intervention consisted of 24 sessions of 45 minutes, divided into 2 sessions per week over 3 months. Each session was structured as follows: ➢Reception, psychoeducation and orientation to the tool; ➢Exercise psychoeducation; ➢Psychoeducation to the function to be learned during the exercise; ➢Generalization phase, in which the function and its importance were explained in the participants' life context (bio-psycho-socio-cultural approach based on cognition); ➢Execution of the exercise in VR with positive and corrective feedback; ➢Post-exercise comment; ➢Second exercise that used the same method mentioned above (the maximum duration of the exposure to Virtual Reality was 15-20 minutes); ➢Final comment; ➢Homework, intended as practical suggestions to be implemented by the patients in their daily life. Sessions included an Attention and Working Memory exercise plus one Memory / Learning exercise or one Cognitive Estimation exercise. In some sessions, depending on the participant, the session and the operator's assessment, an extra exercise of any type could also be done

A multidisciplinary team (psychiatric rehabilitation technicians, psychologists, and a psychiatrist) was involved in the intervention. The methods used to structure the sessions were replicable and allowed to promote a human-centered approach [Gagnon et al., 2021], to accomplish cognitive outcomes and improvements in clinical and personal functioning, and to achieve the generalization of the skills trained according to the new framework for developing complex intervention [Skivington et al., 2021], thanks to the

coherence with the theorical background in terms of health needs, the type of intervention and the real health outcomes.

3.2.4. Outcomes

The primary outcome was measured as the proportion of patients recruited among those considered eligible and as the proportion of patients completing the trial intervention among those included.

Secondary outcomes included: 1) the intervention's safety (number of adverse events and severe adverse events); 2) Patients' satisfaction*;3)* Clinical Effectiveness in improving cognitive process, personal and social functioning, levels of perceived anxiety, quality of life, emotional awareness and psychopathological symptoms, thanks to a person-centered and recovery-oriented rehabilitation intervention [Saxena, Funk & Chisholm 2013], in which the participants could enhance their skills and obtain a global improvement in their health and well-being.

3.2.5. Data Collection

After the patients were screened and enrolled at the Consultation and Psychosomatic Psychiatry Center of the University Hospital of Cagliari (San Giovanni di Dio Civil Hospital), a personal data sheet was created to collect data. The secondary outcomes were evaluated through a self-report questionnaire for the assessment of the presence of possible side effects and patients' satisfaction (Appendix 1), whereas the indicators of the remaining secondary outcomes were evaluated through a standardized evaluation tool validated in Italian and used in psycho-social research. In order to prevent learning effects, we administered different versions of the assessments for retests. Participants were assessed before the treatment, after the end of the intervention and 6

and 12 months after the end of the intervention by the same evaluators who were blinded to the groups that they had been assigned to.

The cognitive evaluation was performed using the Rey Figure Test to evaluate the visuospatial function (Appendix 2) [Cafarra et al., 2002 (1)], the Matrix test (Appendix 3) [Spinner & Tognoni, 1987], the Rey's Words Test Immediate recall (Appendix 4) [Carlesimo et al., 2002; Caltagirone et al., 1995], the Forward Digit Span (Appendix 5) [Orsini et al., 1987; Bisiacchi et al., 2003] and the Trail Making Test part A (Appendix 6) [Giovagnoli et al., 1996] to evaluate the attention function; the Rey's Words Test Delayed recall (Appendix 4) [Carlesimo et al., 2002; Caltagirone et al., 1995], the Backward Digit Span (Appendix 5) [Orsini et al., 1987; Bisiacchi et al., 2003] and the Test of the Tale (Appendix 7) [Novelli et al., 1986 (1); Carlesimo et al., 2002] to evaluate the memory function; the Phonological and Semantic Verbal Fluency Test in the two versions (Appendix 8) [Caltagirone et al., 1995; Novelli et al., 1986 (2)] to evaluate the language function; and the Digital Symbol Substitution Test (Appendix 9) [Amodio et al., 2002; Amodio et al., 2008], the Trail Making Test part B (Appendix 6) [Giovagnoli et al., 1996], the Stroop Test (Appendix 10) [Cafarra et al., 2002 (2)], the Frontal Assessment Battery - FAB (Appendix 11) [Dubois et al., 2000] and the test of Cognitive Estimates (CET) in the two versions (Appendix 12) [Scarpina et al., 2015; Della Sala et al., 2003] to evaluate the executive function. All the instruments are validated in Italian and were used for the research.

The general clinical evaluation was performed using: 1) the SF-12, Short Form Health Survey with 12 items (Appendix 13) [Ware, Koninski & Keller 1996], a self-administered scale which investigates the following dimensions of quality of life and well-being: vitality, physical function, physical pain, perception of general health, mental health, physical and emotional health, work functioning and social role; 2) the TAS-20

Toronto Alexithymia Scale (Appendix 14) [Bagby, Parker & Taylor 1994], a self-administered scale that evaluates the level of emotional awareness; 3) the Self-Rating Scale (SAS), a self-administered scale (Appendix 15) [Zung, 1971] that evaluates perceived anxiety levels regardless of diagnosis; 4) the Patient Health Questionnaire - PHQ-9, a self-administered scale (Appendix 16) [Rizzo et al., 2000], which evaluates depressive symptoms; 5) the Health of The Nation Outcome Scale - HoNOS (Appendix 17) [Wing et al., 1998], that evaluates general, personal and social functioning and clinical performance; 6) the Italian validated version of the Biological Rhythms Interview of Assessment in Neuropsychiatry - BRIAN (Appendix 18) [Moro et al., 2014], an interview consisting of 18 items that investigates 4 main areas related to the dysregulation of circadian rhythms (sleep, activity, social rhythms and nutrition).

The *sample variables* included gender and age; marital status; educational qualification; previous and current employment status; past and current organic physical pathologies; previous and current mental health diagnosis; and drugs in use.

3.2.6. Data Analysis

The statistical data were analyzed using the software SPSS (version 21).
Frequencies (percentages) or mean±standard deviation were used for descriptive statistics about sociodemographic variables such as “sex” and “age”, as well as about the level of satisfaction with the experimental intervention and the occurrence of side effects. Chi square test and one-way ANOVA were used to test the homogeneity between experimental and control groups regarding “sex” and “age” distributions.
A series of repeated-measure ANOVA was performed, one for each of the outcomes considered, to compare means between the intervention and non-intervention groups over time (pre- and post-intervention), with Bonferroni’s correction. The normality

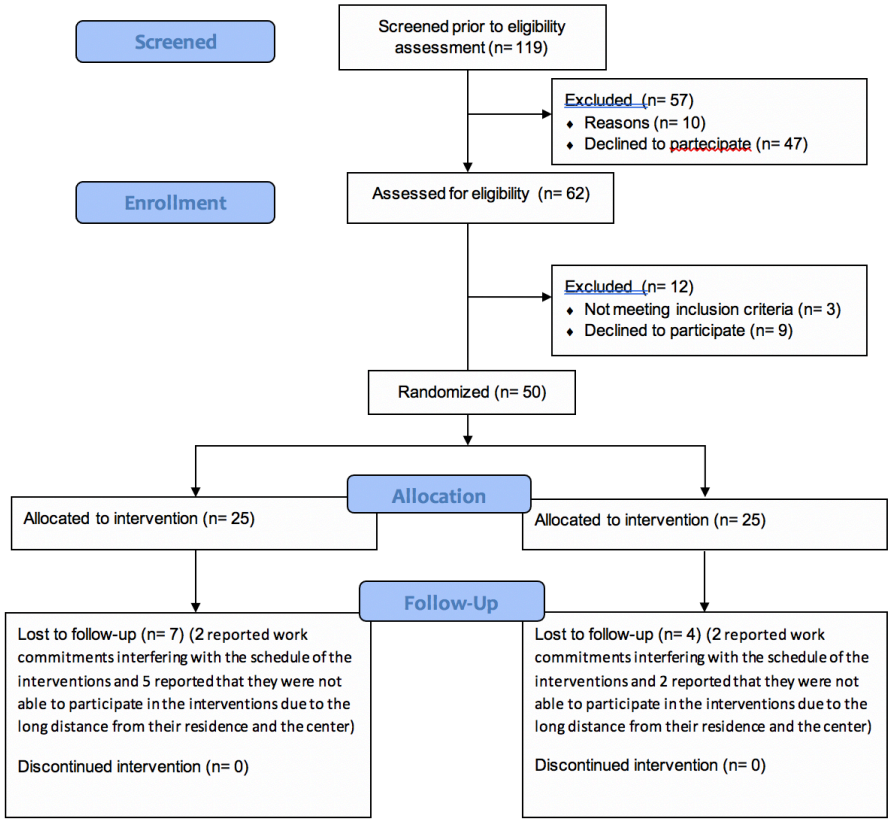
assumption of the dependent variables was tested as sphericity (i.e.: variances of the differences between all combinations of related groups must be equal), with Mauchly's test.

4. Results

119 people with psycho-social disabilities treated at the Psychosomatic Psychiatry Center of the University Hospital of Cagliari (San Giovanni di Dio Civil Hospital) were contacted. 62 people were enrolled and 12 were excluded after evaluation, as 3 of them did not meet the inclusion criteria and 9 declined to participate. 50 participants were randomized (Figure 1): 25 of them were assigned to group A and received the intervention first; the remaining 25 participants were assigned to the control group (group B) and were initially put on a waiting list. They later crossed over and received the experimental intervention. Thanks to the cross-over method, we could include 50 people in the experimental group, and 25 subjects in the control group. The participants that did not complete at least 50% of the sessions were considered dropouts. Out of the 25 participants of the group A, 18 completed all the sessions and 7 dropped out, due to work commitments interfering with the schedule of the interventions or to the long distance from their residence and our Psychiatry Center, where patients from different parts of the Sardinia Region are treated. Out of the 25 participants of the group B, 21 completed all the sessions after the cross-over and 4 dropped out for the same reasons that led the participants of the group A to drop out. No one dropped out while on the waiting list. Overall, at the end of the intervention, the experimental group sample and the control group (waiting list) consisted of 39 and 25 participants respectively (Figure 1). The analysis of the primary outcome revealed that, in terms of acceptability and tolerability, around 20% of subjects dropped out and less than 45% of the people that were contacted did not respond or refused to participate in this randomized clinical trial. As regards the secondary outcomes, we evaluated the occurrence of side effects after the VR exposure

and the satisfaction with the intervention through a Likert scale (ad hoc questionnaire) from 1 (low satisfaction) to 5 (excellent satisfaction).

Figure 1. CONSORT flow diagram extension for feasibility study.



48.7% of the participants of the experimental group (19/39) considered the intervention excellent in terms of experience, whereas 28.2% and 23.1% considered it great and good respectively (Table 1).

Table 1. Frequencies of Satisfaction

Levels	Counts	% of Total	Cumulative %
3 Good	9	23.1 %	23.1 %
4 Great	11	28.2 %	51.3 %
5 Excellent	19	48.7 %	100.0 %

In terms of side effects during the first fully immersive VR exposure session, 76.9% (30/39) of participants did not report any side effects. The remaining 23.1% reported the following side effects: emptiness/disorientation, nausea/feeling of emptiness, headache, disorientation, dizziness, tremors/nausea/blurred vision/dizziness, nausea, vertigo and sense of unreality (Table 2). At the end of the intervention, 87.2% of participants did not report any side effects. As showed in Table 3, the remaining 12.8% reported the following side effects: nausea (two participants), daze (two participants) and a feeling of emptiness/unreality (one participant). In general, most participants did not experience any side effects and the side effects that were reported were not severe.

Table 2. Frequencies of Side_Effects_T0

Levels	Counts	% of Total	Cumulative %
NO	30	76.9 %	76.9 %
Feeling of Emptiness - Disorientation	1	2.6 %	79.5 %
Nausea, Feeling of Emptiness	1	2.6 %	82.1 %
Headache	1	2.6 %	84.6 %
Disorientation	1	2.6 %	87.2 %
Dizziness	1	2.6 %	89.7 %
Tremors, Nausea, Blurred Vision, Dizziness	1	2.6 %	92.3 %
Dizziness	1	2.6 %	94.9 %
Vertigo	1	2.6 %	97.4 %
Sense of Unreality	1	2.6 %	100.0 %

Table 3. Frequencies of Side Effects T1

Levels	Counts	% of Total	Cumulative %
NO	34	87.2 %	87.2 %

Nausea	2	5.1 %	92.3 %
Daze	2	5.1 %	97.4 %
Feeling of Unreality Emptiness	1	2.6 %	100.0 %

As a secondary outcome, we also evaluated the cognitive and the general clinical functioning impairment of the experimental group that received the fully immersive VR-based CR intervention and compared it with that of the control group that received conventional treatment. Both groups were balanced for sex and age (Table 4). Statistically significant differences between the experimental and the control group emerged after the intervention both in terms of the cognitive outcome and the general clinical functioning outcome. In general, all cognitive domains improved after the VR-based CR intervention (Table 5).

Table 4. Baseline demographic characteristics

		GROUP EXP CONTR		
		EXP	CONTR	TOT
SEX	F - N (%)	32 (64)	18 (72)	50 (66,7)
	M - N (%)	18 (36)	7 (28)	25 (33,3)
AGE	N	50	25	75
	Mean ± SD	47,76 ± 13,34	46,16 ± 13,63	47,23 ± 13,37

Table 5. Cognitive Test-Descriptive Analysis (Mean and Standard Deviation)

	VR/CR GROUP (N=39)		CONTROL GROUP (N=25)	
	PRE	POST	PRE	POST
Fig. Rey Immediate (Vis.Sp.)	28,74 ± 8,43	30,92 ± 6,68	28,16 ± 10,20	28,12 ± 8,65
Matrix (Attent.)	1,95 ± 1,38	2,38 ± 1,46	2,52 ± 1,53	2,16± 1,34
Digit Span Forward (Attent.)	2,77 ± 1,53	2,74 ± 1,48	2,84 ± 1,62	2,88 ± 1,48
Rey's Words Immediate (Attent.)	2,33 ± 1,57	2,95 ± 1,52	2,52 ± 1,55	1,40 ± 1,56

TMT-A (Attent.)	2,87 ± 1,28	3.03 ± 1,42	2,64 ± 1,44	2,96 ± 1,17
Ray's Words Delayed (Memory)	2,15 ± 1,31	2,77 ± 1,54	2,68 ± 1,31	2,20 ± 1,58
Digit Span Backward (Memory)	1,92 ± 1,62	2,23 ± 1,64	1,84 ± 1,70	2,36 ± 1,68
Test Of Tale (Memory)	2,13 ± 1,39	2,72 ± 1,14	1,84 ± 1,34	2,28 ± 1,34
Verbal Phonological Test (Leng.)	2,64 ± 1,47	3,08 ± 1,26	2,64 ± 1,57	2,84 ± 1,31
Verbal Semantic Test (Leng.)	2,62 ± 1,35	3,23 ± 1,13	2,72 ± 1,51	2,72 ± 1,37
Substit. Digit Symbol (Ex. Fun.)	36,36 ± 14,67	39,04 ± 12,11	37,75 ± 12,19	39,04 ± 12,92
TMT-B (Ex. Fun.)	2,90 ± 1,35	3,05 ± 1,19	2,56 ± 1,32	2,80 ± 1,38
Stroop Test Time (Ex. Fun.)	2,62 ± 1,54	3,03 ± 1,42	2,40 ± 1,68	2,44 ± 1,55
FAB (Ex. Fun.)	15,08 ± 3,12	15,72 ± 2,60	14,64 ± 2,92	15,08 ± 3,61
Cognitive Estimation Test (Ex. Fun.)	1,95 ± 1,46	2,77 ± 1,15	2,60 ± 1,19	2,16 ± 1,46

Specifically, we found a statistically significant change after the VR-based CR intervention in the experimental group compared to the control group (Table 6) in terms of attention (Matrix, $p<0.002$; Rey's Words immediate recall, $p<0.019$), memory (Rey's Words delayed recall, $p<0.003$), verbal function (Verbal Semantic Test, $p< 0.010$), and executive function (CET, $p<0.003$).

