PERSPECTIVE-TAKING, SELF-AWARENESS AND SOCIAL COGNITION IN NEURODEGENERATIVE DISORDERS, CEREBRAL ABNORMALITIES AND ACQUIRED BRAIN INJURIES (ABI): A NEUROCOGNITIVE APPROACH.

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PERSPECTIVE-TAKING, SELF-AWARENESS AND SOCIAL COGNITION IN NEURODEGENERATIVE DISORDERS, CEREBRAL ABNORMALITIES AND ACQUIRED BRAIN INJURIES (ABI): A NEUROCOGNITIVE APPROACH.

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EDITORIAL
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Editorial: Perspective-Taking, Self-Awareness and Social Cognition in Neurodegenerative Disorders, Cerebral Abnormalities and Acquired Brain Injuries (ABI): A Neurocognitive Approach

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Editorial on the Research Topic

Perspective-Taking, Self-Awareness and Social Cognition in Neurodegenerative Disorders, Cerebral Abnormalities and Acquired Brain Injuries (ABI): A Neurocognitive Approach

Human beings are not isolated entities but are embedded in a network of social relationships that influence them and by which they are influenced. A fundamental characteristic of the human being is the ability to cooperate, which has been a crucial step in the evolution of complex social interactions (Tomasello, 2009; Morese et al., 2016; Lo Gerfo et al., 2019).

According to Frith (2008), social cognition concerns the psychological processes that allow individuals to live in different social contexts, to benefit from belonging to social groups. It makes possible various aspects of daily life that are based on empathic processes, such as the perception and recognition of the emotions of the other and the consequent appropriate behavior. The discoveries of recent decades on the mirror neuron system offer an important contribution to the development of knowledge about the neurophysiological correlates underlying social cognition. This progress can be considered an important step in understanding people's actions, emotions, and beliefs.

This new trend has opened a new interdisciplinary field, called "social neuroscience," dedicated to the understanding of the relationship between social psychology and neuroscience. The aim is to investigate the links between mind, body, and behavior by analyzing how social interactions affect cognitive abilities, brain, and physiological functioning (Cacioppo, 2002). This branch of neuroscience aims to analyze phenomena at three levels of analysis: the social level, which concerns the motivations and social factors that influence behavior; the cognitive level, as a mechanism of information processing; and the neural level, which concerns the brain mechanisms underlying the cognitive processes involved.

The Research Topic here presented aims to provide knowledge on the (neuro)psychological models and the neuro-functional architecture of social and affective processes to foster the understanding of the cognitive, emotional, and behavioral functioning of individuals with

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specific disorders. Some cognitive processes such as metacognition, perspective-taking, empathy, self-awareness, executive functions and social cognition are not just a matter of debate of neuroscience, but they have raised increasingly attention as they have clinical effects on patients' quality of life, compliance with treatment, and prognosis. Moreover, these cognitive higher-order cognitive processes are crucial for interpersonal relationships and effective communication. This is even more true in the case of clinical settings: deficits in these domains have a deleterious impact on the doctor-patient relationship and, subsequently, on therapeutic interventions. There is also more. The neurocognitive approach has formerly emphasized the association among brain pathology, metacognitive-executive dysfunctions, and self-awareness reduction.

The goal of this Research Topic is to bring together theoretical models and experimental research pertaining to all these aspects in neurodegenerative disorders, cerebral abnormalities, and acquired brain injuries. The intention is to provide the reader with the most up-to-date perspective on how the interplay between neurophysiological mechanisms and neuropsychological factors leads to multifaceted and highly organized behaviors.

This e-book comprises a special issue collection of 11 contributions represented by one full review, one general commentary, two perspective articles, one study protocol, three original research articles, one brief research report, and two case reports, which are classified into Part A: Neurodegenerative Disorders; Part B: Acquired Brain Injuries.

NEURODEGENERATIVE DISORDERS

Anosognosia and reduced self-awareness are frequently used as alternative expressions and an overlay between them has been emphasized. This is a delicate matter since according to the interpretation given to those terms, evaluation and understanding of the phenomenon change (Morese et al., 2018). Interpretative models and vocabulary are discussed in an interesting commentary (Bertrand et al.). The authors explore fundamental issues such as executive anosognosia, apathy, and error Monitoring.