Table 6. Cognitive Test-Repeated Measures ANOVA Analysis

	TIME		GROUP		TIME X GROUP	
	F(df)	p	F(df)	p	F(df)	p
Fig. Rey Immediate (Vis.Sp.)	10.755 (1,62)	0.002*	1.942 (1,62)	0.168	0.297 (1,62)	0.588
Matrix (Attent.)	0.098 (1,62)	0.755	0.252 (1,62)	0.617	10.810 (1,62)	0.002*
Digit Span Forward (Attent.)	0.002 (1,62)	0.968	0.090 (1,62)	0.765	0.035 (1,62)	0.853
Rey's Words Immediate (Attent.)	2.638 (1,62)	0.109	0.239 (1,62)	0.627	5.813 (1,62)	0.019*
TMT-A (Attent.)	3.287 (1,62)	0.075	0.220 (1,62)	0.527	0.006 (1,62)	0.527
Ray's Words Delayed (Memory)	0.143 (1,62)	0.707	0.004 (1,62)	0.950	9.330 (1,62)	0.003*

Digit Span Backward (Memory)	4.739 (1,62)	0.033	0.004 (1,62)	0.952	0.312 (1,62)	0.579
Test Of Tale (Memory)	8.374 (1,62)	0.005*	1.651 (1,62)	0.204	0.177 (1,62)	0.675
Verbal Phonological Test (Leng.)	8.026 (1,62)	0.006*	0.121 (1,62)	0.729	1.104 (1,62)	0.297
Verbal Semantic Test (Leng.)	6.982 (1,62)	0.010*	0.404 (1,62)	0.527	6.982 (1,62)	0.010*
Substit. Digit Symbol (Ex. Fun.)	1.084 (1,62)	0.302	0.109 (1,62)	0.743	0.055 (1,62)	0.815
TMT-B (Ex. Fun.)	2.732 (1,62)	0.103	0.886 (1,62)	0.350	0.131 (1,62)	0.719
Stroop Test Time (Ex. Fun.)	1.645 (1,62)	0.204	1.283 (1,62)	0.262	1.112 (1,62)	0.296
FAB (Ex. Fun.)	4.776 (1,62)	0.033	0.528 (1,62)	0.47	0.165 (1,62)	0.686
Cog. Estimation Test (Ex. Fun.)	0.900 (1,62)	0.346	0.006 (1,62)	0.939	9.880 (1,62)	0.003*

In general, the other clinical functioning outcomes improved in all the domains that we evaluated (Table 7). In particular, after the VR-based CR intervention, we found a statistically significant improvement (Table 8) in the depressive symptoms (PHQ-9, $p<0.30$), in the biological rhythms, in the specific sleep wake rhythm, in the social and the occupational activity, in nutrition (BRIAN, $p<0.029$) and in the alexithymia level (TAS-20, $p<0.007$) in the experimental group compared to the control group.

Table 7. Personal and Social functioning Test-Descriptive Analysis (Mean and Standard Deviation)

	VR/CR GROUP (N=39)		CONTROL GROUP (N=25)	
	PRE	POST	PRE	POST
TAS-20	55,00 ± 14,747	49,85 ± 14,982	52,08 ± 14,821	55,76 ± 16,465
BRIAN	49,82 ± 12,380	47,23 ± 11,773	48,12 ± 12,551	50,24 ± 12,387
PHQ-9	13,72 ± 6,121	10,82 ± 6,456	12,20 ± 6,265	11,92 ± 7,455
SF-12	25,95 ± 8,448	28,62 ± 9,193	28,08 ± 7,129	28,48 ± 8,842
SAS	61,05 ± 17,220	53,64 ± 17,609	56,92 ± 15,689	57,96 ± 16,900

HONOS	9,67 ± 6,417	7,38 ± 6,364	10,48 ± 6,771	8,12 ± 6,579

Table 8. Personal and Social functioning Test -Repeated Measures ANOVA Analysis

	TIME		GROUP		TIME X GROUP	
	F(df)	p	F(df)	p	F(df)	p
TAS-20	0.220 (1,62)	0.641	0.177 (1,62)	0.675	7.888 (1,62)	0.007*
BRIAN	0.050 (1,62)	0.824	0.049 (1,62)	0.825	4.498 (1,62)	0.029*
PHQ-9	7.243 (1,62)	0.009*	0.018 (1,62)	0.894	4.915 (1,62)	0.030*
SF-12	1.318 (1,62)	0.255	0.333 (1,62)	0.566	0.720 (1,62)	0.399
SAS	1.434 (1,62)	0.236	0.001 (1,62)	0.978	2.524 (1,62)	0.117
HONOS	8.027 (1,62)	0.006*	0.285 (1,62)	0.595	0.002 (1,62)	0.962

5. Discussion

Our study's hypothesis was that a fully immersive VR-based CR intervention (ecological instrument), with a recovery-oriented protocol of intervention, was feasible in the treatment of BD and could not only improve cognitive abilities, but also the other social and personal outcomes related to the BD-specific health needs. In terms of feasibility outcomes, this study showed that a fully immersive VR-based CR intervention for people with BD has an excellent acceptability and tolerability (primary outcome), as our 20% dropout rate is in line with the average dropout range in psychosocial treatments [Abdulatif, Mukhtar & Obayah 2015; Wright et al., 2021; Amico, 2009]. Even the percentage (45%) of the people that we contacted and did not respond or refused to participate in our randomized clinical trial is in line with the non-response and refusal rates for psychosocial treatments [Jenkins & Fallowfield, 2000]. It should also be noted that higher dropout rates (around 30%) are usually found in traditional CR interventions for people with BD [Tsapekos et al., 2020]. This negative data and uncertain research point could be interpreted considering the behavioral characteristics of this disorder. As BD is associated with a hyperthymic and exploratory temperament [Carta et al., 2017], traditional methods are not actually engaging, particularly in an ecological setting. A dropout rate of around 20% is a very important result in the treatment of CI in BD and suggests that the implementation of innovative interventions allows the achievement of the engagement goal in the treatment of CI, as well as improvements in terms of personal and social functioning. The use of the cross-over method is undoubtedly another strength, as a crossover study ensures low statistical variance and has the ethical advantage of including all randomized participants in the clinical intervention.

As regards our secondary outcomes, we found a preliminary effective clinical evidence of improved clinical rehabilitation outcomes after a fully immersive VR-based CR intervention, specifically in terms of attention, memory, verbal function, executive function, depressive symptoms, biological rhythms, specific sleep wake rhythm, social and occupational activity, nutrition and in the alexithymia level. Using a person-centered method, the VR-based CR intervention is an innovative intervention that allows the participants to learn about their personal resources and to develop strategies for their daily life, thanks to the generalization of the improved skills through a personal objectives-focused homework, which contributes to the achievement of a global impact in improving their clinical, personal, and social functioning. Despite the poor methodological quality of the trials, the implementation of CR interventions with traditional methods (paper and pencil and computerized) showed preliminary evidence for people with BD [Tsapekos et al., 2020]. The results of our study are consistent with other preliminary studies on the effectiveness of the use of traditional CR in the treatment of BD and suggest that it is important to implement randomized clinical trials with larger samples to evaluate the clinical effectiveness of CR interventions with fully immersive VR and to confirm this data.

Risk and benefits

The use of fully immersive VR could be associated with different side effects like dizziness, nausea, headache, eye fatigue, reduced limb control, reduced postural control, reduced sense of presence, and development of inadequate responses to the real world. However, important side effects are not expected, as the VR tool has already been used in people with psychosocial disabilities without substantial side effects [Garcia-Palacios et al., 2002; Klinger et al., 2005]. The benefits of VR in terms of satisfaction and

ecological learning and the few side effects satisfy the need to implement an innovative rehabilitation approach in mental health.

Conclusion

To date there is no evidence of the use of fully immersive VR as a CR intervention tool to train all cognitive domains of people with BD, even if cognitive impairment is a core component of the social and personal functioning in this disorder. Implementing a randomized clinical trial with a reproducible method developed by a multidisciplinary team specialized in the specific health needs of BD patients, is an important research goal in the field of psychiatric rehabilitation. Additionally, professionals should follow a logical framework to develop complex interventions in mental health and ensure that the outcomes that are measured are consistent with the skills trained and the functional improvement. Mental health is a fundamental resource that allows people to achieve daily life goals and exercise their role as citizens of a community [World Health Organization, 2021]. In line with the digital era and the WHO innovation objective, increasing the use of technologies in psychiatric rehabilitation could better respond to health needs. The results are preliminary and cannot be considered exhaustive due to the little sample size. However, the evidence of efficacy, together with the excellent acceptability of the intervention found, are of interest and suggest the need to conduct studies with more extensive samples that can confirm this data.

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References

- Abdulatif, M., Mukhtar, A., & Obayah, G. (2015). Pitfalls in reporting sample size calculation in randomized controlled trials published in leading anaesthesia journals: a systematic review. British journal of anaesthesia, 115(5), 699–707. https://doi.org/10.1093/bja/aev166
- Adams, R., Finn, P., Moes, E., Flannery, K., & Rizzo, A. S. (2009). Distractibility in Attention/Deficit/ Hyperactivity Disorder (ADHD): the virtual reality classroom. Child neuropsychology : a journal on normal and abnormal development in childhood and adolescence, 15(2), 120–135. https://doi.org/10.1080/09297040802169077
- Albert, U., Rosso, G., Maina, G., & Bogetto, F. (2008). Impact of anxiety disorder comorbidity on quality of life in euthymic bipolar disorder patients: differences between bipolar I and II subtypes. Journal of affective disorders, 105(1-3), 297–303. https://doi.org/10.1016/j.jad.2007.05.020
- Albiol-Pérez, S., Gil-Gómez, J. A., Muñoz-Tomás, M. T., Gil-Gómez, H., Vial-Escolano, R., & Lozano-Quilis, J. A. (2017). The Effect of Balance Training on Postural Control in Patients with Parkinson's Disease Using a Virtual Rehabilitation System. Methods of information in medicine, 56(2), 138–144. https://doi.org/10.3414/ME16-02-0004
- Alves, J., Magalhães, R., Machado, A., Gonçalves, O. F., Sampaio, A., & Petrosyan, A. (2013). Non-pharmacological cognitive intervention for aging and dementia: Current perspectives. World journal of clinical cases, 1(8), 233–241. https://doi.org/10.12998/wjcc.v1.i8.233

- American Psychiatric Association. (2000). Diagnostic and statistical manual of mental disorders, American Psychiatric Association.[PM, aTS, RT] Diagnostic and statistical manual of mental disorders
- American Psychiatric Association (2002). Practice guideline for the treatment of patients with bipolar disorder (revision). The American journal of psychiatry, 159(4 Suppl), 1–50.
- Amico K. R. (2009). Percent total attrition: a poor metric for study rigor in hosted intervention designs. American journal of public health, 99(9), 1567–1575. https://doi.org/10.2105/AJPH.2008.134767
- Amodio, P., Wenin, H., Del Piccolo, F., Mapelli, D., Montagnese, S., Pellegrini, A., Musto, C., Gatta, A., & Umiltà, C. (2002). Variability of trail making test, symbol digit test and line trait test in normal people. A normative study taking into account age-dependent decline and sociobiological variables. Aging clinical and experimental research, 14(2), 117–131. https://doi.org/10.1007/BF03324425
- Amodio, P., Campagna, F., Olianas, S., Iannizzi, P., Mapelli, D., Penzo, M., Angeli, P., & Gatta, A. (2008). Detection of minimal hepatic encephalopathy: normalization and optimization of the Psychometric Hepatic Encephalopathy Score. A neuropsychological and quantified EEG study. Journal of hepatology, 49(3), 346–353. https://doi.org/10.1016/j.jhep.2008.04.022
- Arksey H, O'Malley L (2005) Scoping studies: towards a methodological framework. Int J Soc Res Methodol 8(1):19–32. https://doi.org/10.1080/1364557032 00011 9616
- Balanzá-Martínez, V., Selva, G., Martínez-Arán, A., Prickaerts, J., Salazar, J., González-Pinto, A., Vieta, E., & Tabarés-Seisdedos, R. (2010). Neurocognition in bipolar disorders--a closer look at comorbidities and medications. European

journal of pharmacology, 626(1), 87–96. https://doi.org/10.1016/j.ejphar.2009.10.018

- Bagby, R. M., Parker, J. D., & Taylor, G. J. (1994). The twenty-item Toronto Alexithymia Scale--I. Item selection and cross-validation of the factor structure. Journal of psychosomatic research, 38(1), 23–32. https://doi.org/10.1016/0022-3999(94)900051
- Bellani, M., Biagianti, B., Zovetti, N., Rossetti, M. G., Bressi, C., Perlini, C., & Brambilla, P. (2019). The effects of cognitive remediation on cognitive abilities and real-world functioning among people with bipolar disorder: A systematic review: Special Section on "Translational and Neuroscience Studies in Affective Disorders". Section Editor, Maria Nobile MD, PhD. This Section of JAD focuses on the relevance of translational and neuroscience studies in providing a better understanding of the neural basis of affective disorders. The main aim is to briefly summaries relevant research findings in clinical neuroscience with particular regards to specific innovative topics in mood and anxiety disorders. Journal of affective disorders, 257, 691–697. https://doi.org/10.1016/j.jad.2019.07.059
- Bird, M. L., Cannell, J., Jovic, E., Rathjen, A., Lane, K., Tyson, A., ... & Smith, S. (2017). A randomized controlled trial investigating the efficacy of virtual reality in inpatient stroke rehabilitation. Archives of Physical Medicine and Rehabilitation, 98(10), e27
- Bisiacchi, P. S., Mapelli, D., Mondini, S., & Vestri, A. (2003). Esame neuropsicologico breve, una batteria di test per lo screening neuropsicologico. Milano: Raffaello Cortina Editore
- Bortolato, B., Miskowiak, K. W., Köhler, C. A., Vieta, E., & Carvalho, A. F. (2015). Cognitive dysfunction in bipolar disorder and schizophrenia: a systematic

review of meta-analyses. Neuropsychiatric disease and treatment, 11, 3111–3125. https://doi.org/10.2147/NDT.S76700

- Brasure, M., Desai, P., Davila, H., Nelson, V. A., Calvert, C., Jutkowitz, E., Butler, M., Fink, H. A., Ratner, E., Hemmy, L. S., McCarten, J. R., Barclay, T. R., & Kane, R. L. (2018). Physical Activity Interventions in Preventing Cognitive Decline and Alzheimer-Type Dementia: A Systematic Review. Annals of internal medicine, 168(1), 30–38. https://doi.org/10.7326/M17-1528
- Brissos, S., Dias, V. V., & Kapczinski, F. (2008). Cognitive performance and quality of life in bipolar disorder. Canadian journal of psychiatry. Revue canadienne de psychiatrie, 53(8), 517–524. https://doi.org/10.1177/070674370805300806
- Caffarra, P., Vezzadini, G., Dieci, F., Zonato, F., & Venneri, A. (2002). Rey-Osterrieth complex figure: normative values in an Italian population sample. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology, 22(6), 443–447. https://doi.org/10.1007/s100720200003 (1)
- Caffarra, P., Vezzadini, G., Dieci, F., Zonato, F., & Venneri, A. (2002). Una versione abbreviata del test di Stroop: dati normativi nella popolazione italiana. Nuova Rivista di Neurologia, 12(4), 111-115 (2)
- Caltagirone, C., Gainotti, G., Carlesimo, G. A., & Parnetti, L. (1995). Batteria per la valutazione del deterioramento mentale: I/II. Descrizione di uno strumento di diagnosi neuropsicologica. Archivio di Psicologia, Neurologia e Psichiatria
- Carlesimo, G. A., Buccione, I., Fadda, L., Graceffa, A., Mauri, M., Lorusso, S., ... & Caltagirone, C. (2002). Standardizzazione di due test di memoria per uso

clinico: Breve Racconto e Figura di Rey. Nuova Rivista di Neurologia, 12(1), 1-13

- Carta, M. G., & Angst, J. (2016). Screening for bipolar disorders: A public health issue. Journal of affective disorders, 205, 139–143. https://doi.org/10.1016/j.jad.2016.03.072
- Carta, M. G., Perra, A., Atzeni, M., D'Oca, S., Moro, M. F., Kurotschka, P. K., Moro, D., Sancassiani, F., Minerba, L., Brasesco, M. V., Mausel, G., Nardi, A. E., & Tondo, L. (2017). An evolutionary approach to mania studying Sardinian immigrants to Argentina. Revista brasileira de psiquiatria (Sao Paulo, Brazil : 1999), 39(2), 147–153. https://doi.org/10.1590/1516-4446-2016-2005
- Carta, M. G., Ouali, U., Perra, A., Ben Cheikh Ahmed, A., Boe, L., Aissa, A., Lorrai, S., Cossu, G., Aresti, A., Preti, A., & Nacef, F. (2021). Living With Bipolar Disorder in the Time of Covid-19: Biorhythms During the Severe Lockdown in Cagliari, Italy, and the Moderate Lockdown in Tunis, Tunisia. Frontiers in psychiatry, 12, 634765. https://doi.org/10.3389/fpsyt.2021.634765 (1)
- Carta, M. G., Cossu, G., Pintus, E., Zaccheddu, R., Callia, O., Conti, G., Pintus, M., Aviles Gonzalez, C. I., Massidda, M. V., Mura, G., Sardu, C., Contu, P., Minerba, L., Demontis, R., Pau, M., Finco, G., Cocco, E., Penna, M. P., Orr, G., Kalcev, G., … Preti, A. (2021). Moderate Exercise Improves Cognitive Function in Healthy Elderly People: Results of a Randomized Controlled Trial. Clinical practice and epidemiology in mental health : CP & EMH, 17, 75–80. https://doi.org/10.2174/1745017902117010075 (2)
- Cella, M., Preti, A., Edwards, C., Dow, T., & Wykes, T. (2017). Cognitive remediation for negative symptoms of schizophrenia: A network meta-

analysis. Clinical psychology review, 52, 43–51. https://doi.org/10.1016/j.cpr.2016.11.009

- Choi, J., & Medalia, A. (2005). Factors associated with a positive response to cognitive remediation in a community psychiatric sample. Psychiatric services (Washington, D.C.), 56(5), 602–604. https://doi.org/10.1176/appi.ps.56.5.602
- Cohen J (1988) Statistical power analysis for the behavioral sciences, 2nd edn. Erlbaum, Hillsdale, NJ
- Cooper, H. M., Hedges, L. V., & Valentine, J. C. (2009). The handbook of research synthesis and meta-analysis (2nd ed.). New York: Russell Sage Foundation
- Costa, M. T. S., Vieira, L. P., Barbosa, E. O., Mendes Oliveira, L., Maillot, P., Otero Vaghetti, C. A., Giovani Carta, M., Machado, S., Gatica-Rojas, V., & Monteiro-Junior, R. S. (2019). Virtual Reality-Based Exercise with Exergames as Medicine in Different Contexts: A Short Review. Clinical practice and epidemiology in mental health : CP & EMH, 15, 74. https://doi.org/10.2174/1745017901915010074
- Cotelli, M., Manenti, R., Brambilla, M., Gobbi, E., Ferrari, C., Binetti, G., & Cappa, S. F. (2019). Cognitive telerehabilitation in mild cognitive impairment, Alzheimer's disease and frontotemporal dementia: A systematic review. Journal of telemedicine and telecare, 25(2), 67–79. https://doi.org/10.1177/1357633X17740390
- Cullen, C., Kappelmann, N., Umer, M., Abdolizadeh, A., Husain, M. O., Bonato, S., Sharma, G., Xue, S., Ortiz, A., Kloiber, S. M., Mulsant, B. H., & Husain, M. I. (2021). Efficacy and acceptability of pharmacotherapy for comorbid anxiety

symptoms in bipolar disorder: A systematic review and meta-analysis. Bipolar disorders, 23(8), 754–766. https://doi.org/10.1111/bdi.13125

- Dandil, Y., Smith, K., Kinnaird, E., Toloza, C., & Tchanturia, K. (2020). Cognitive Remediation Interventions in Autism Spectrum Condition: A Systematic Review. Frontiers in psychiatry, 11, 722. https://doi.org/10.3389/fpsyt.2020.00722
- da Silva, J., Gonçalves-Pereira, M., Xavier, M., & Mukaetova-Ladinska, E. B. (2013). Affective disorders and risk of developing dementia: systematic review. The British journal of psychiatry : the journal of mental science, 202(3), 177–186. https://doi.org/10.1192/bjp.bp.111.101931
- Della Sala, S., MacPherson, S. E., Phillips, L. H., Sacco, L., & Spinnler, H. (2003). How many camels are there in Italy? Cognitive estimates standardised on the Italian population. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology, 24(1), 10–15. https://doi.org/10.1007/s100720300015
- Douglas, K. M., Gallagher, P., Robinson, L. J., Carter, J. D., McIntosh, V. V., Frampton, C. M., Watson, S., Young, A. H., Ferrier, I. N., & Porter, R. J. (2018). Prevalence of cognitive impairment in major depression and bipolar disorder. Bipolar disorders, 20(3), 260–274. https://doi.org/10.1111/bdi.12602
- Dubois, B., Slachevsky, A., Litvan, I., & Pillon, B. (2000). The FAB: a Frontal Assessment Battery at bedside. Neurology, 55(11), 1621–1626. https://doi.org/10.1212/wnl.55.11.1621
- Duval, S., & Tweedie, R. (2000). Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics, 56(2), 455–463. https://doi.org/10.1111/j.0006-341x.2000.00455.x

- Egger, M., Davey Smith, G., Schneider, M., & Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. BMJ (Clinical research ed.), 315(7109), 629–634. https://doi.org/10.1136/bmj.315.7109.629
- Eldridge, S. M., Chan, C. L., Campbell, M. J., Bond, C. M., Hopewell, S., Thabane, L., Lancaster, G. A., & PAFS consensus group (2016). CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ (Clinical research ed.), 355, i5239. https://doi.org/10.1136/bmj.i5239
- Elgamal, S., McKinnon, M. C., Ramakrishnan, K., Joffe, R. T., & MacQueen, G. (2007). Successful computer-assisted cognitive remediation therapy in patients with unipolar depression: a proof of principle study. Psychological medicine, 37(9), 1229–1238. https://doi.org/10.1017/S0033291707001110
- Elkind, J. S., Rubin, E., Rosenthal, S., Skoff, B., & Prather, P. (2001). A simulated reality scenario compared with the computerized Wisconsin card sorting test: an analysis of preliminary results. Cyberpsychology & behavior : the impact of the Internet, multimedia and virtual reality on behavior and society, 4(4), 489–496. https://doi.org/10.1089/109493101750527042
- Ferrari, A. J., Stockings, E., Khoo, J. P., Erskine, H. E., Degenhardt, L., Vos, T., & Whiteford, H. A. (2016). The prevalence and burden of bipolar disorder: findings from the Global Burden of Disease Study 2013. Bipolar Disord, 18(5), 440-450. doi:10.1111/bdi.12423
- Firth, J., Stubbs, B., Rosenbaum, S., Vancampfort, D., Malchow, B., Schuch, F., Elliott, R., Nuechterlein, K. H., & Yung, A. R. (2017). Aerobic Exercise Improves Cognitive Functioning in People With Schizophrenia: A Systematic Review and Meta-Analysis. Schizophrenia bulletin, 43(3), 546–556. https://doi.org/10.1093/schbul/sbw115

- Foucault, M. (2003). Madness and civilization. Routledge
- Freeman, D., Reeve, S., Robinson, A., Ehlers, A., Clark, D., Spanlang, B., & Slater, M. (2017). Virtual reality in the assessment, understanding, and treatment of mental health disorders. Psychological medicine, 47(14), 2393–2400. https://doi.org/10.1017/S003329171700040X
- Gagnon Shaigetz, V., Proulx, C., Cabral, A., Choudhury, N., Hewko, M., Kohlenberg, E., Segado, M., Smith, M., & Debergue, P. (2021). An Immersive and Interactive Platform for Cognitive Assessment and Rehabilitation (bWell): Design and Iterative Development Process. JMIR rehabilitation and assistive technologies, 8(4), e26629. https://doi.org/10.2196/26629
- Galbraith, R. F. (1994). Some applications of radial plots. Journal of the American Statistical Association, 89(428), 1232-1242
- García-Betances, R. I., Arredondo Waldmeyer, M. T., Fico, G., & Cabrera-Umpiérrez, M. F. (2015). A succinct overview of virtual reality technology use in Alzheimer's disease. Frontiers in aging neuroscience, 7, 80. https://doi.org/10.3389/fnagi.2015.00080
- Garcia-Palacios, A., Hoffman, H., Carlin, A., Furness, T. A., 3rd, & Botella, C. (2002). Virtual reality in the treatment of spider phobia: a controlled study. Behaviour research and therapy, 40(9), 983–993. https://doi.org/10.1016/s0005-7967(01)00068-7
- Gazzetta Ufficiale della Repubblica Italiana, Decreto Legislativo 30 giugno 2003, n. 196
- GBD 2017 Disease and Injury Incidence and Prevalence Collaborators (2018). Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-

2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet (London, England), 392(10159), 1789–1858. https://doi.org/10.1016/S0140-6736(18)32279-7

- Giovagnoli, A. R., Del Pesce, M., Mascheroni, S., Simoncelli, M., Laiacona, M., & Capitani, E. (1996). Trail making test: normative values from 287 normal adult controls. Italian journal of neurological sciences, 17(4), 305–309. https://doi.org/10.1007/BF01997792
- Goff, D. C., Jr, Lloyd-Jones, D. M., Bennett, G., Coady, S., D'Agostino, R. B., Gibbons, R., Greenland, P., Lackland, D. T., Levy, D., O'Donnell, C. J., Robinson, J. G., Schwartz, J. S., Shero, S. T., Smith, S. C., Jr, Sorlie, P., Stone, N. J., Wilson, P. W., Jordan, H. S., Nevo, L., Wnek, J., … American College of Cardiology/American Heart Association Task Force on Practice Guidelines (2014). 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation, 129(25 Suppl 2), S49–S73. https://doi.org/10.1161/01.cir.0000437741.48606.98
- Gold, A. K., Montana, R. E., Sylvia, L. G., Nierenberg, A. A., & Deckersbach, T. (2016). Cognitive Remediation and Bias Modification Strategies in Mood and Anxiety Disorders. Current behavioral neuroscience reports, 3(4), 340–349. https://doi.org/10.1007/s40473-016-0090-5
- Goodwin, G. M., Haddad, P. M., Ferrier, I. N., Aronson, J. K., Barnes, T., Cipriani, A., Coghill, D. R., Fazel, S., Geddes, J. R., Grunze, H., Holmes, E. A., Howes, O., Hudson, S., Hunt, N., Jones, I., Macmillan, I. C., McAllister-Williams, H., Miklowitz, D. R., Morriss, R., Munafò, M., … Young, A. H. (2016). Evidence-based guidelines for treating bipolar disorder: Revised third edition

recommendations from the British Association for Psychopharmacology. Journal of psychopharmacology (Oxford, England), 30(6), 495–553. https://doi.org/10.1177/0269881116636545

- Grynszpan, O., Perbal, S., Pelissolo, A., Fossati, P., Jouvent, R., Dubal, S., & Perez-Diaz, F. (2011). Efficacy and specificity of computer-assisted cognitive remediation in schizophrenia: a meta-analytical study. Psychological medicine, 41(1), 163–173. https://doi.org/10.1017/S0033291710000607
- Harvey P. D. (2014). What is the evidence for changes in cognition and functioning over the lifespan in patients with schizophrenia?. The Journal of clinical psychiatry, 75 Suppl 2, 34–38. https://doi.org/10.4088/JCP.13065su1.08
- Hedges, L. V., & Olkin, I. (2014). Statistical methods for meta-analysis. Academic press
- Higgins, J. P., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. BMJ (Clinical research ed.), 327(7414), 557–560. https://doi.org/10.1136/bmj.327.7414.557
- Huedo-Medina, T. B., Sánchez-Meca, J., Marín-Martínez, F., & Botella, J. (2006). Assessing heterogeneity in meta-analysis: Q statistic or I2 index?. Psychological methods, 11(2), 193–206. https://doi.org/10.1037/1082-989X.11.2.193
- Hwang, J., & Lee, S. (2017). The effect of virtual reality program on the cognitive function and balance of the people with mild cognitive impairment. Journal of physical therapy science, 29(8), 1283–1286. https://doi.org/10.1589/jpts.29.1283
- Iriarte, Y., Diaz-Orueta, U., Cueto, E., Irazustabarrena, P., Banterla, F., & Climent, G. (2016). AULA-Advanced Virtual Reality Tool for the Assessment of Attention: Normative Study in Spain. Journal of attention disorders, 20(6), 542–568. https://doi.org/10.1177/1087054712465335

- Jahn, F. S., Skovbye, M., Obenhausen, K., Jespersen, A. E., & Miskowiak, K. W. (2021). Cognitive training with fully immersive virtual reality in patients with neurological and psychiatric disorders: A systematic review of randomized controlled trials. Psychiatry research, 300, 113928. https://doi.org/10.1016/j.psychres.2021.113928
- Jenkins, V., & Fallowfield, L. (2000). Reasons for accepting or declining to participate in randomized clinical trials for cancer therapy. British journal of cancer, 82(11), 1783–1788. https://doi.org/10.1054/bjoc.2000.1142
- Kang, J. M., Kim, N., Lee, S. Y., Woo, S. K., Park, G., Yeon, B. K., Park, J. W., Youn, J. H., Ryu, S. H., Lee, J. Y., & Cho, S. J. (2021). Effect of Cognitive Training in Fully Immersive Virtual Reality on Visuospatial Function and Frontal-Occipital Functional Connectivity in Predementia: Randomized Controlled Trial. Journal of medical Internet research, 23(5), e24526. https://doi.org/10.2196/24526
- Keefe, R. S., Fox, K. H., Harvey, P. D., Cucchiaro, J., Siu, C., & Loebel, A. (2011). Characteristics of the MATRICS Consensus Cognitive Battery in a 29-site antipsychotic schizophrenia clinical trial. Schizophrenia research, 125(2-3), 161–168. https://doi.org/10.1016/j.schres.2010.09.015
- Keefe, R. S., Vinogradov, S., Medalia, A., Buckley, P. F., Caroff, S. N., D'Souza, D. C., Harvey, P. D., Graham, K. A., Hamer, R. M., Marder, S. M., Miller, D. D., Olson, S. J., Patel, J. K., Velligan, D., Walker, T. M., Haim, A. J., & Stroup, T. S. (2012). Feasibility and pilot efficacy results from the multisite Cognitive Remediation in the Schizophrenia Trials Network (CRSTN) randomized controlled trial. The Journal of clinical psychiatry, 73(7), 1016–1022. https://doi.org/10.4088/JCP.11m07100

- Kim, H., Hong, J. P., Kang, J. M., Kim, W. H., Maeng, S., Cho, S. E., Na, K. S., Oh, S. H., Park, J. W., Cho, S. J., & Bae, J. N. (2021). Cognitive reserve and the effects of virtual reality-based cognitive training on elderly individuals with mild cognitive impairment and normal cognition. Psychogeriatrics : the official journal of the Japanese Psychogeriatric Society, 21(4), 552–559. https://doi.org/10.1111/psyg.12705
- Klinger, E., Bouchard, S., Légeron, P., Roy, S., Lauer, F., Chemin, I., & Nugues, P. (2005). Virtual reality therapy versus cognitive behavior therapy for social phobia: a preliminary controlled study. Cyberpsychology & behavior : the impact of the Internet, multimedia and virtual reality on behavior and society, 8(1), 76–88. https://doi.org/10.1089/cpb.2005.8.76
- Kurtz, M. M., & Gerraty, R. T. (2009). A meta-analytic investigation of neurocognitive deficits in bipolar illness: profile and effects of clinical state. Neuropsychology, 23(5), 551–562. https://doi.org/10.1037/a0016277
- Kwan, R., Liu, J., Fong, K., Qin, J., Leung, P. K., Sin, O., Hon, P. Y., Suen, L. W., Tse, M. K., & Lai, C. K. (2021). Feasibility and Effects of Virtual Reality Motor-Cognitive Training in Community-Dwelling Older People With Cognitive Frailty: Pilot Randomized Controlled Trial. JMIR serious games, 9(3), e28400. https://doi.org/10.2196/28400
- La Paglia, F., La Cascia, C., Rizzo, R., Sanna, M., Cangialosi, F., Sideli, L., ... & La Barbera, D. (2016). Virtual reality environments to rehabilitation attention deficits in schizophrenic patients.
- Lasalvia, A., Zoppei, S., Van Bortel, T., Bonetto, C., Cristofalo, D., Wahlbeck, K., Bacle, S. V., Van Audenhove, C., van Weeghel, J., Reneses, B., Germanavicius, A., Economou, M., Lanfredi, M., Ando, S., Sartorius, N., Lopez-

Ibor, J. J., Thornicroft, G., & ASPEN/INDIGO Study Group (2013). Global pattern of experienced and anticipated discrimination reported by people with major depressive disorder: a cross-sectional survey. Lancet (London, England), 381(9860), 55–62. https://doi.org/10.1016/S0140-6736(12)61379-8