A reduction in self-awareness is a crucial aspect in the symptomatology of various neurodegenerative disorders. An intriguing theoretical proposal regarding the use of virtual reality as fruitful addition to self-awareness assessment is presented (Muratore et al.). ICT-IoT technology can also promote a perspective change about neurodegenerative diseases that encourages a more inclusive view of patients. To ensure this, Dementia-Friendly Communities have recently been developed (Morganti et al.). In this scenario, a personalized approach that enhances the emotional state of cognitively impaired patients seems to be increasingly necessary: the Lüscher color test is proposed as a simple and unconventional approach to understand the emotional life of Alzheimer's disease patients (Maserati et al.). "Unconventional" approaches and neuroimaging findings prove to be useful in pathologies with different etiopathogenesis especially when atypical. The report of a case of Creutzfeldt-Jakob disease with an unusual clinical presentation is presented here. The clinical picture was characterized by dynamic aphasia in the context of a prominent dysexecutive syndrome and a lack of emotional insight and concern over the health status (Prodi et al.).

The damage of metacognitive-executive functions has previously been associated also with dyskinesias-reduced-self-awareness (Palermo et al., 2017a, 2018a,b; Palermo et al., 2019b) and impulse control disorder (Palermo et al., 2017b; Palermo and Morese, 2018) in Parkinson's disease (PD). A perspective article on altruistic punishment and impulsivity in PD suggested that metacognitive-executive functions and neurophysiological abnormalities, which associates disinhibition with volition, are also associated with social cognition impairment (Morese and Palermo). This kind of symptomatology requires a person-centered perspective capable of addressing the unmet needs of PD patients (Palermo et al., 2019a). In line with the above, a PD-specific intervention for increasing patients' mindfulness—and thereby reducing impaired self-awareness for motor symptoms—has successfully been tested and described: IPSUM (Buchwitz et al.). Its impact on self-awareness and patients' daily living is now being assessed. Another original approach to the disease sheds light on a possible use of complex action observation to improve or slow the deterioration of motor abilities and levodopa-induced dyskinesias (Palermo et al.). Never had anyone tried to study the neural correlates involved in empathy and embodiment in PD through observation of choreutical arts.

The section closes with an interesting study on resting-state functional correlates (RS-FC) of social cognition in multiple sclerosis (Bisecco et al.). For the first time, an association between social cognition and RS-FC changes of DMN, executive and limbic networks has been verified.

ACQUIRED BRAIN INJURIES

Traumatic brain injury (TBI) can be serious partly due to the challenges of assessing and treating its neurocognitive and affective sequelae. Impairment in social cognition and its neural underpinnings have not been explored thoroughly in TBI. Findings on the cognitive and affective consequences of TBI in relation to neuropsychological testing strategies, to neurobiological and neuroimaging correlates, and to patient age at and assessment time after injury are presented in a full review (Calvillo and Irimia).

A last research focuses on moral emotions, aiming to investigate the differences in moral functioning that characterize TBI patients. The Moral Emotional Agent (MEA) methodology and implications for the design of rehabilitation applications based on virtual agents are presented (Ceccaldi et al.).

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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PERSPECTIVE
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Virtual Reality as a Possible Tool for the Assessment of Self-Awareness

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The absence of self-awareness is a crucial aspect in the symptomatology of various neurodegenerative disorders. This characteristic becomes relevant due to the strong implications it has on the patient's quality of life, on the effects that functional dependence has on the caregiver and on the efficacy of the therapy. Faced with a construct as complex as self-awareness, there are in the literature investigations on different aspects of this phenomenon, such as the creation of cognitive models, the study of the neural substrate and the research of appropriate assessment methods that can reliably detect this function. With regard to the assessment methods, there are methodologies in the literature that provide complementary information. The first modality is a quantitatively online measurement based on the discrepancy between the estimate of the patient of his performance and his actual performance, but often neglecting the ecological validity and the real functioning of the subject. The second kind collecting subjective information on the actual daily functioning of the patient resulting from clinical observation or interviews with the subject and caregivers, but obtaining offline information on the functioning of the subject, liable to bias that may imply an overestimation or underestimation of subject's ability. The absence of acknowledged metacognitive functional assessment with normative data to evaluate awareness winks at the emerging and increasingly consistent use of virtual reality (VR) also in the context of cognitive research and clinical assessment. This article aims to make a theoretical proposal regarding the use of this innovative and promising tool as a supplement to the assessment methods of self-awareness.

Keywords: self-awareness, virtual reality, assessment, neurodegenerative disorders, anosognosia

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SELF-AWARENESS IN NEURODEGENERATIVE DISORDERS

Self-awareness is defined by Morin (2011) as the ability of the individual to bring attention to a series of aspects concerning themselves, such as his own behavior, emotions, personality traits, cognitive abilities, goals, perceptions, bodily sensations. In the context of neurodegenerative diseases, it is addressed as awareness of one's own illness, of one's own deficits, both cognitive, physical, behavioral or concerning the emotional sphere (Rosen, 2011). This phenomenon, called anosognosia, is very common in neurodegenerative diseases such as Alzheimer's disease (AD) and the behavioral variant of frontotemporal dementia (bvFTD). In patients with AD, anosognosia concerns, in particular, the absence of awareness of difficulties on the activities of daily living (ADL) and impaired cognitive functions, such as episodic memory and spatial cognition

(Starkstein et al., 2006). Consequently, the research focused on the analysis of the awareness of one's own memory capacity, also called meta-memory (Zamboni and Wilcock, 2011; Cosentino et al., 2015). In bvFTD, wherein the self-awareness deficit emerges in very early stages and appears to have even more important entity than in AD, awareness of changes in behavioral, emotional and social skills is often assessed (Neary et al., 1998; Desmarais et al., 2018).