- Lasaponara, S., Marson, F., Doricchi, F., & Cavallo, M. (2021). A Scoping Review of Cognitive Training in Neurodegenerative Diseases via Computerized and Virtual Reality Tools: What We Know So Far. Brain sciences, 11(5), 528. https://doi.org/10.3390/brainsci11050528
- Lee, R. S., Hermens, D. F., Scott, J., Redoblado-Hodge, M. A., Naismith, S. L., Lagopoulos, J., Griffiths, K. R., Porter, M. A., & Hickie, I. B. (2014). A meta-analysis of neuropsychological functioning in first-episode bipolar disorders. Journal of psychiatric research, 57, 1–11. https://doi.org/10.1016/j.jpsychires.2014.06.019
- Li, W., Zhou, F. C., Zhang, L., Ng, C. H., Ungvari, G. S., Li, J., & Xiang, Y. T. (2020). Comparison of cognitive dysfunction between schizophrenia and bipolar disorder patients: A meta-analysis of comparative studies. Journal of affective disorders, 274, 652–661. https://doi.org/10.1016/j.jad.2020.04.051
- Liao, Y. Y., Chen, I. H., Lin, Y. J., Chen, Y., & Hsu, W. C. (2019). Effects of Virtual Reality-Based Physical and Cognitive Training on Executive Function and Dual-Task Gait Performance in Older Adults With Mild Cognitive Impairment: A Randomized Control Trial. Frontiers in aging neuroscience, 11, 162. https://doi.org/10.3389/fnagi.2019.00162
- Liao, Y. Y., Tseng, H. Y., Lin, Y. J., Wang, C. J., & Hsu, W. C. (2020). Using virtual reality-based training to improve cognitive function, instrumental activities of daily living and neural efficiency in older adults with mild cognitive

impairment. European journal of physical and rehabilitation medicine, 56(1), 47–57. https://doi.org/10.23736/S1973-9087.19.05899-4

- Lima, J. L., Axt, G., Teixeira, D. S., Monteiro, D., Cid, L., Yamamoto, T., Murillo-Rodriguez, E., & Machado, S. (2020). Exergames for Children and Adolescents with Autism Spectrum Disorder: An Overview. Clinical practice and epidemiology in mental health : CP & EMH, 16, 1–6. https://doi.org/10.2174/1745017902016010001
- Liu, Y., Tan, W., Chen, C., Liu, C., Yang, J., & Zhang, Y. (2019). A Review of the Application of Virtual Reality Technology in the Diagnosis and Treatment of Cognitive Impairment. Frontiers in aging neuroscience, 11, 280. https://doi.org/10.3389/fnagi.2019.00280
- MacKay, D. (2006). The United Nations Convention on the rights of persons with disabilities. Syracuse J. Int'l L. & Com., 34, 323.
- Maeng, S., Hong, J. P., Kim, W. H., Kim, H., Cho, S. E., Kang, J. M., Na, K. S., Oh, S. H., Park, J. W., Bae, J. N., & Cho, S. J. (2021). Effects of Virtual Reality-Based Cognitive Training in the Elderly with and without Mild Cognitive Impairment. Psychiatry investigation, 18(7), 619–627. https://doi.org/10.30773/pi.2020.0446
- Manera, V., Chapoulie, E., Bourgeois, J., Guerchouche, R., David, R., Ondrej, J., Drettakis, G., & Robert, P. (2016). A Feasibility Study with Image-Based Rendered Virtual Reality in Patients with Mild Cognitive Impairment and Dementia. PloS one, 11(3), e0151487. https://doi.org/10.1371/journal.pone.0151487
- Maples-Keller, J. L., Bunnell, B. E., Kim, S. J., & Rothbaum, B. O. (2017). The Use of Virtual Reality Technology in the Treatment of Anxiety and Other

Psychiatric Disorders. Harvard review of psychiatry, 25(3), 103–113. https://doi.org/10.1097/HRP.0000000000000138

- Martinez-Aran, A., & Vieta, E. (2015). Cognition as a target in schizophrenia, bipolar disorder and depression. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology, 25(2), 151–157. https://doi.org/10.1016/j.euroneuro.2015.01.007
- Martino, D. J., Samamé, C., Ibañez, A., & Strejilevich, S. A. (2015). Neurocognitive functioning in the premorbid stage and in the first episode of bipolar disorder: a systematic review. Psychiatry research, 226(1), 23–30. https://doi.org/10.1016/j.psychres.2014.12.044
- McGuinness, L.A. Robvis: An R package and web application for visualising risk-of-bias assessments. 2019. Available at https://github.com/mcguinlu/robvis
- McGurk,S., Twamley,E., Sitzer,D., McHugo,G. ,and Mueser,K.(2007).A meta analysis of cognitive remediation in schizophrenia. AmJPsychiatry 164,1791–1802. doi: 10.1176/appi.ajp.2007.07060906
- Merikangas, K. R., Jin, R., He, J. P., Kessler, R. C., Lee, S., Sampson, N. A., . . . Zarkov, Z. (2011). Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Arch Gen Psychiatry, 68(3), 241-251. doi:10.1001/archgenpsychiatry.2011.12
- Mesa-Gresa, P., Gil-Gómez, H., Lozano-Quilis, J. A., & Gil-Gómez, J. A. (2018). Effectiveness of Virtual Reality for Children and Adolescents with Autism Spectrum Disorder: An Evidence-Based Systematic Review. Sensors (Basel, Switzerland), 18(8), 2486. https://doi.org/10.3390/s18082486
- Milne-Ives, M., de Cock, C., Lim, E., Shehadeh, M. H., de Pennington, N., Mole, G., Normando, E., & Meinert, E. (2020). The Effectiveness of Artificial

Intelligence Conversational Agents in Health Care: Systematic Review. Journal of medical Internet research, 22(10), e20346. https://doi.org/10.2196/20346

- Montemagni, C., Del Favero, E., Riccardi, C., Canta, L., Toye, M., Zanalda, E., & Rocca, P. (2021). Effects of Cognitive Remediation on Cognition, Metacognition, and Social Cognition in Patients With Schizophrenia. Frontiers in psychiatry, 12, 649737. https://doi.org/10.3389/fpsyt.2021.649737
- Moro, M. F., Carta, M. G., Pintus, M., Pintus, E., Melis, R., Kapczinski, F., Vieta, E., & Colom, F. (2014). Validation of the Italian Version of the Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN): Some Considerations on its Screening Usefulness. Clinical practice and epidemiology in mental health : CP & EMH, 10, 48–52. https://doi.org/10.2174/1745017901410010048
- Morris, S. B. (2008). Estimating effect sizes from pretest-posttest-control group designs. Organizational Research Methods, 11(2), 364–386
- Musat, E. M., Marlinge, E., Leroy, M., Olié, E., Magnin, E., Lebert, F., Gabelle, A., Bennabi, D., Blanc, F., Paquet, C., & Cognat, E. (2021). Characteristics of Bipolar Patients with Cognitive Impairment of Suspected Neurodegenerative Origin: A Multicenter Cohort. Journal of personalized medicine, 11(11), 1183. https://doi.org/10.3390/jpm11111183
- Norr, A. M., Smolenski, D. J., & Reger, G. M. (2018). Effects of prolonged exposure and virtual reality exposure on suicidal ideation in active duty soldiers: An examination of potential mechanisms. Journal of psychiatric research, 103, 69–74. https://doi.org/10.1016/j.jpsychires.2018.05.009

- Novelli, G., Papagno, C., Capitani, E., & Laiacona, M. (1986). Tre test clinici di memoria verbale a lungo termine: Taratura su soggetti normali. Archivio di psicologia, neurologia e psichiatria (1)
- Novelli, G., Papagno, C., Capitani, E., & Laiacona, M. (1986). Tre test clinici di ricerca e produzione lessicale. Taratura su sogetti normali. Archivio di psicologia, neurologia e psichiatria (2)
- Orsini, A., Grossi, D., Capitani, E., Laiacona, M., Papagno, C., & Vallar, G. (1987). Verbal and spatial immediate memory span: normative data from 1355 adults and 1112 children. Italian journal of neurological sciences, 8(6), 539–548. https://doi.org/10.1007/BF02333660
- Ott, C. V., Macoveanu, J., Bowie, C. R., Fisher, P. M., Knudsen, G. M., Kessing, L. V., & Miskowiak, K. W. (2021). Change in prefrontal activity and executive functions after action-based cognitive remediation in bipolar disorder: a randomized controlled trial. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 46(6), 1113–1121. https://doi.org/10.1038/s41386-020-00901-7
- Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., McGuinness, L. A., … Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ (Clinical research ed.), 372, n71. https://doi.org/10.1136/bmj.n71
- Park, M. J., Kim, D. J., Lee, U., Na, E. J., & Jeon, H. J. (2019). A Literature Overview of Virtual Reality (VR) in Treatment of Psychiatric Disorders: Recent

Advances and Limitations. Frontiers in psychiatry, 10, 505. https://doi.org/10.3389/fpsyt.2019.00505

- Park, J. H., Liao, Y., Kim, D. R., Song, S., Lim, J. H., Park, H., Lee, Y., & Park, K. W. (2020). Feasibility and Tolerability of a Culture-Based Virtual Reality (VR) Training Program in Patients with Mild Cognitive Impairment: A Randomized Controlled Pilot Study. International journal of environmental research and public health, 17(9), 3030. https://doi.org/10.3390/ijerph17093030
- Parsons, T. D., Courtney, C. G., Arizmendi, B., & Dawson, M. (2011). Virtual Reality Stroop Task for neurocognitive assessment. Studies in health technology and informatics, 163, 433–439
- Patel V. (2007). Mental health in low- and middle-income countries. British medical bulletin, 81-82, 81–96. https://doi.org/10.1093/bmb/ldm010
- Peyroux, E., & Franck, N. (2014). RC2S: A Cognitive Remediation Program to Improve Social Cognition in Schizophrenia and Related Disorders. Frontiers in human neuroscience, 8, 400. https://doi.org/10.3389/fnhum.2014.00400
- Piras M, Perra A, Gureje O, Preti A, Carta MG. (2022). The Current Quality of Web-Based Information on the Treatment of Bipolar Disorder: A Systematic Search. Journal of Clinical Medicine. 11(18):5427.https://doi.org/10.3390/jcm11185427
- Powers, M. B., & Emmelkamp, P. M. (2008). Virtual reality exposure therapy for anxiety disorders: A meta-analysis. Journal of anxiety disorders, 22(3), 561–569. https://doi.org/10.1016/j.janxdis.2007.04.006
- Qian, J., McDonough, D. J., & Gao, Z. (2020). The Effectiveness of Virtual Reality Exercise on Individual's Physiological, Psychological and Rehabilitative

Outcomes: A Systematic Review. International journal of environmental research and public health, 17(11), 4133. https://doi.org/10.3390/ijerph17114133

- R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, 2020. URL https://www.R-project.org/
- Rampino, A., Falcone, R. M., Giannuzzi, A., Masellis, R., Antonucci, L. A., & Torretta, S. (2021). Strategies for Psychiatric Rehabilitation and their Cognitive Outcomes in Schizophrenia: Review of Last Five-year Studies. Clinical practice and epidemiology in mental health : CP & EMH, 17, 31–47. https://doi.org/10.2174/1745017902117010031
- Regolamento, U. E. (2016). 679 Regolamento (UE) 2016/679 del Parlamento europeo e del Consiglio, del 27 aprile 2016, relativo alla protezione delle persone fisiche con riguardo al trattamento dei dati personali, nonché alla libera circolazione di tali dati e che abroga la direttiva 95/46. CE (regolamento generale sulla protezione dei dati)
- Riva, G., Wiederhold, B. K., & Mantovani, F. (2019). Neuroscience of Virtual Reality: From Virtual Exposure to Embodied Medicine. Cyberpsychology, behavior and social networking, 22(1), 82–96. https://doi.org/10.1089/cyber.2017.29099.gri
- Riva, G., Mancuso, V., Cavedoni, S., & Stramba-Badiale, C. (2020). Virtual reality in neurorehabilitation: a review of its effects on multiple cognitive domains. Expert review of medical devices, 17(10), 1035–1061. https://doi.org/10.1080/17434440.2020.1825939
- Rizzo, R., Piccinelli, M., Mazzi, M. A., Bellantuono, C., & Tansella, M. (2000). The Personal Health Questionnaire: a new screening instrument for detection of

ICD-10 depressive disorders in primary care. Psychological medicine, 30(4), 831–840. https://doi.org/10.1017/s0033291799002512

- Robert, P. H., König, A., Amieva, H., Andrieu, S., Bremond, F., Bullock, R., Ceccaldi, M., Dubois, B., Gauthier, S., Kenigsberg, P. A., Nave, S., Orgogozo, J. M., Piano, J., Benoit, M., Touchon, J., Vellas, B., Yesavage, J., & Manera, V. (2014). Recommendations for the use of Serious Games in people with Alzheimer's Disease, related disorders and frailty. Frontiers in aging neuroscience, 6, 54. https://doi.org/10.3389/fnagi.2014.00054
- Rodakowski, J., Saghafi, E., Butters, M. A., & Skidmore, E. R. (2015). Non-pharmacological interventions for adults with mild cognitive impairment and early stage dementia: An updated scoping review. Molecular aspects of medicine, 43-44, 38–53. https://doi.org/10.1016/j.mam.2015.06.003
- Rotenberg, M., Anderson, K. K., & McKenzie, K. (2020). Social capital and psychosis: a scoping review. Social psychiatry and psychiatric epidemiology, 55(6), 659–671. https://doi.org/10.1007/s00127-019-01812-9
- Sancassiani, F., Cocco, A., Cossu, G., Lorrai, S., Trincas, G., Floris, F., Mellino, G., Machado, S., Nardi, A. E., Fabrici, E. P., Preti, A., & Carta, M. G. (2017). "VelaMente?!" - Sailin in a Crew to Improve Self-Efficacy in People with Psychosocial Disabilities: A Randomized Controlled Trial. Clinical practice and epidemiology in mental health : CP & EMH, 13, 200–212. https://doi.org/10.2174/1745017901713010200
- Saxena, S., Funk, M., & Chisholm, D. (2013). World Health Assembly adopts Comprehensive Mental Health Action Plan 2013-2020. Lancet (London, England), 381(9882), 1970–1971. https://doi.org/10.1016/S0140-6736(13)61139-3

- Saxena, S., & Setoya, Y. (2014). World Health Organization's Comprehensive Mental Health Action Plan 2013-2020. Psychiatry and clinical neurosciences, 68(8), 585–586. https://doi.org/10.1111/pcn.12207
- Sayma, M., Tuijt, R., Cooper, C., & Walters, K. (2020). Are We There Yet? Immersive Virtual Reality to Improve Cognitive Function in Dementia and Mild Cognitive Impairment. The Gerontologist, 60(7), e502–e512. https://doi.org/10.1093/geront/gnz132
- Scarpina, F., D'Aniello, G. E., Mauro, A., Castelnuovo, G., & MacPherson, S. E. (2015). How many segments are there in an orange: normative data for the new Cognitive Estimation Task in an Italian population. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology, 36(10), 1889–1895. https://doi.org/10.1007/s10072-015-2276-0
- Schaefer, J., Giangrande, E., Weinberger, D. R., & Dickinson, D. (2013). The global cognitive impairment in schizophrenia: consistent over decades and around the world. Schizophrenia research, 150(1), 42–50. https://doi.org/10.1016/j.schres.2013.07.009
- Seidel, R. J., & Chatelier, P. R. (Eds.). (1997). Virtual reality, training's future?: perspectives on virtual reality and related emerging technologies (Vol. 6). Springer Science & Business Media
- Shamsi, S., Lau, A., Lencz, T., Burdick, K. E., DeRosse, P., Brenner, R., Lindenmayer, J. P., & Malhotra, A. K. (2011). Cognitive and symptomatic predictors of functional disability in schizophrenia. Schizophrenia research, 126(1-3), 257–264. https://doi.org/10.1016/j.schres.2010.08.007