Lack of awareness has very important implications on several aspects of the management of the disease, for example, the exposure of the patient to risky situations due to a wrong evaluation of their abilities, less adherence and collaboration to treatment, difficulty in exploiting the proposed strategies which often results in reduced functional autonomy and a consequent greater burden on the caregiver (Asmus et al., 2006). Moreover, this is an aspect that often precedes the cognitive and functional decline. Therefore, many researches have investigated even those condition with a high probability of conversion in neurodegenerative disorders, such as MCI, in which it is present, rather than an evident anosognosia, a reduced self-awareness of one's cognitive abilities, an element that is associated with an increase in the probability of development of dementia (Tabert et al., 2007). Before that a significant functional and cognitive decline occurs in these patients, an accurate assessment of this condition would allow formulating treatments useful to the intervention (Cummings et al., 2013; Jessen et al., 2014).

The Traditional Assessment of Self-Awareness

In parallel with the current lack of clarity about the psychological mechanisms and the neural networks that underlie the processes of self-awareness, there is no acknowledged method of measurement that allows quantifying this construct (Rosen, 2011; Sunderaraman and Cosentino, 2017). To date, there are three main evaluation methods in the literature, which are complementary to each other due to the strengths and weaknesses of the type of information that can be obtained. The first modality, related to clinical studies, involves the evaluation of a clinician through using structured or unstructured interviews (Prigatano, 2010); the second one provides a discrepancy measure between the self-report of the subject and that of a caregiver through questionnaires that investigate an aspect of functioning of the patient (Hart et al., 2003; Orfei et al., 2010; Zamboni et al., 2012). Through these first two modes, we obtain information from subjective evaluations, which are therefore subject to bias due to a series of factors (e.g., caregiver burden, limited interaction with the patient, errors in reporting information, etc.) that could lead to overestimation or underestimation of the patient's abilities. Furthermore, this information refers to the functioning of self-awareness in general, not related to a specific task (in an offline fashion), although they refer to the functioning of the subject in his natural environment, theoretically with greater ecological validity. The third modality, mainly used in experimental studies dealing with meta-cognition, is based on the quantification of the accuracy of the subject in judging previously or after his performance to a standardized neuropsychological task (typically memory or executive functions) and comparing it with its actual performance (Fragkiadaki et al., 2016). This methodology has the undoubted advantage of being able to have an online quantification of the subject's self-awareness, but at the same time, the used tasks and the traditional neuropsychological tests are useful for evaluating specific cognitive domains and deficient in an ecological evaluation of functional abilities. Furthermore, neuropsychological testing is lacking in the assessment of social skills, which are often affected by anosognosia, especially in bvFTD, in which these deficits are among the first to appear (Eslinger et al., 2005). Despite this, according to the study conducted by Levy et al. (2018), the methodology based on evaluation by a clinician is more associated with brain areas and with executive dysfunction evaluations, both theoretically associated with self-awareness. Furthermore, it is more associated with neuropsychological test performance than the discrepancy method used with the Frontal Systems Behavioral Scale (Levy et al., 2018). In the next section, the properties and technical features of VR will be described and proposed as a method for assessing self-awareness that could compensate for the limitations of the traditional ways above described, integrating their points of strength.

SELF-AWARENESS ASSESSMENT: THE POTENTIAL OF VIRTUAL REALITY

Rizzo et al. (1998) has defined virtual reality (VR) as an advanced computer interface that allows the user to interact and become immersed within computer-generated simulated environments.

The VR label contains multiple technological solutions with different characteristics that can comply with specific research and clinical practice requirements (Li et al., 2017). Devices types can be categorized according to the level of immersion they can induce. Non-immersive systems present the virtual environment through a desktop, they are the simplest and relatively cheaper systems available. Immersive systems use devices, such as head-mounted displays (HMDs), that visually isolating user providing a more complete experience, allowing to perceive a 3D stereoscopic images, to detect position in the virtual environment *via* motion tracking sensors integrated into the helmet and providing different levels of interaction with the environment (**Table 1**). Semi-immersive systems, such as the Cave Automatic Virtual Environment (CAVE), a system that use projectors providing a stereo image of a 3D scene directed on three or more walls of a room, cost more than the other systems, but give a higher sense of reality thanks to the illusion of technological non-mediation (Cipresso et al., 2018). The different kinds of HMDs can require from the simple use of a smartphone to the more powerful systems that need to be connected to a PC. Interaction modes also vary between device types, allowing from simple exposure to an environment up to the manipulation of items in the environment through one or two controllers. The more complex systems allow the planning of more interactive tasks but, besides having a higher cost, implies a greater difficulty in the development of the program. However, there are platforms for the development of

TABLE 1 | Comparison of reality systems.