- Sharma, T., & Antonova, L. (2003). Cognitive function in schizophrenia. Deficits, functional consequences, and future treatment. The Psychiatric clinics of North America, 26(1), 25–40. https://doi.org/10.1016/s0193-953x(02)00084-9
- Simon, S. S., Yokomizo, J. E., & Bottino, C. M. (2012). Cognitive intervention in amnestic Mild Cognitive Impairment: a systematic review. Neuroscience and biobehavioral reviews, 36(4), 1163–1178. https://doi.org/10.1016/j.neubiorev.2012.01.007
- Skivington, K., Matthews, L., Simpson, S. A., Craig, P., Baird, J., Blazeby, J. M., Boyd, K. A., Craig, N., French, D. P., McIntosh, E., Petticrew, M., Rycroft-Malone, J., White, M., & Moore, L. (2021). A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance. BMJ (Clinical research ed.), 374, n2061. https://doi.org/10.1136/bmj.n2061
- Slater M. (2004). Presence and emotions. Cyberpsychology & behavior : the impact of the Internet, multimedia and virtual reality on behavior and society, 7(1), 121–123. https://doi.org/10.1089/109493104322820200
- Solé, B., Jiménez, E., Torrent, C., Reinares, M., Bonnin, C. D. M., Torres, I., Varo, C., Grande, I., Valls, E., Salagre, E., Sanchez-Moreno, J., Martinez-Aran, A., Carvalho, A. F., & Vieta, E. (2017). Cognitive Impairment in Bipolar Disorder: Treatment and Prevention Strategies. The international journal of neuropsychopharmacology, 20(8), 670–680. https://doi.org/10.1093/ijnp/pyx032
- Spinnler H, Tognoni G (1987). Standardizzazione e taratura italiana di test neuropsicologici. Ital J Neurol Sci 8
- Steardo, L., Jr, de Filippis, R., Carbone, E. A., Segura-Garcia, C., Verkhratsky, A., & De Fazio, P. (2019). Sleep Disturbance in Bipolar Disorder: Neuroglia and

Circadian Rhythms. Frontiers in psychiatry, 10, 501. https://doi.org/10.3389/fpsyt.2019.00501

- Thérond, A., Pezzoli, P., Abbas, M., Howard, A., Bowie, C. R., & Guimond, S. (2021). The Efficacy of Cognitive Remediation in Depression: A Systematic Literature Review and Meta-Analysis. Journal of affective disorders, 284, 238–246. https://doi.org/10.1016/j.jad.2021.02.009
- Tchanturia, K., Davies, H., & Campbell, I. C. (2007). Cognitive remediation therapy for patients with anorexia nervosa: preliminary findings. Annals of general psychiatry, 6, 14. https://doi.org/10.1186/1744-859X-6-14
- Thapa, N., Park, H. J., Yang, J. G., Son, H., Jang, M., Lee, J., Kang, S. W., Park, K. W., & Park, H. (2020). The Effect of a Virtual Reality-Based Intervention Program on Cognition in Older Adults with Mild Cognitive Impairment: A Randomized Control Trial. Journal of clinical medicine, 9(5), 1283. https://doi.org/10.3390/jcm9051283
- Thornicroft, G., Brohan, E., Rose, D., Sartorius, N., Leese, M., & INDIGO Study Group (2009). Global pattern of experienced and anticipated discrimination against people with schizophrenia: a cross-sectional survey. Lancet (London, England), 373(9661), 408–415. https://doi.org/10.1016/S0140-6736(08)61817-6
- Thorsen, A. L., Johansson, K., & Løberg, E. M. (2014). Neurobiology of cognitive remediation therapy for schizophrenia: a systematic review. Frontiers in psychiatry, 5, 103. https://doi.org/10.3389/fpsyt.2014.00103
- Torres, I. J., DeFreitas, V. G., DeFreitas, C. M., Kauer-Sant'Anna, M., Bond, D. J., Honer, W. G., Lam, R. W., & Yatham, L. N. (2010). Neurocognitive functioning in patients with bipolar I disorder recently recovered from a first

manic episode. The Journal of clinical psychiatry, 71(9), 1234–1242. https://doi.org/10.4088/JCP.08m04997yel

- Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D et al (2018) PRISMA extension for scoping reviews (PRISMAScR): checklist and explanation. Ann Intern Med 169(7):467. https ://doi.org/10.7326/M18-0850
- Tsapekos, D., Seccomandi, B., Mantingh, T., Cella, M., Wykes, T., & Young, A. H. (2020). Cognitive enhancement interventions for people with bipolar disorder: A systematic review of methodological quality, treatment approaches, and outcomes. Bipolar disorders, 22(3), 216–230. https://doi.org/10.1111/bdi.12848
- Tulliani, N., Bissett, M., Fahey, P., Bye, R., & Liu, K. P. Y. (2022). Efficacy of cognitive remediation on activities of daily living in individuals with mild cognitive impairment or early-stage dementia: a systematic review and meta-analysis. Systematic reviews, 11(1), 156. https://doi.org/10.1186/s13643-022-02032-0
- Valmaggia, L. R., Latif, L., Kempton, M. J., & Rus-Calafell, M. (2016). Virtual reality in the psychological treatment for mental health problems: An systematic review of recent evidence. Psychiatry research, 236, 189–195. https://doi.org/10.1016/j.psychres.2016.01.015
- Velligan, D. I., Kern, R. S., & Gold, J. M. (2006). Cognitive rehabilitation for schizophrenia and the putative role of motivation and expectancies. Schizophrenia bulletin, 32(3), 474–485. https://doi.org/10.1093/schbul/sbj071
- Viechtbauer, W. (2010). Conducting meta-analyses in R with the metafor package. Journal of statistical software, 36(3), 1-48

- Vieta E. (2009). The influence of medications on neurocognition in bipolar disorder. Acta psychiatrica Scandinavica, 120(6), 414–415. https://doi.org/10.1111/j.1600-0447.2009.01503.x
- Vigo, D., Thornicroft, G., & Atun, R. (2016). Estimating the true global burden of mental illness. The lancet. Psychiatry, 3(2), 171–178. https://doi.org/10.1016/S2215-0366(15)00505-2
- Vita, A., Deste, G., Barlati, S., Poli, R., Cacciani, P., De Peri, L., & Sacchetti, E. (2018). Feasibility and effectiveness of cognitive remediation in the treatment of borderline personality disorder. Neuropsychological rehabilitation, 28(3), 416–428. https://doi.org/10.1080/09602011.2016.1148054
- Vita, A., Barlati, S., Ceraso, A., Nibbio, G., Ariu, C., Deste, G., & Wykes, T. (2021). Effectiveness, Core Elements, and Moderators of Response of Cognitive Remediation for Schizophrenia: A Systematic Review and Meta-analysis of Randomized Clinical Trials. JAMA psychiatry, 78(8), 848–858. https://doi.org/10.1001/jamapsychiatry.2021.062
- Wang J. F. (2007). Defects of mitochondrial electron transport chain in bipolar disorder: implications for mood-stabilizing treatment. Canadian journal of psychiatry. Revue canadienne de psychiatrie, 52(12), 753–762. https://doi.org/10.1177/070674370705201202
- Ware, J., Jr, Kosinski, M., & Keller, S. D. (1996). A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Medical care, 34(3), 220–233. https://doi.org/10.1097/00005650-199603000-00003
- Whiteford, H. A., Degenhardt, L., Rehm, J., Baxter, A. J., Ferrari, A. J., Erskine, H. E., . . . Vos, T. (2013). Global burden of disease attributable to mental and

substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet, 382(9904), 1575-1586. doi:10.1016/s0140-6736(13)61611-6

- Wing, J. K., Beevor, A. S., Curtis, R. H., Park, S. B., Hadden, S., & Burns, A. (1998). Health of the Nation Outcome Scales (HoNOS). Research and development. The British journal of psychiatry : the journal of mental science, 172, 11–18. https://doi.org/10.1192/bjp.172.1.11
- World Health Organization. (2001). The World Health Report 2001: Mental health: new understanding, new hope
- World Health Organization. (2006). Working together for health: the World health report 2006: policy briefs
- World Health Organization. (2014). European Advisory Committee on Health Research: fourth meeting, Copenhagen, Denmark, 10–11 December 2013 (No. WHO/EURO: 2014-4530-44293-62565). World Health Organization. Regional Office for Europe.
- World Health Organization. (2021). Comprehensive mental health action plan 2013–2030
- World Medical Association (2013). World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA, 310(20), 2191–2194. https://doi.org/10.1001/jama.2013.281053
- Wright, I., Mughal, F., Bowers, G., & Meiser-Stedman, R. (2021). Dropout from randomised controlled trials of psychological treatments for depression in children and youth: a systematic review and meta-analyses. Journal of affective disorders, 281, 880–890. https://doi.org/10.1016/j.jad.2020.11.039

- Wykes, T., & Spaulding, W. D. (2011). Thinking about the future cognitive remediation therapy--what works and could we do better?. Schizophrenia bulletin, 37 Suppl 2(Suppl 2), S80–S90. https://doi.org/10.1093/schbul/sbr064
- Young, J., Angevaren, M., Rusted, J., & Tabet, N. (2015). Aerobic exercise to improve cognitive function in older people without known cognitive impairment. The Cochrane database of systematic reviews, (4), CD005381. https://doi.org/10.1002/14651858.CD005381.pub4
- Zając-Lamparska, L., Wiłkość-Dębczyńska, M., Wojciechowski, A., Podhorecka, M., Polak-Szabela, A., Warchoł, Ł., Kędziora-Kornatowska, K., Araszkiewicz, A., & Izdebski, P. (2019). Effects of virtual reality-based cognitive training in older adults living without and with mild dementia: a pretest-posttest design pilot study. BMC research notes, 12(1), 776. https://doi.org/10.1186/s13104-019-4810-2
- Zakzanis, K. K., Quintin, G., Graham, S. J., & Mraz, R. (2009). Age and dementia related differences in spatial navigation within an immersive virtual environment. Medical science monitor : international medical journal of experimental and clinical research, 15(4), CR140–CR150
- Zung W. W. (1971). A rating instrument for anxiety disorders. Psychosomatics, 12(6), 371–379. https://doi.org/10.1016/S0033-3182(71)71479-0

Appendix

Appendix 1: Side effects and satisfaction questionnaire

Questionario

Feedback sulla prova di utilizzo di CEREBRUM - Versione 1.0

Sesso: **M** **F**

Età: _____ anni Scolarità: _____ anni

1) Può indicarmi la qualità video dell'esperienza?

1 scarsa	**2** mediocre	**3** buona	**4** ottima	**5** eccellente

2) Può indicarmi la qualità audio dell'esperienza?

1 scarsa	**2** mediocre	**3** buona	**4** ottima	**5** eccellente

3) Può indicarmi l'entità della sensazione di sentirsi dentro e immerso nell'esperienza?

1 scarsa	**2** mediocre	**3** buona	**4** ottima	**5** eccellente

4) Può indicarmi quali eventuali effetti indesiderati, quali nausea, senso di irrealtà, senso di vuoto, altro, ha notato durante l'esperienza?

_____

5) Può indicarmi quali eventuali effetti indesiderati, quali nausea, senso di irrealtà, senso di vuoto, altro, ha notato negli istanti successivi all'esperienza?

_____

6) Può indicarmi quali emozioni e sensazioni ha provato:

Prima dell'esperienza: _____

Durante l'esperienza: _____

Dopo l'esperienza: _____

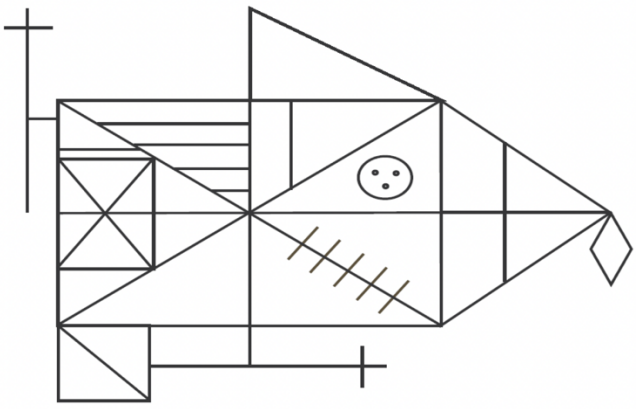
7) Può indicarmi l'entità del gradimento globale dell'esperienza?

1 scarsa	**2** mediocre	**3** buona	**4** ottima	**5** eccellente

8) Può indicarmi l'entità dell'interesse e dell'importanza che avrebbe utilizzare CEREBRUM in terapia?

1 scarsa	**2** mediocre	**3** buona	**4** ottima	**5** eccellente

Appendix 2: Rey Figure Test



Appendix 3: Matrix test

Test delle Matrici (visual search)

H. Spinnler e G. Tognoni (1987)

Test per la valutazione dell'attenzione selettiva visiva.

Vengono mostrate al soggetto tre matrici; ciascuna di esse è costituita da 13 righe di 10 numeri da 0 a 9 ciascuna, disposti in una sequenza casuale. Il soggetto deve sbarrare tutti i numeri uguali a quelli stampati in cima alla matrice ("5" nella I, "2-6" nella II, "1-4-9" nella III). Le matrici vanno presentate dalla più semplice alla più difficile.

N.B. le prime due righe di ogni matrice (A e B) sono di prova per verificare che il soggetto abbia capito il compito quindi non vanno conteggiate nel punteggio finale.

Il tempo massimo per ogni matrice è di ***45 sec***, ma si permette comunque al soggetto di terminare il compito nel caso in cui gli occorresse un tempo maggiore. Se il soggetto impiega meno di 45sec. per completare le singole matrici, è necessario indicare il tempo impiegato scrivendolo in fondo alla matrice stessa.

Viene calcolato il numero di risposte esatte (range 0-60 complessivamente nelle tre matrici); il numero di falsi allarmi (range 0-270 complessivamente nelle tre matrici); le omissioni (range 0-60).

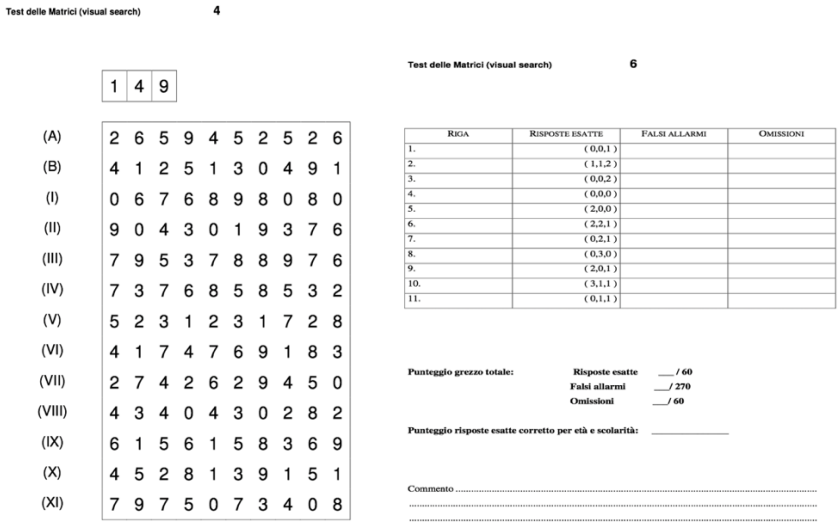
Vedere tabelle di correzione e correggere il punteggio grezzo relativo alle risposte corrette in base all'età e alla scolarità. Confrontare punteggio corretto con i dati normativi.

Test delle Matrici (visual search) 2

	5
(A)	2 6 5 9 4 5 2 5 2 6
(B)	4 1 2 5 1 3 0 4 9 1
(I)	0 6 7 6 8 9 8 0 8 0
(II)	9 0 4 3 0 1 9 3 7 6
(III)	7 9 5 3 7 8 8 9 7 6
(IV)	7 3 7 6 8 5 8 5 3 2
(V)	5 2 3 1 2 3 1 7 2 8
(VI)	4 1 7 4 7 6 9 1 8 3
(VII)	2 7 4 2 6 2 9 4 5 0
(VIII)	4 3 4 0 4 3 0 2 8 2
(IX)	6 1 5 6 1 5 8 3 6 9
(X)	4 5 2 8 1 3 9 1 5 1
(XI)	7 9 7 5 0 7 3 4 0 8

Test delle Matrici (visual search) 3

	2 6
(A)	2 6 5 9 4 5 2 5 2 6
(B)	4 1 2 5 1 3 0 4 9 1
(I)	0 6 7 6 8 9 8 0 8 0
(II)	9 0 4 3 0 1 9 3 7 6
(III)	7 9 5 3 7 8 8 9 7 6
(IV)	7 3 7 6 8 5 8 5 3 2
(V)	5 2 3 1 2 3 1 7 2 8
(VI)	4 1 7 4 7 6 9 1 8 3
(VII)	2 7 4 2 6 2 9 4 5 0
(VIII)	4 3 4 0 4 3 0 2 8 2
(IX)	6 1 5 6 1 5 8 3 6 9
(X)	4 5 2 8 1 3 9 1 5 1
(XI)	7 9 7 5 0 7 3 4 0 8



Test delle Matrici (visual search) 4

	1	4	9

(A)	2	6	5	9	4	5	2	5	2	6
(B)	4	1	2	5	1	3	0	4	9	1
(I)	0	6	7	6	8	9	8	0	8	0
(II)	9	0	4	3	0	1	9	3	7	6
(III)	7	9	5	3	7	8	8	9	7	6
(IV)	7	3	7	6	8	5	8	5	3	2
(V)	5	2	3	1	2	3	1	7	2	8
(VI)	4	1	7	4	7	6	9	1	8	3
(VII)	2	7	4	2	6	2	9	4	5	0
(VIII)	4	3	4	0	4	3	0	2	8	2
(IX)	6	1	5	6	1	5	8	3	6	9
(X)	4	5	2	8	1	3	9	1	5	1
(XI)	7	9	7	5	0	7	3	4	0	8

Test delle Matrici (visual search) 6

RIGA	RISPOSTE ESATTE	FALSI ALLARMI	OMISSIONI
1.	(0,0,1)		
2.	(1,1,2)		
3.	(0,0,2)		
4.	(0,0,0)		
5.	(2,0,0)		
6.	(2,2,1)		
7.	(0,2,1)		
8.	(0,3,0)		
9.	(2,0,1)		
10.	(3,1,1)		
11.	(0,1,1)		

Punteggio grezzo totale: **Risposte esatte** ___ / 60
Falsi allarmi ___ / 270
Omissioni ___ / 60

Punteggio risposte esatte corretto per età e scolarità: _____

Commento .....
.....
.....

Appendix 4: Rey's Words Test

Test di Parole di Rey
(Test di Rey, 1958)

PAROLE	M B T	RIP 2	RIP 3	RIP 4	RIP 5	MLT (dopo 15')	RICON
BRODO							
VIOLINO							
CAMPAGNA							
CORNICE							
LIRA							
PARETE							
BASTONE							
PALAZZO							
NOTTE							
FRECCIA							
LAGO							
FIAMMIFERO							
ISOLA							
TEMPO							
BARCA							
N° PAROLE							

Intrusioni

Punteggio a breve termine: ...../15
Punteggio a Lungo termine: ...../15
Intrusioni: .....

Test di Riconoscimento (dopo 15 minuti)

N°	Item	Risp.	N°	Item	Risp.	N°	Item	Risp.	N°	Item	Risp.
1	VAGONE		13	COLORE		25	CORNICE	X	37	CINTURA	
2	VIOLINO	X	14	LAGO	X	26	TENDA		38	CAMINO	
3	UOMO		15	NOTTE	X	27	PANE		39	PAESANO	
4	BASTONE	X	16	SOLE		28	FRECCIA	X	40	CAROTA	
5	TACCHINO		17	BRODO	X	29	PALAZZO	X	41	CAPPELLO	
6	MONETA		18	GIORNALE		30	LUCE		42	GIARDINO	
7	FINESTRA		19	CAFFE'		21	LIRA	X	43	PAGINA	
8	TROMBA		20	SCUOLA		32	FIAMMIFERO	X	44	LAMPADA	
9	BAFFI		21	FIUME		33	CASA		45	PARETE	X
10	CAMPAGNA	X	22	LETTO		34	ALBERGO		46	MANICO	
11	TEMPO	X	23	ISOLA	X	35	BARCA	X			
12	MONTE		24	SERA		36	TAMBURO				

CORRETTE:	FALSI RICONOSCIMENTI

TABELLE DI CORREZIONE E PUNTEGGI EQUIVALENTI

Rievocazione immediata (somma delle rievocazioni delle prime 5 serie iniziali)

Età	20	25	30	35	40	45	50	55	60	65	70	75	80	PE
Scol														0= 0-28.52
5	-6.1	-5.0	-3.9	-2.7	-1.4	-0.1	1.3	2.8	4.4	6.1	8.0	10.0	12.2	1= 28.53-32.24
8	-8.1	-7.1	-5.9	-4.8	-3.5	-2.2	-0.8	0.7	2.3	4.0	5.9	7.9	10.1	2= 32.25-36.34
13	-10.9	-9.8	-8.7	-7.5	-6.2	-4.9	-3.5	-2.0	0.4	1.3	3.1	5.2	7.4	3= 36.35-41.69
17	-12.7	-11.6	-10.5	-9.3	-8.0	-6.7	-5.3	-3.8	-2.2	-0.5	1.3	3.3	5.6	4= 41.70 ed oltre

Rievocazione differita (parole ricordate dopo 15 minuti)

Età	20	25	30	35	40	45	50	55	60	65	70	75	80	PE
Scol														0= 0-4.68
5	-2.3	-1.9	-1.6	-1.2	-0.7	-0.3	0.2	0.7	1.2	1.8	2.4	3.1	3.8	1= 4.69-5.78
8	-2.8	-2.5	+2.1	-1.7	-1.3	-0.8	-0.4	0.2	0.7	1.3	1.9	2.6	3.3	2= 5.79-7.16
13	-3.5	-3.1	-2.8	-2.4	-1.9	-1.5	-1.0	-0.5	0	0.6	1.2	1.9	2.6	3= 7.17-8.72
17	-3.9	-3.6	-3.2	-2.8	-2.4	-1.9	-1.5	-1.0	-0.4	0.1	0.8	1.4	2.2	4= 8.73 ed oltre

Appendix 5: Digit Span Forward and backward

DIGIT SPAN – SPAN DI NUMERI

(Orsini et al., 1987)

L'esaminatore legge una lista di numeri di lunghezza crescente. Il soggetto deve ripetere la sequenza di numeri immediatamente dopo la presentazione. I numeri vengono letti alla velocità di circa uno al secondo. Quando il paziente ripete correttamente la sequenza, l'esaminatore passa alla sequenza successiva più lunga, finché il soggetto non fallisca entrambe le prove di una determinata lunghezza. Il punteggio è dato dal numero di cifre che costituiscono la sequenza più lunga correttamente ripetuta.

Sequenze	*Riproduzione del Soggetto*	*Span*
Prove Preliminari: 7 - 9 4 - 2		2
5 - 8 – 2 6 - 9 - 4		3
6 - 4 - 3 – 9 7 - 2 - 8 - 6		4
4 - 2 - 7 - 3 – 1 7 - 5 - 8 - 3 - 6		5
6 - 1 - 9 - 4 - 7 - 3 3 - 9 - 2 - 4 - 8 - 7		6
5 - 9 - 1 - 7 - 4 - 2 – 8 4 - 1 - 7 - 9 - 3 - 8 - 6		7
5 - 8 - 1 - 9 - 2 - 6 - 4 – 7 3 - 8 - 2 - 9 - 5 - 1 - 7 - 4		8
2 - 7 - 5 - 8 - 6 - 2 - 5 - 8 - 4 7 - 1 - 3 - 9 - 4 - 2 - 5 - 6 - 8		9

PUNTEGGIO GREZZO:		/ 9
PUNTEGGIO CORRETTO:		
PUNTEGGIO EQUIVALENTE:		

DIGIT SPAN – FORWARD

Sequenze	Riproduzione Soggetto	Span
2-4 5-8		**2**
6-2-9 4-1-5		**3**
3-2-7-9 4-9-6-8		**4**
1-5-2-8-6 6-1-8-4-3		**5**
5-3-9-4-1-8 7-2-4-8-5-6		**6**
8-1-2-9-3-6-5 1-7-3-9-1-2-8		**7**
9-4-3-7-6-2-5-8 7-2-8-1-9-6-5-3		**8**
5-8-3-2-6-1-4-9-1 2-7-3-1-4-8-5-9-6		**9**

Punteggio Grezzo	**_ /9**
Punteggio Corretto	
P.E.	

Appendix 6: Trail Making Test

TRAIL MAKING TEST

Scopo

Il test valuta il modo di procedere in compiti di ricerca visiva e spaziale, indaga le capacità attentive del soggetto e la sua abilità nel passare velocemente da uno stimolo di tipo numerico ad uno alfabetico.

Indicazioni all'utilizzo

E' uno dei test neuropsicologici più frequentemente usati per la sua semplicità di somministrazione e sensibilità nel rilievo del danno cerebrale. Può essere proposto a soggetti con deficit attentivi dai 15 anni fino ad oltre i 70, con la specificazione che essi conoscano l'ordine numerico e alfabetico.

Stimoli

Il TMT comprende due prove. Nella prima (prova A) gli stimoli sono costituiti una serie di numeri da 1 a 25, cerchiati e stampati in ordine sparso su un foglio formato A4; il numero 1 corrisponde all'inizio, il 25 alla fine. Nella seconda (prova B) gli stimoli sono formati sia da numeri che da lettere; il numero 1 corrisponde all'inizio e il 13 alla fine, le lettere vanno dalla A alla N. Ciascuna delle due prove è preceduta da una prova di comprensione con lo scopo di far capire correttamente al soggetto le regole del compito. Gli stimoli di queste prove sono costruiti con i medesimi principi ma sono di minore quantità.

Istruzioni

Al soggetto viene mostrata la prova della parte A. Gli si richiede di unire con dei segmenti tracciati a penna i numeri cerchiati seguendo l'esatto ordine dall'inizio (n° 1) alla fine (n°8).
Si specifica che la prova è a tempo e che quindi la velocità di esecuzione è una variabile fondamentale. Una volta appurato che il soggetto ha capito come svolgere correttamente la prova si passa al vero e proprio test. Il cronometro viene fatto partire in corrispondenza dell'inizio della prova e l'esaminatore deve stare attento agli errori compiuti dal soggetto e correggerli, nel caso in cui questa operazione richiedesse troppo tempo viene fermato il cronometro e fatto ripartire quando il soggetto è pronto. Il principio della prova B è lo stesso, con la differenza che qui il paziente deve alternare lo stimolo numerico a quello alfabetico,sempre seguendo l'ordine. Anche qui, dopo un'iniziale prova di comprensione, si somministra il vero e proprio test con il calcolo del tempo impiegato.

Commenti

TMT-A

La parte A richiede al soggetto di attivare una serie di operazioni cognitive quali la ricerca spaziale e visiva dei numeri nella loro giusta sequenza impiegando il minor tempo possibile. E' una prova che rileva il livello attentivo del paziente e dall'analisi dei risultati si può notare che i soggetti mano a mano più anziani hanno prestazioni peggiori.

TMT-B

Questa seconda parte del TMT è certamente più complessa e impegnativa rispetto alla prima. Qui infatti, oltre a un compito di ricerca visiva e spaziale, viene richiesto al soggetto un compito di shifting attenzionale, cioè di alternanza continua da uno stimolo di tipo numerico a uno di tipo alfabetico. I tempi di prestazione di questa prova sono molto più elevati, soprattutto nei soggetti anziani che spesso hanno difficoltà a capire la natura del compito e a mantenere costante lo shifting tra le due diverse categorie di stimoli .

TMT-BA

La sottrazione della prova A da quella B rileva delle informazioni fondamentali sulla natura del deficit attentivo del paziente .
Infatti se i tempi della prova B sono patologici mentre quelli della prova A sono nella norma , questo sta a significare che il soggetto è deficitario nel compito di shifting, poiché nella prova volta a valutare la sua capacità di ricerca visiva non si discosta dalla media della popolazione. Se invece i risultati delle due prove si avvicinano abbastanza, allora il deficit del paziente è nel compito di ricerca visiva poiché quello di shifting non aumenta in modo significativo i tempi del soggetto, quindi lo sforzo cognitivo dato dall'alternanza degli stimoli non peggiora le sue prestazioni in modo considerevole .

Cognome		Nome
Età	Scolarità	Data

TRAIL MAKING TEST

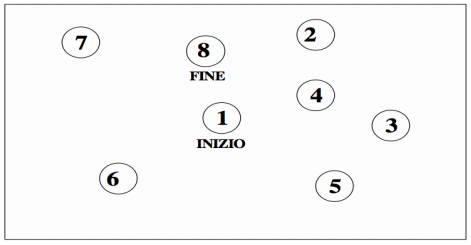
PROVA	GREZZO (in sec.)	CORREZIONE (in sec.)	CORRETTO (in sec.)	PE
Parte A				
Parte B				
B - A				

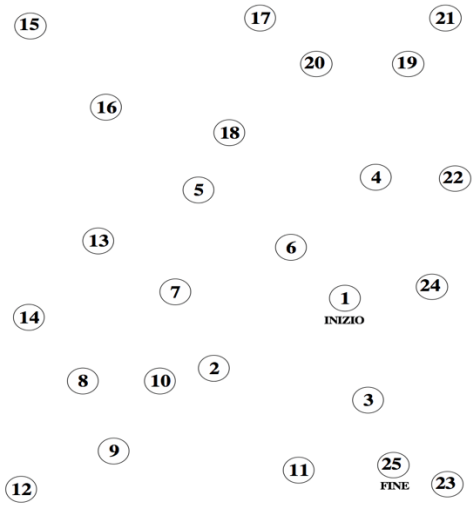
Commento

_____
_____
_____
_____
_____
_____

TRAIL MAKING TEST
Parte A

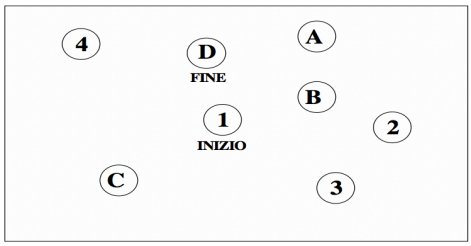
ESEMPIO

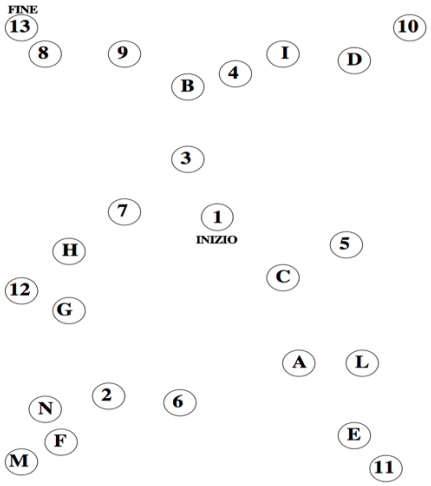




TRAIL MAKING TEST
Parte B

ESEMPIO





Appendix 7: Test of Tale

TEST DI MEMORIA DI PROSA
(Babcock, 1930; Spinnler e Tognoni, 1987)

***Istruzioni**: l' esaminatore dice al paziente: "**Ora le leggerò un raccontino; non appena ho finito, mi dovrà ripetere tutto ciò che ricorda**". L' esaminatore non fornisce alcun suggerimento e trascrive per esteso tutto ciò che il paziente rievoca. Dopo la rievocazione del paziente, l' esaminatore legge il raccontino per una seconda volta. Dopo 10 minuti di attività inteferente non verbale, ha luogo la seconda ripetizione.*

"Sei / dicembre/. La scorsa / settimana / un fiume / straripò / in una piccola / città / situata / a 20 km / da Torino/. L' acqua / invase / le strade / e le case/. Quattordici / persone / annegarono / e seicento / si ammalarono / a causa dell' umidità / e del freddo/. Nel tentativo di salvare / un ragazzo / un uomo / si ferì / le mani."

Rievocazione immediata:.....

.....

.....

.....

.....

.....

.....

.....

Punteggio rievocazione immediata: _____/8

Punteggio:
Solo se vengono riferiti gli eventi "straripamento","morti", "ammalati", "tentativo di salvataggio"si valorizzano anche i dettagli relativi:

"Straripamento"	**3**	**punti**
⇩		
"Piccola città" e/o "Vicino a Torino"	0.3	punti
"La scorsa settimana" e/o "6 dicembre"	0.3	punti
"Morti"	**2**	**punti**
⇩		
"Numero morti" (da 9 a 19)	0.2	punti
"Ammalati"	**1**	**punto**
⇩		
"Numero ammalati" (da 500 a 700)	0.1	punti
"Tentativo di salvataggio"	**1**	**punto**
⇩		
"Ferimento" e/o "ragazzo"	0.1	punti

Il punteggio massimo per ogni ripetizione è 8, il punteggio totale massimo è 16.

2

Appendix 8: Phonological and semantic test

TEST DI FLUENZA VERBALE FONOLOGICA

(Caltagirone et al., 1995. Carlesimo et al., 1995)

Istruzioni: L'esaminatore dice al paziente: "Ora le chiederò di dirmi tutte le parole che le vengano in mente che iniziano con una determinata lettera dell'alfabeto. Non può dirmi nomi propri di persona o nomi di città, ad esempio non può dirmi né Franco né Firenze; tutto il resto va bene: verbi, aggettivi, sostantivi... . Cominciamo con la lettera F."