	PC-based			Mobile-based			Console-based	Standalone mobility		
Mobilty required										
System	Oculus Rift	HTC Vive/Vive Pro	Microsoft Mixed Reality	Samsung Gear VR	Google Cardboard	Google Daydream	Playstation VR	Oculus Go	Oculus Quest	Mirage Solo
Cost	399 US$	499/799 US$	249/449 US$	99 US$	10–50 US$	69–149 US$	299 US$	199 US$	399 US$	299 US$
Hardware requirements	High End PC (>1,000 US$)	High End PC (>1,000 US$)	Mid Level PC (>600 US$)	High End Samsung Phone (>600 US$)	Middle/High end Android phone or iPhone (>299 US$)	High End Android Phone (>499 US$)	PS4 (299 US$) or PS4 Pro (399 US$)	None (Internal Snapdragon 821 processor)	None (Internal Snapdragon 835 processor)	None (Internal Snapdragon 835 processor)
Resolution	2,160 × 1,200	2,160 × 1,200/2,880 × 1,660	2,880 × 1,440	2,560 × 1,440	Depends from the phone (minimum 1,024 × 768)	Depends from the phone (minimum 1,920 × 1,080)	1,920 × 1,080	2,560 × 1,440	2,560 × 1,440	2,560 × 1,440
Refresh rate	90 Hz	90 Hz	90 Hz	60 Hz	60 Hz	90 Hz minimum	120 Hz	72 Hz	72 Hz	75 Hz
Field of view	110°	110°	100/110°	101°	from 70°	96°	100°	90°	100°	100°
Body tracking	Medium/High: head tracking (rotation) and positional tracking (forward/ backward)	High: head tracking (rotation) and volumetric tracking (full room size – 15 ft x 15 ft—movement)	Medium/High: head tracking (rotation) and positional tracking (forward/ backward)	Medium: head tracking (rotation)	Medium: head tracking (rotation)	Medium: head tracking (rotation)	Medium/High: head tracking (rotation) and positional tracking (forward/ backward)	Medium: head tracking (rotation)	Medium/High: head tracking (rotation) and positional tracking (forward/ backward)	Medium/High: head tracking (rotation) and positional tracking (forward/ backward)
User interaction with VR	High (using a joystick or controllers)	High (using controllers)	High (using a joystick or controllers)	Medium (using gaze, a built in pad or joystick)	Low (using gaze or a button)	Medium (using gaze or joystick)	High (using a joystick or controllers)	Medium (using gaze, a built in pad or joystick)	High (using a joystick or controllers)	Medium (using gaze, a built in pad or joystick)
Software availability	Oculus Store	Steam Store	Microsoft Store	Oculus Store	Google Play or IOS Store	Google Play	Playstation Store	Oculus Store	Oculus Store	Google Play

VR environments, such as Neuro VR (Riva et al., 2007), suitable for use by non-experts, with the possibility of creating high-quality environments.

This technological tool is proposed as a mean that can improve different aspects of traditional neuropsychological assessment (Riva, 1997, 2002). Traditional neuropsychological tests investigate isolated cognitive functions and often under artificial conditions that imply low ecological validity and consequently provide poor information on the actual daily functioning of the subject. The VR, on the other hand, allows using a series of settings that simulate those of the real world, such as cities, supermarkets, workstations and domestic environments, for the assessment of complex capabilities and the actual functioning of the patient. This new technologic tool allows the use of interactive, multimodal sensory stimuli with a high degree of ecological validity and provides a high degree of control over the content variables and stimulus delivery and responses measurement and storage in clinical assessment or rehabilitation settings (Lee et al., 2003; Rizzo et al., 2004; Bohil et al., 2011). According to the study of Lopez Maite et al. (2016), the functional assessment with VR provides a mean to objectively experimentally evaluate the functional impact of the disorders in situations close to the constraints of real life, but offers the advantage to avoid the dangers of real-life environments, becoming a suitable tool for testing vulnerable adults, such as patients with neurodegenerative disease (Elkind et al., 2001). Another important feature of this technology is the potential impact of the VR experience. There is evidence of a good learning of the skills trained in VR and that these skills can be transferred to similar tasks in the real world (McComas and Sveistrup, 2002), making it an interesting tool both for cognitive assessment as for rehabilitation.