Il tempo massimo per ogni lettera è di 1 minuto, se il paziente si interrompe prima che sia trascorso 1 minuto si può incoraggiare a trovare altre parole.

N.B. Non considerare nel punteggio finale le parole con lo stesso suffisso, es. Acqua e Acquedotto

F	A	S
1._____	1._____	1._____
2._____	2._____	2._____
3._____	3._____	3._____
4._____	4._____	4._____
5._____	5._____	5._____
6._____	6._____	6._____
7._____	7._____	7._____
8._____	8._____	8._____
9._____	9._____	9._____
10._____	10._____	10._____
11._____	11._____	11._____
12._____	12._____	12._____
13._____	13._____	13._____
14._____	14._____	14._____
15._____	15._____	15._____
16._____	16._____	16._____
17._____	17._____	17._____
18._____	18._____	18._____
19._____	19._____	19._____
TOT: _____	TOT: _____	TOT: _____

TEST DI FLUENZA VERBALE PER CATEGORIE

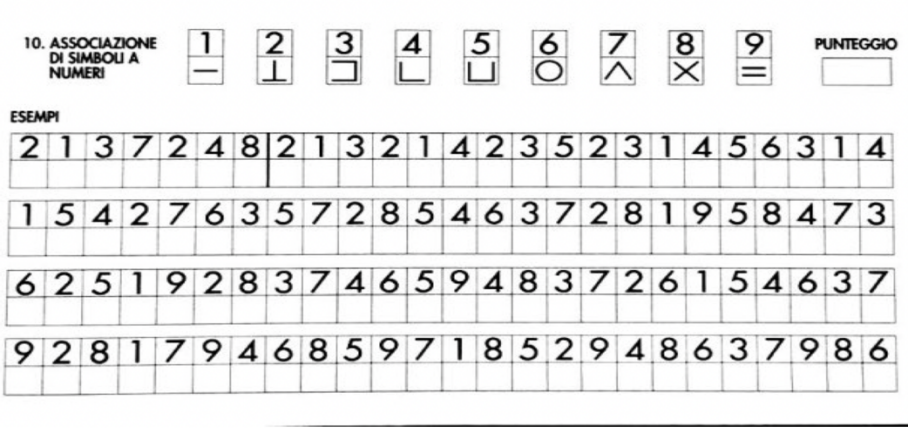
(Novelli, 1986)

Istruzioni: L'esaminatore dice al paziente: "Ora le chiederò di dirmi tutti i nomi che conosce appartenenti a determinate categorie che le dirò. Cominciamo con i frutti."

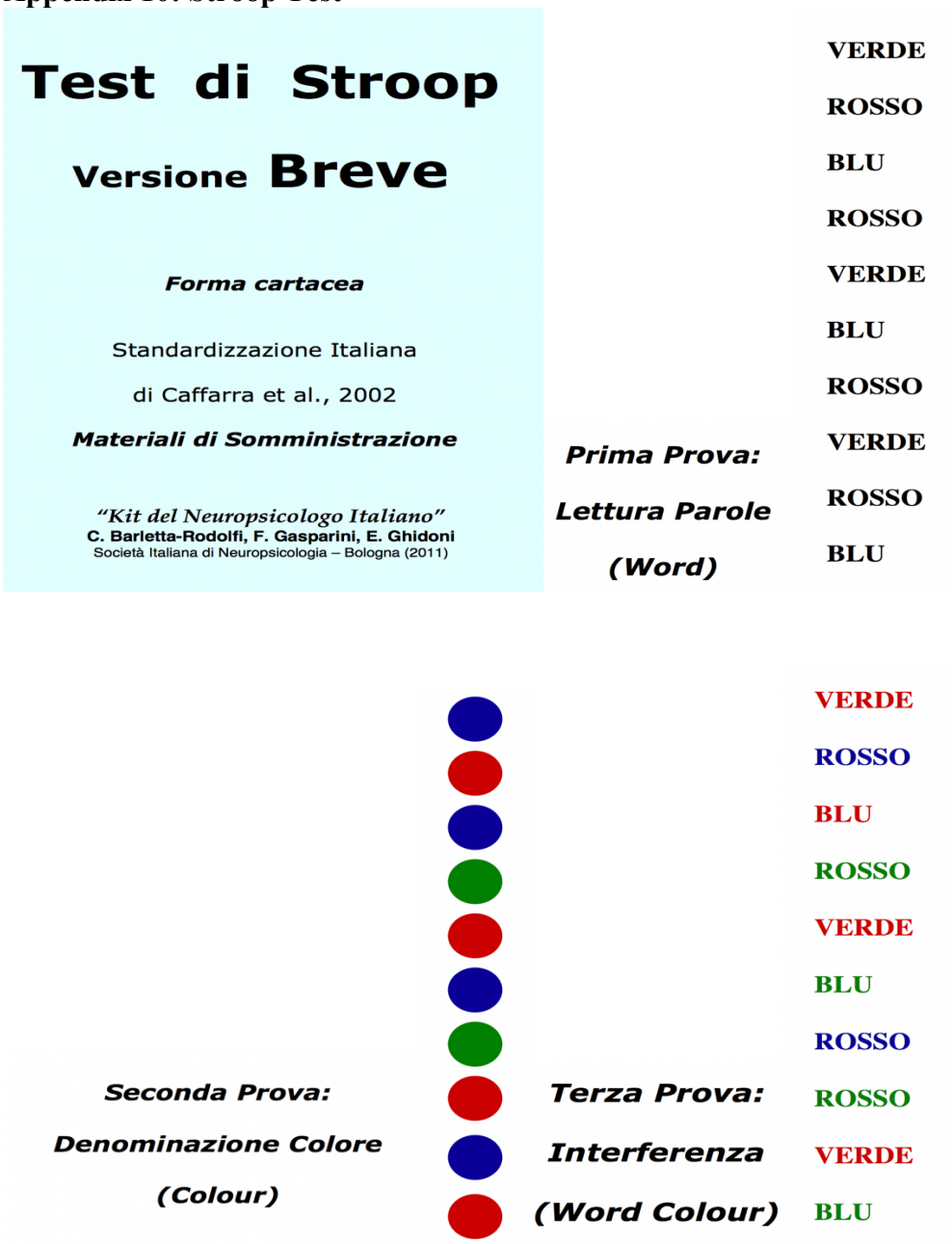
Il tempo massimo per ogni categoria è di 1 minuto, se il paziente si interrompe prima che sia trascorso 1 minuto si può incoraggiare a trovare altre parole.

FRUTTI	ANIMALI	MARCHE D'AUTO
1._____	1._____	1._____
2._____	2._____	2._____
3._____	3._____	3._____
4._____	4._____	4._____
5._____	5._____	5._____
6._____	6._____	6._____
7._____	7._____	7._____
8._____	8._____	8._____
9._____	9._____	9._____
10._____	10._____	10._____
11._____	11._____	11._____
12._____	12._____	12._____
13._____	13._____	13._____
14._____	14._____	14._____
15._____	15._____	15._____
16._____	16._____	16._____
17._____	17._____	17._____
18._____	18._____	18._____
19._____	19._____	19._____
20._____	20._____	20._____
21._____	21._____	21._____
TOT: _____	TOT: _____	TOT: _____

Appendix 9: Digit Symbol Substitution Test



Appendix 10: Stroop Test



Appendix 11: FAB

Frontal Assessment Battery (FAB)

B Dubois-B Pillon-A Slachevsky-I Litvan

Hôpital del la Salpêtrière, 75013 Paris, France

Sei test da usare al letto del paziente (non richiedono più di 10 minuti)

1. **Somiglianza** (concettualizzazione)
   - *"In che cosa sono simili :*
   - *una banana e un'arancia*

(In caso di fallimento totale: "non sono simili" o di fallimento parziale : "entrambe hanno la buccia", aiutare il paziente : *" la banana e l'arancia sono entrambe …."*; ma assegnare 0 a questa risposta; non aiutare i paziente per i due successivi item)

   - *un tavolo e una sedia?*
   - *Un tulipano, una rosa e una margherita?"*

- punteggio : solo le risposte categoriali (frutta, mobili, fiori) sono considerate corrette.

3 risposte corrette	3
2 risposte corrette	2
1 risposta corretta	1
nessuna risposta corretta	0

2. **Fluenza fonemica** (flessibilità mentale)
   - *"Dica il maggior numero possibile di parole che cominciano con la lettera "S", qualsiasi parola eccetto cognomi o nomi propri"*.

Se il paziente non dà nessuna risposta nei primi 5 secondi, dire : *"Per esempio, serpente"*. Se il paziente si ferma per oltre 10 secondi, stimolarlo dicendo : *"Qualsiasi parola che cominci con la lettera "S"* . La prova dura 60 secondi.

- Punteggio: ripetizioni o variazioni (scarpa, scarpone), cognomi o nomi propri non sono contate come risposte corrette.

Più di 9 parole	3
Da 6 a 9 parole	2
Da 3 a 5 parole	1
Meno di 3 parole	0

3. **Serie Motorie** (programmazione)
   - *"Guardi con attenzione quello che faccio"*.

L'esaminatore seduto di fronte al paziente effettua tre volte, da solo, con la mano sinistra la serie di Luria "pugno-taglio-piatto".

   - *"Ora faccia lo stesso, con la mano destra prima con me poi da solo"*.

L'esaminatore effettua tre volte la stessa serie con il paziente, poi gli dice : *"continui da solo"*

- Punteggio:

- il paziente effettua da solo, correttamente, 6 serie consecutive	3
- il paziente effettua da solo, correttamente, almeno 3 serie consecutive	2
- il paziente sbaglia da solo, ma effettua correttamente almeno 3 serie consecutive con l'esaminatore	1
- il paziente non riesce ad effettuare 3 serie consecutive neppure con l'esaminatore.	0

C:\Documents and Settings\UK\Documenti\PSICO\Test-Scales\FAB.doc

4. **Istruzioni contrastanti** (sensibilità all'interferenza)

- *"Batta due volte quando io batto una volta"*.

Per essere sicuri che il paziente abbia capito le istruzioni, si effettua una serie di tre prove : 1-1-1.

- *"Batta una volta quando io batto due volte"*.

Per essere sicuri che il paziente abbia capito le istruzioni, si effettua una serie di tre prove : 2-2-2.

L'esaminatore effettua la serie seguente : 1-1-2-1-2-2-2-1-1-2.

- punteggio :
  - nessun errore 3
  - 1 o 2 errori 2
  - più di 2 errori 1
  - il paziente batte come l'esaminatore per almeno 4 prove consecutive 0

5. **Go – No - Go** (controllo inibitorio)

- *"Batta una volta quando io batto una volta"*.

Per essere sicuri che il paziente abbia capito le istruzioni, si effettua una serie di tre prove : 1-1-1.

- *"Non batta quando io batto due volte"*.

Per essere sicuri che il paziente abbia capito le istruzioni, si effettua una serie di tre prove : 2-2-2-2.

L'esaminatore effettua la serie seguente : 1-1-2-1-2-2-2-1-1-2.

- punteggio :
  - nessun errore 3
  - 1 o 2 errori 2
  - più di 2 errori 1
  - il paziente batte come l'esaminatore per almeno 4 prove consecutive 0

6. **Comportamento di prensione** (autonomia ambientale)

- L'esaminatore è seduto di fronte al paziente. Mettere le mani del paziente con le palme in alto, appoggiate sulle ginocchia. Senza dire nulla e senza guardare il paziente, l'esaminaotre porte le sue mani vicino a quelle del paziente e ne tocca le palme, contemporaneamente da ambo i lati, osservando se il paziente spontanemaente le afferra. Se il paziente le afferra, l'esaminatore prova di nuovo dopo avergli detto: *"Non prenda le mie mani"*

- punteggio :
  - il paziente non afferra le mani dell'esaminatore 3
  - il paziente e vita o chiede cosa deve fare 2
  - il paziente afferra le mani senza esitazione 1
  - il paziente afferra le mani dell'esaminatore anche dopo che gli ha chiesto di non farlo 0

TOTALE …../18

C:\Documents and Settings\UK\Documenti\PSICO\Test-Scales\FAB.doc

Appendix 12: Cognitive Estimation Test

Nome: M F
Cognome: Età:

VERSIONE A

	Punteggio	
Quale è la velocità massima che può raggiungere una motocicletta Harley-Davidson? (km/h)	130<x<200	0
	120≤x<130 o 200<x≤240	1
	100≤x<120 o 240<x≤250	2
	x<100 o x>250	3
In media quanto è alto un neonato? (cm)	40<x<50	0
	35≤x<40 o 50<x≤55	1
	30≤x<35 o 55<x≤60	2
	x<30 o x>60	3
Quale è la velocità di un cavallo da corsa? (km/h)	50<x<80	0
	40≤x<50 o 80<x≤87.5	1
	30≤x<40 o 87.5<x≤100	2
	x<30 o x>100	3
Quale è la velocità media di un corridore di jogging non professionista? (km/h)	8<x<20	0
	6≤x<8 o 20<x≤25	1
	5≤x<6 o 25<x≤30	2
	x<5 o x>30	3
Da quanti spicchi è formata un'arancia? (numero di segmenti)	8<x<12	0
	x=8 o 12<x≤12.8	1
	7≤x<8 o 12.8<x≤16	2
	x<7 o x>16	3
Quanto è lunga una matita nuova? (cm)	15<x<20	0
	10≤x<15 o 20<x≤22	1
	22<x≤25	2
	x<10 o x>25	3
Quale è la velocità massima che può raggiungere un ghepardo? (km/h)	80<x<120	0
	60≤x<80 o 120<x≤130	1
	50≤x<60 o 130<x≤150	2
	x<50 o x>150	3
Quanto è lunga la mountain bike di un uomo di media altezza? (m)	130<x<180	0
	120≤x<130 o 180<x≤200	1
	100≤x<120 o x=200	2
	x<100 o x>200	3
Quanti tasti ci sono in una normale tastiera di computer? (numero di tasti)	40<x<60	0
	35≤x<40 o 60<x≤70	1
	30≤x<35 o 70<x≤80	2
	x<30 o x>80	3
	Tot =	

Nome: M F
Cognome: Età:

VERSIONE B

	Punteggio	
A che velocità media cammina un uomo adulto in salute? (km/h)	3<x<5	0
	2.6≤x<3 o 5<x≤6	1
	2≤x<2.6 o 6<x≤7.7	2
	x<2 o x>7.7	3
Quanto è lunga mediamente una cravatta? (m)	40<x<110	0
	30≤x<40 o 110<x≤130	1
	25≤x<30 o 130<x≤150	2
	x<25 o x>150	3
Quale è la massima velocità che può raggiungere la pallina da tennis al servizio di battuta?(km/h)	50<x<200	0
	30≤x<50 o 200<x≤219	1
	15≤x<30 o 219<x≤230	2
	x<15 o x>230	3
Quanti tasti ci sono su una tastiera da pianoforte? (numero di tasti)	40<x<83.2	0
	32≤x<40 o 83.2<x≤100	1
	30≤x<32 o 100<x≤102	2
	x<30 o x>102	3
Quanti anni ha la persona più anziana d'Italia? (età)	105<x<114	0
	104≤x<105 o 114<x≤115	1
	103≤x<104 o 115<x≤116	2
	x<103 o x>116	3
Quanto è lunga la spina dorsale di un uomo di media altezza? (cm)	60<x<90	0
	50≤x<60 o 90<x≤100	1
	40<x≤50	2
	x<40 o x>100	3
Quale è la massima velocità che può raggiungere un ciclista? (km/h)	50<x<100	0
	40≤x<50 o 100<x≤110	1
	30≤x<40 o 110<x≤120	2
	x<30 o x>120	3
Quante corde ci sono in un'arpa? (numero di corde)	15<x<50	0
	10≤x<15 o 50<x≤70	1
	6≤x<10 o 70<x≤80.25	2
	x<6 o x>80.25	3
Quale è la velocità massima che può raggiungere una macchina di Formula 1? (km/h)	300<x<350	0
	280≤x<300 o 350<x≤360	1
	250≤x<280 o 360<x≤385	2
	x<250 o x>385	3
	Tot =	

Appendix 13: SF-12

STRUMENTO PER LA VALUTAZIONE DELLO STATO DI SALUTE
SF-12

Versione italiana a cura dell'Istituto Superiore di Sanità – Roma

La preghiamo di rispondere alle seguenti domande relative al suo stato di salute. Le informazioni che ci darà rimarranno strettamente confidenziali e non saranno comunicate a nessuno senza il suo permesso. Ci serviranno per capire meglio come si sente e fino a che punto è in grado di svolgere le sue normali attività.