There are several studies that have used VR in the evaluation of cognitive functioning, both in healthy subjects and patients with brain injury or with neurodegenerative diseases, of the latter, patients with AD, bvFTD and Parkinson's disease. Moreover, according to a study by Flynn et al. (2003), aimed at assessing whether the use of VR as a clinical tool is applicable to people with dementia, it seems that this kind of patients experience a good sense of presence, but above all that VR does not involve problems with physical or psychological well-being for these kinds of patients. The feasibility of VR has been studied to extend it also to the application on non-AD dementias, less considered in the adoption of this technology. Mendez et al. (2015), in a study evaluating the feasibility of a virtual environment through HMD, state that the characteristics and procedures of VR are feasible and well tolerated by their sample of patients with bvFTD, who also reach sufficient levels of presence.

Cognitive assessment studies with VR focused on episodic memory aspects (Plancher et al., 2012; Plancher and Piolino, 2017), spatial navigation skills (Cushman and Duffy, 2008; Serino et al., 2015), executive functions (Davison et al., 2018), up to the evaluation of skills in daily life activities (Flynn et al., 2003; Lee et al., 2003; Allain et al., 2014). Interestingly, Allain et al. (2014) suggest that by its peculiarities VR testing can point out subtle deficits, often not detected using traditional neuropsychological tests (Pallavicini et al., 2015), that allows a more accurate evaluation and to plan a more targeted rehabilitation.

VR and its benefits have been successfully combined and integrated with different methodologies of assessment and rehabilitation of several cognitive functions. Unfortunately, to date, there are no VR systems that directly assess the self-awareness deficit. There are, however, some studies that provide insights for the use of VR for this purpose. Lloréns et al. (2013) have developed a virtual board game with a multi-touch table for the rehabilitation of self-awareness in patients with acquired brain injury. In this competitive game, two groups of patients will have to answer questions (e.g., about the implications of brain damage or the limits it entails) to reach first the end of a goose game-like path. Their methodology uses the virtual tool to increase involvement, participation and interaction among multiple patients to strengthen the pedagogical process and recognition of the limits on which their treatment approach is based (Lloréns et al., 2013). Another example is the study by Mendez et al. (2015), in which a comparison is made between a traditional insight assessment and an insight assessment through a VR interview in patients with bvFTD. The patient is immersed through an HMD in a virtual environment where there are five avatars and has to answer a series of avatar questions, including those related to the insight assessment of the UCLA Structured Insight Interview. The results show that subjects provide longer, more elaborate answers when questions are expressed by avatars than in the real world, providing more information and demonstrating greater self-awareness in the virtual condition (Mendez et al., 2015). Although both of these approaches suggest the usefulness of using VR in the investigation and treatment of self-awareness, the virtual tool is used for an intervention that is not performance-centered. Through the virtual game in the Lloréns study, awareness of deficits is raised through a psychoeducational process rather than exploiting VR to allow a more experiential process based on comparing one's expectations of functioning with one's actual performance. The virtual assessment in Mendez's study is also done by collecting information offline through a virtual interview and not from the patient's assessment during the performance.

The overcoming of this aspect emerges in an interesting study by Koenig et al. (2011) who use a VR task for the assessment or training of short-term memory and the ability to imagine different perspectives in 3D space Virtual Memory Task (VMT). The object of the authors was to create a clinical tool designed to have a higher ecological validity than traditional tests, to be able to keep higher motivation for patients to practice the task frequently in a meaningful test environment and record precise measurements in 3D space for analyzing the task's results. The task consists in a coding phase, wherein subject needs to memorize the exact position of some target object on a table, and a test phase, wherein the target objects position and point of view was changed, and the participant should precisely move the items back to the initial locations. An important aspect of this protocol is that was recorded a distance error score for each trial (calculated for each target by finding the distance between the participant's answer and the object's original position during the coding phase) and that a

feedback was given to the patient after each session. Although self-awareness issues are not part of the focus of this study, the authors report interesting information about the induced effect of using their task. In fact, in addition to the results concerning the validation of the task, the authors highlight how the execution of this exercise led to a significant change in the awareness of the cognitive deficit in several participants. This result is attributed by the authors to the highly realistic semi-familiar virtual environment, that allows making comparisons to the real environment whenever participants were skeptical about test results or the nature of the task. It is also plausible that the use of viewable and quantifiable feedback has also played a role in this process. This study, compared to the previous one, carries out "unintentionally" a method of intervention on self-awareness based on the use of VR as an environment in which to perform an ecological performance. Thanks to the high ecological characteristics of the proposed condition and to the possibility of recording and displaying the performance outputs graphically, this simple task is able to stimulate objective self-evaluation through comparison and therefore the awareness of the patient's deficit.

Despite the absence of studies that directly test VR systems for self-awareness assessment, taken together these studies provide interesting premises for implementing the assessment procedure with this type of technology.

Thanks to its features, a self-awareness assessment method supported by a VR system would allow to overcome the limits and integrate the positive sides of traditional assessment methodologies. In particular, as already introduced above, both the assessment by a clinician through interview, and the method based on the measure of discrepancy between the answers to questionnaires by the patient and the caregiver, have the advantage of providing information on the functioning of the subject in real daily situations (having high ecological validity), but both methods rely on offline subjective evaluations, regarding general cognitive functioning rather than specific performance and liable to judgment bias that can lead to a wrong assessment. On the contrary, a VR system would allow to objectively record and quantify the subject's performance, to make a comparison and to measure the discrepancy between the subject's evaluation and his effective performance. Instead, the traditional method of measuring the discrepancy between subjective estimation and actual patient performance in traditional neuropsychological assessment tests has the advantage of being able to carry out an online and quantifiable assessment of performance, but it uses extremely specific material for specific cognitive domains and is often lacking in functional ecological assessment. In this sense, the VR system would compensate low ecological validity of traditional tests, thanks to controllable environments that simulate realistic conditions, recognizable as concrete by the subject, which therefore leads to a quantifiable ecological assessment of the awareness of cognitive deficits and possible repercussions in realistic everyday situations (**Figure 1**).

CONCLUSION

Carrying out an evaluation method based on the comparison between the subject's prediction of his performance and his actual performance in high-ecological VR tasks would provide an effective method for reliable self-awareness detection. Moreover, the presence of cognitive tests in VR for the evaluation of different cognitive functions (e.g., episodic memory, spatial cognition, executive functions), would allow to assess the degree of awareness for the compromised functions associated with the patient's pathology (Zhang et al., 2001; Parsons et al., 2008). This combination through the use of VR would

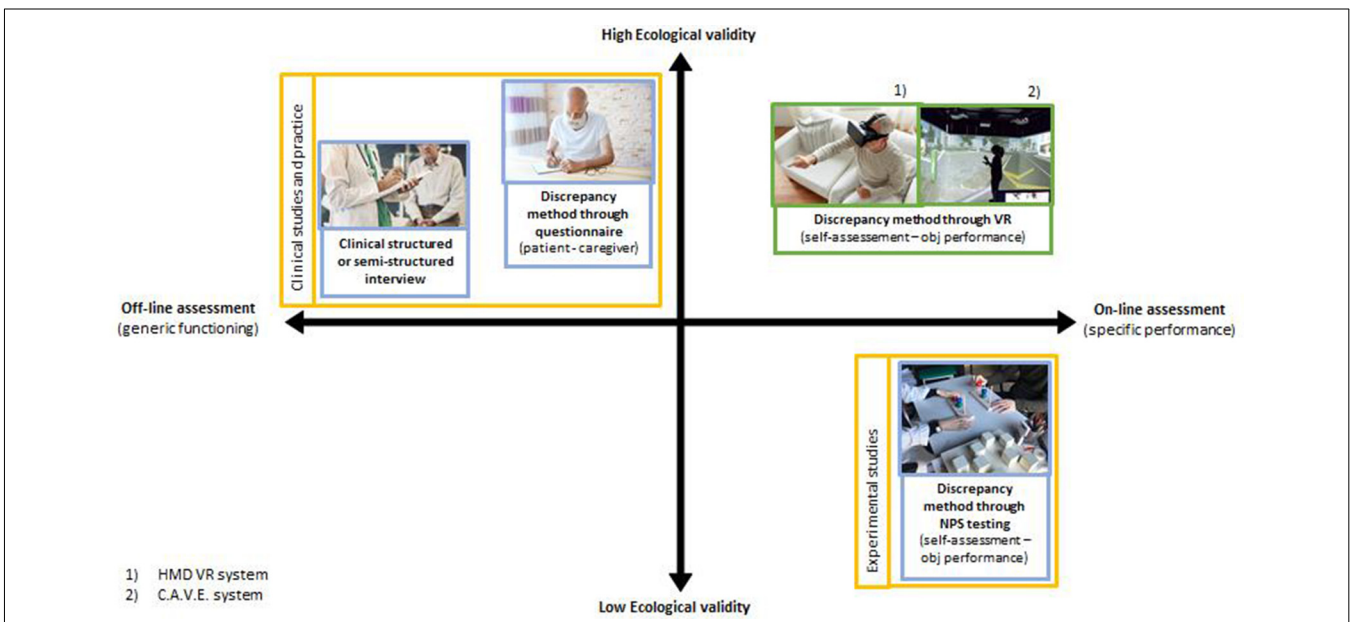

FIGURE 1 | Comparison of self-awareness assessment method.