1. **Come giudica nel suo complesso la sua salute?**

5 - eccellente
4 - molto buona
3 – buona
2 – passabile
1 – cattiva

Le seguenti domande riguardano le attività che ptrebbe fare in un giorno qualsiasi. In che misura le sue condizioni di salute le rendono difficile, la limitano nel fare le seguenti attività:

2. **attività che richiedono discreti sforzi fisici (come spostare un tavolo, manovrare un'aspirapolvere, fare un giro in bicicletta…)**

1 – mi limitano molto
2 – mi limitano un po'
3 – non mi limtano per niente

3. **salire alcune rampe di scale**

1 – mi limitano molto
2 – mi limitano un po'
3 – non mi limtano per niente

Nelle ultime 4 settimane, a causa di malattie fisiche, ha avuto i seguenti problemi al lavoro, o nelle altre attività di tutti i giorni?

4. **ha reso meno o fatto meno bene di quello che avrebbe voluto?** SI NO

5. **ha dovuto rinunciare a fare alcune cose sul lavoro o nelle altre attività?** SI NO

Nelle ultime 4 settimane, a causa di problemi psicologici, ad esempio perché si sentiva depresso o ansioso, o perché gli altri non le credevano o volevano fargli del male:

6. **ha reso meno di quello che avrebbe voluto?** NO SI

7. **Non ha fatto le cose con la stessa cura e attenzione che avrebbe voluto?** SI NO

8. nelle ultime 4 settimane, il dolore fisico le ha reso difficile il lavoro o le altre attività, in casa e fuori?

5 – per niente
4 – un po'
3 – abbastanza
2 – molto
1 – moltissimo

Le seguenti domande riguardano il suo stato d'animo nelle ultime 4 settimane. Per quanto tempo nelle ultime 4 settimane si è sentito:

9. calmo e sereno?

6 – sempre
5- la maggior parte del tempo
4 – più o meno metà del tempo
3 – qualche volta
2 – raramente
1 – mai

10. pieno di energia?

6 – sempre
5- la maggior parte del tempo
4 – più o meno metà del tempo
3 – qualche volta
2 – raramente
1 – mai

11. scoraggiato e triste?

1 – sempre
2 - la maggior parte del tempo
3 – più o meno metà del tempo
4 – qualche volta
5 – raramente
6 – mai

12. Nelle ultime 4 settimane, per qunto tempo la sua salute fisica o le sue condizioni psicologiche le hanno causato problemi nella vita sociale (ad esempio nei suoi rapporti con parenti e amici?

1 – sempre
2 – la maggior parte del tempo
3 – qualche volta
4 – raramente
5 - mai

Appendix 14: TAS-20

TAS – 20

Toronto Alexithymia Scale

G.J. TAYLOR, R.M. BAGBY, J.D.A. PARKER, 1992

Seguendo le istruzioni sotto elencate indichi quanto è d'accordo o no con ciascuna delle seguenti affermazioni segnando una **x** sopra il numero corrispondente.

Segnare una sola risposta per ciascuna frase.

1 = NON SONO PER NIENTE D'ACCORDO
2 = NON SONO MOLTO D'ACCORDO
3 = NON SONO NÉ D'ACCORDO NÉ IN DISACCORDO
4 = SONO D'ACCORDO IN PARTE
5 = SONO COMPLETAMENTE D'ACCORDO

1.	Sono spesso confuso/a circa le emozioni che provo	1	2	3	4	5
2.	Mi è difficile trovare le parole giuste per esprimere i miei sentimenti	1	2	3	4	5
3.	Provo delle sensazioni fisiche che neanche i medici capiscono	1	2	3	4	5
4.	Riesco facilmente a descrivere i miei sentimenti	1	2	3	4	5
5.	Preferisco approfondire i miei problemi piuttosto che descriverli semplicemente	1	2	3	4	5
6.	Quando sono sconvolto/a non so se sono triste, spaventato/a o arrabbiato/a	1	2	3	4	5
7.	Sono spesso disorientato dalle sensazioni che provo nel mio corpo	1	2	3	4	5
8.	Preferisco lasciare che le cose seguano il loro corso piuttosto che capire perché sono andate in quel modo	1	2	3	4	5
9.	Provo sentimenti che non riesco proprio ad identificare	1	2	3	4	5
10.	È essenziale conoscere le proprie emozioni	1	2	3	4	5
11.	Mi è difficile descrivere ciò che provo per gli altri	1	2	3	4	5
12.	Gli altri mi chiedono di parlare di più dei miei sentimenti	1	2	3	4	5
13.	Non capisco cosa stia accadendo dentro di me	1	2	3	4	5
14.	Spesso non so perché mi arrabbio	1	2	3	4	5
15.	Con le persone preferisco parlare di cose di tutti i giorni piuttosto che delle loro emozioni	1	2	3	4	5
16.	Preferisco vedere spettacoli leggeri, piuttosto che spettacoli a sfondo psicologico	1	2	3	4	5
17.	Mi è difficile rivelare i sentimenti più profondi anche ad amici più intimi	1	2	3	4	5
18.	Riesco a sentirmi vicino ad una persona, anche se ci capita di stare in silenzio	1	2	3	4	5
19.	Trovo che l'esame dei miei sentimenti mi serve a risolvere i miei problemi personali	1	2	3	4	5
20.	Cercare significati nascosti in films o commedie distoglie dal piacere dello spettacolo	1	2	3	4	5

Appendix 15: Self Anxiety Scale

565

SELF-RATING ANXIETY STATE
SAS - # 054

Cognome e Nome..... Data di nascita.....

Codice Paziente..... Valutatore..... Data valutazione.....

ISTRUZIONI GENERALI

Legga attentamente ciascuna delle 20 frasi elencate qui sotto: in che misura ciascuna di queste frasi descrive come lei si è sentito nel corso di quest'ultima settimana? Si è sentito così "quasi mai o raramente", "qualche volta", "spesso", "quasi sempre"? Per ogni frase faccia una crocetta nella colonna che le sembra la più appropriata a descrivere come si è sentito.

	Quasi mai o Raramente	Qualche volta	Spesso	Quasi sempre
1. Mi sento più nervoso ed ansioso del solito	1	2	3	4
2. Mi sento impaurito senza alcun motivo	1	2	3	4
3. Mi spavento facilmente o sono preso dal panico	1	2	3	4
4. Mi sento a pezzi e mi sembra di stare per crollare	1	2	3	4
5. Mi sembra che tutto vada bene e che non capiterà niente di male	4	3	2	1
6. Mi tremano le braccia e le gambe	1	2	3	4
7. Sono tormentato dal mal di testa e dai dolori al collo e alla schiena	1	2	3	4
8. Mi sento debole e mi stanco facilmente	1	2	3	4
9. Mi sento calmo e posso star seduto facilmente	4	3	2	1
10. Sento che il mio cuore batte veloce	1	2	3	4
11. Soffro di vertigini	1	2	3	4
12. Mi sembra di stare per svenire	1	2	3	4
13. Respiro con facilità	4	3	2	1
14. Ho sensazioni di intorpidimento e di formicolio alle dita delle mani e dei piedi	1	2	3	4
15. Soffro di mal di stomaco o di indigestione	1	2	3	4
16. Ho bisogno di urinare spesso	1	2	3	4
17. Le mie mani sono in genere asciutte e calde	4	3	2	1
18. La mia faccia diventa facilmente calda e arrossata	1	2	3	4
19. Mi addormento facilmente e mi sveglio riposato	4	3	2	1
20. Ho degli incubi	1	2	3	4

Appendix 16: Patient Health Questionnaire

PHQ9P

QUESTIONARIO SULLA SALUTE DEL/DELLA PAZIENTE-9 72883
(Italian version of the PHQ-9)

THIS SECTION FOR USE BY STUDY PERSONNEL ONLY.

Were data collected? **No** ☐ *(provide reason in comments)*

If **Yes**, data collected on visit date ☐ **or** specify date: _____
DD-Mon-YYYY

Comments:

Only the patient (subject) should enter information onto this questionnaire.

Nelle ultime 2 settimane, con quale frequenza le ha dato fastidio ciascuno dei seguenti problemi?	**Mai**	**Alcuni giorni**	**Per più della metà del tempo**	**Quasi ogni giorno**
1. Scarso interesse o piacere nel fare le cose	0	1	2	3
2. Sentirsi giù, triste o disperato/a	0	1	2	3
3. Problemi ad addormentarsi o a dormire tutta la notte senza svegliarsi, o a dormire troppo	0	1	2	3
4. Sentirsi stanco/a o avere poca energia	0	1	2	3
5. Scarso appetito o mangiare troppo	0	1	2	3
6. Avere una scarsa opinione di sé, o sentirsi un fallimento o aver deluso se stesso/a o i propri familiari	0	1	2	3
7. Difficoltà a concentrarsi su qualcosa, per esempio leggere il giornale o guardare la televisione	0	1	2	3
8. Muoversi o parlare così lentamente da poter essere notato/a da altre persone. O, al contrario, essere così irrequieto/a da muoversi molto più del solito	0	1	2	3
9. Pensare che sarebbe meglio morire o farsi del male in un modo o nell'altro	0	1	2	3

SCORING FOR USE BY STUDY PERSONNEL ONLY

0 + _____ + _____ + _____

=Total Score: _____

Se ha fatto una crocetta su uno qualsiasi di questi problemi, quanto questi problemi le hanno reso difficile fare il suo lavoro, occuparsi delle sue cose a casa o avere buoni rapporti con gli altri?

Per niente difficile	**Abbastanza difficile**	**Molto difficile**	**Estremamente difficile**
☐	☐	☐	☐

 EPI0905.PHQ9P

Confermo l'esattezza di queste informazioni.	Iniziali del/della paziente o del soggetto:	Data:

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Appendix 17: HoNOS

HEALTH OF THE NATION OUTCOME SCALES
HoNOS - # 348

Cognome e Nome..... Data di nascita.....

Codice Paziente..... Valutatore..... Data valutazione.....

1. Comportamento iperattivo, aggressivo, clastico o agitato (0-4) ..... __

2. Automutilazioni non accidentali (0-4) ..... __

3. Problemi legati all'assunzione di alcol o di sostanze (0-4) ..... __

4. Problemi cognitivi (0-4) ..... __

5. Malattie fisiche o problemi di invalidità (0-4) ..... __

6. Problemi associati ad allucinazioni e deliri (0-4) ..... __

7. Problemi di umore depresso (0-4) ..... __

8. Altri problemi psichici e comportamentali (0-4) ..... __

Specificare il disturbo (A-J) ..... __

A - Fobie; B - Ansia; C - Ossessioni-compulsioni; D - Tensione/logorio psichico;
E - Dissociazione; F - Disturbi somatoformi; G - Alimentazione; H - Sonno;
I - Sessuali; J - Altro (specificare)

9. Problemi nei rapporti interpersonali (0-4) ..... __

10. Problemi nelle attività della vita quotidiana (0-4) ..... __

11. Problemi nelle condizioni di vita (0-4) ..... __

12. Problemi nelle attività occupazionali e ricreative (0-4) ..... __

Punteggio totale: **0-48** ..... __ __

Sede della valutazione (1-7) ..... __

1 - Strutt. per acuti; 2- Strutt. per cronici; 3 - Day hospital; 4 - Centro diurno;
5 - Ambulatorio; 6 - Domicilio; 7 - Altro (specificare)

Diagnosi primaria (1-7) ..... __

0 - Demenza; 1 - Abuso di alcol/farmaci/sostanze; 2 - Schizofrenia/deliri;
3 - Disturbo dell'umore; 4 - Nevrosi/ansia; 5 - Disturbi alimentari/
del sonno/sessuali; 6 - Disturbi di personalità; 7 - Altro (specificare)

Appendix 18: Biological Rythms Interview Of Assessment In Neuropsychiatry (Brian)

Tra gli aspetti riportati di seguito indichi l'opzione che la descrive meglio negli ultimi 15 giorni:

SONNO

1. Quanto ha difficoltà ad addormentarsi alla solita ora?

1	PER NULLA
2	POCO
3	ABBASTANZA
4	MOLTO

2. Quanto ha difficoltà a svegliarsi alla solita ora?

1	PER NULLA
2	POCO
3	ABBASTANZA
4	MOLTO

3. Quanto ha difficoltà ad alzarsi dal letto dopo essersi svegliato?

1	PER NULLA
2	POCO
3	ABBASTANZA
4	MOLTO

4. Quanto ha difficoltà sentirsi riposato con le ore di sonno che sta facendo (questo in riferimento alla sensazione soggettiva di sentirsi riposato per lo svolgimento delle attività quotidiane come guidare, ragionare e lavorare)?

1	PER NULLA
2	POCO
3	ABBASTANZA
4	MOLTO

5. Quanto ha difficoltà a "staccare" nei momenti di riposo?

1	PER NULLA
2	POCO
3	ABBASTANZA
4	MOLTO

ATTIVITÀ

6. Quanto ha difficoltà a portare a termine tutte le attività del suo lavoro?

1	PER NULLA
2	POCO
3	ABBASTANZA
4	MOLTO

7. Quanto ha difficoltà a portare a termine le sue attività abituali (pulizie di casa, fare le spesa)?

1	PER NULLA
2	POCO
3	ABBASTANZA
4	MOLTO

8. Quanto ha difficoltà a mantenere il suo ritmo di attività fisica (per esempio: prendere l'autobus/metro, o praticare uno sport - se questo fa parte delle sue abitudini)?

1	PER NULLA
2	POCO
3	ABBASTANZA
4	MOLTO

9. Quanto ha difficoltà a rispettare il programma abituale delle sue attività?

1	PER NULLA
2	POCO
3	ABBASTANZA
4	MOLTO

10. Quanto ha difficoltà a mantenere il suo livello di desiderio/attività sessuale?

1	PER NULLA
2	POCO
3	ABBASTANZA
4	MOLTO

SOCIALE

11. Quanto ha difficoltà a relazionarsi e comunicare con le persone del suo ambiente?

1	PER NULLA
2	POCO
3	ABBASTANZA
4	MOLTO

12. Quanto ha difficoltà a non abusare dell'uso di apparecchi elettronici come TV, internet, ecc. (senza che tale uso alteri il contatto con le persone del suo ambiente o che sottragga troppo tempo ad altre attività)?

1	PER NULLA
2	POCO
3	ABBASTANZA
4	MOLTO

13. Quanto ha difficoltà ad adattare le sue abitudini e il suo sonno a quelli delle persone con cui vive (famigliari, vicini, amici)?

1	PER NULLA
2	POCO
3	ABBASTANZA
4	MOLTO

14. Quanto ha difficoltà a disporre di tempo e attenzione per le persone con cui vive (famigliari, vicini, amici)?

1	PER NULLA
2	POCO
3	ABBASTANZA

4	MOLTO

ALIMENTAZIONE

15. Quanto ha difficoltà a rispettare gli orari dei pasti (colazione, pranzo e cena)?

1	PER NULLA
2	POCO
3	ABBASTANZA
4	MOLTO

16. Quanto ha difficoltà a rispettare le sue abitudini alimentari in termini di non saltare i pasti?

1	PER NULLA
2	POCO
3	ABBASTANZA
4	MOLTO

17. Quanto ha difficoltà a rispettare le sue abitudini alimentari in termini di quantità di cibo?

1	PER NULLA
2	POCO
3	ABBASTANZA
4	MOLTO

18. Quanto ha difficoltà a non consumare in eccesso sostanze stimolanti (come caffé o coca- cola), o cioccolato/dolci?

1	PER NULLA
2	POCO
3	ABBASTANZA
4	MOLTO

RITMO PREDOMINANTE (serale o mattutino)

Questa parte della scala è opzionale e si riferisce alle sue abitudini. Consideri qui gli ultimi 12 mesi.

19. Ha la tendenza a essere più attivo durante la notte (lavoro, relazioni interpersonali)?

1	MAI
2	RARAMENTE
3	QUASI SEMPRE
4	SEMPRE

20. Ha la sensazione di essere più produttivo la mattina?

1	MAI
2	RARAMENTE
3	QUASI SEMPRE
4	SEMPRE

21. Ha la sensazione di scambiare il giorno per la notte?

1	MAI
2	RARAMENTE
3	QUASI SEMPRE
4	SEMPRE