provide the advantages of traditional online evaluation, i.e., the possibility of having quantitative measures of performance, and those of an evaluation related to a functioning comparable to the actual daily one of the subject such as the one emerging from the method based on discrepancy between the information of the subject and those of the caregiver. This approach is encouraged by the affordable prices of several VR devices and available open source software that allows non-expert users to modify pre-existing virtual environment with respect to the needs of clinical or research settings (Riva et al., 2007). Furthermore, the specific features of the different systems, such as the possibility of moving in the real environment, the detection of body movements, levels and modes of interaction with the virtual environment, help to different requests (simple exposure, spatial navigation of the environment, need to interact with elements of the environment) related to the study or clinical assessment of the various cognitive functions.

Regarding the frequency with which the lack of self-awareness occurs in degenerative disorders, and the implications it has on patient management and the planning of an effective therapeutic process (Piras et al., 2016), we believe that VR can be a very interesting means to bring the assessment of this capacity at a higher level of clinical and research reliability and utility.

AUTHOR CONTRIBUTIONS

MM wrote the first version of the manuscript. CT, EP and PC revised and critically contributed to the article. GR supervised and revised the last version of the article.

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frontiers in Psychology

ORIGINAL RESEARCH
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Color Choice Preference in Cognitively Impaired Patients: A Look Inside Alzheimer's Disease Through the Use of Lüscher Color Diagnostic

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Objective: To study the emotional state of cognitively impaired patients through the color choice preference in a group of Alzheimer's disease (AD) patients and compare it with a group of Mild Cognitive Impairment (MCI) patients and a matched control group.

Methods: A total of 71 AD, 50 MCI and 68 controls were consecutively evaluated. All patients and controls underwent the Mini Mental State Evaluation (MMSE) and the Lüscher color test.

Results: Cognitively impaired patients mainly chose auxiliary colors, in particular violet and brown, and rejected black and gray. AD patients predominantly chose forms corresponding to auxiliary colors. The auxiliary color choice negatively correlated with the MMSE score. MCI patients and controls had a higher presence of anxiety on gray table and controls had higher frustration and ambivalence, i.e., psychic complexity, on basic color tables.Data globally suggest that AD patients live with a feeling of personal change due to instability and emotional insecurity, experiencing physical discomfort and a bodily need of being welcomed in a favorable environment. They aspire to a sensitive understanding by someone with whom they can be identified. Differently, MCI patients have less of these needs; however, they feel more anxious.

Conclusion: The comprehension of the inner emotional state of cognitively impaired patients allows us to better communicate with them and effectively approach their behavioral disorders. Like other projective techniques, such as the tree-drawing test and the human figure-drawing test, Lüscher color test is proposed as a simple and unconventional approach to understand the emotional life of AD patients. The awareness of clinicians about the existential fragility and insecurity of such type of patients allows us not only to better manage their behavioral disturbances but also to improve their quality of life and that of their caregivers.

Keywords: Alzheimer's disease, dementia, mild cognitive impairment, color preference, Lüscher color test, personality

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder, primarily affecting memory and attention, that leads to a progressive global cognitive dysfunction. It is the main cause of dementia accounting for 50–75% and doubling in prevalence every 5 years after age 65 (Lane et al., 2018). AD is usually preceded by mild cognitive impairment (MCI), a clinical prodromal syndrome that is an intermediate stage between the expected cognitive decline of normal aging and the very earliest features of dementia (Albert et al., 2011), representing a useful condition to compare to AD since its risk of evolution into dementia. The rate of conversion from MCI to dementia is heterogeneous. In our Cognitive Disorders Center the rate of conversion is 18.4% in a 4-year follow-up (Gallassi et al., 2010) while in literature higher annual rates of progression are reported (6–15%) (Petersen et al., 2009). Thus, MCI and AD represent a continuum from the mildest degree of cognitive impairment to dementia.

AD affects not only cognitive functions but also emotional processing leading to behavioral dysregulation and progressive deficits in social functioning disrupting daily life activities and causing social isolation (Fischer et al., 2019). Thus, interpersonal behavioral changes are likely to be the main cause of interpersonal stress affecting both the patient and the caregiver (Clare et al., 2012). Nevertheless, if compared with other dementias, there is evidence of some preservation of emotional competencies and interpersonal functioning in AD patients (Fernandez-Duque et al., 2010; Dermody et al., 2016).

Exploring the emotional state of such type of patients is therefore important to learn more about their feelings and communicate with them properly, fulfilling their wishes and minimizing pharmacological treatment. Since verbal communication can be difficult over the course of AD due to language deficits that interfere with verbal expression and comprehension, simple tools exploring the inner emotional state that require minimal cognitive involvement, especially of language, are thus desirable.

In this perspective, personality and affectivity, as the background of every behavior, can be studied in cognitively impaired patients in order to point out different types and degrees of cognitive impairment (Stanzani Maserati et al., 2015, 2018). Thus, studying personality and affectivity in such type of patients can be a useful access to infer their needs and subjective emotional states.

Projective techniques for the study of personality and affectivity are instruments of simple administration with the potential to involve unconscious psychic dynamics both in the pediatric and adult life. Among these tools, Lüscher color test is used for exploring the emotional state through an unconscious selection of color preferences (Lüscher and Scott, 1969). Considering that it is a non-verbal tool and that it does not require specific cognitive skills to be performed, it could be a rapid and simple way to access the emotional states of cognitively impaired patients.

Firstly described by Lüscher (1948), the test is a projective technique widely used for orienting psychodiagnosis. Despite its diffusion in clinical practice, its validity has been widely discussed showing its limitations (Donnelly, 1974, 1977; Braün and Bonta, 1979; Stimpson and Stimpson, 1979; Corotto and Hafner, 1980; Holmes et al., 1984, 1986; Picco and Dzindolet, 1994; Kertzman et al., 2003). Because of this critical issue, Lüscher test is more suitable to explore the emotional state of a patient rather than its personality structure and this is the limit through which it was used in this work.

At its foundation there is the assumption that colors are objective stimuli whose psychological meanings are universal but each individual relates to color depending on their psychovegetative and existential state. Faced with the objective color stimuli of the test, subjects react in a personal way by determining the variables that, transcribed in the protocol, allow an adequate interpretation (Lüscher and Scott, 1969). Lüscher color test involves the administration of a series of choices of colored squares distributed in a series of tables selected by the author on an empirical basis. Colors can be preferred or rejected depending on the order of choice. Finally, the resulting order of color choices is matched to descriptive statements that supposedly give a description of the affectivity of the subject examined (Lüscher and Scott, 1969). Therefore, in order to test differences of emotional states in selected groups of cognitively impaired patients, we evaluated color choice preferences in a group of AD patients and compared the results with those of a group of MCI patients and a group of controls.

MATERIALS AND METHODS

We evaluated consecutive outpatients, 71 AD and 50 MCI, referred for cognitive disorders over a 1-year period by their relatives and physicians or who spontaneously presented themselves to the Cognitive Disorders Center of IRCCS Istituto delle Scienze Neurologiche of Bologna, Italy. Patients were compared with a group of 68 controls matched for age, sex, and education.

Inclusion and Exclusion Criteria

Patient inclusion criteria were as follows: (a) major or minor neurocognitive disorder according to DSM-V criteria (American Psychiatric Association, 2013); (b) diagnosis of AD and MCI based on the international criteria (Petersen et al., 2009; McKhann et al., 2011).

Patient exclusion criteria were: (a) current or previous neurological, psychiatric and systemic diseases; (b) alcoholism or other substance abuse; (c) history of color blindness or a history of diseases with a significant impact on color vision (e.g., severe glaucoma, progressive cone dystrophy, severe cataract or macular degeneration); (d) use of neuroleptics or other antipsychotics and tricyclic antidepressants considering their possible negative effects on cognition; (e) evidence of visual agnosia, hemispatial neglect, relevant apraxia or relevant verbal comprehension deficits on neurological examination.

A group of controls, matched for age, sex, and education, was selected. These subjects did not have any past or present neurological, psychiatric or general diseases, alcoholism or

other substance abuse, history of color blindness or diseases with a significant impact on color vision. They were selected mainly from the relatives of the patients. Caregivers of patients were excluded considering a possible interference of anxiety and depression.

All patients and controls gave their informed consent to the study according to the Declaration of Helsinki.

Procedures

All patients and controls underwent a general cognitive screening with the Mini Mental State Examination (MMSE) (Folstein et al., 1975) and a full version of the Lüscher color test (Lüscher and Scott, 1969) (©Copyright 1949 and 2008 by Color-Test-Verlag AG, Theaterstrasse 1, CH-6003 Luzern). The MMSE was administered to patients and controls by an examiner blind to the patient's diagnosis and Lüscher color test results. The MMSE score was corrected for age and education according to Italian standardizations (Magni et al., 1996).

Lüscher Color Test

Lüscher color test consists in the administration of a series of choices of colored squares distributed in a series of eight tables plus a choice of simple forms in a separate table (Lüscher and Scott, 1969). No limits of time are given. Colors can be preferred or rejected depending on the order of choice. Eight colors are selected: four basic colors (blue, green, red and yellow) that underlie basic physiological and psychological needs such as calm, stability, motivation, availability and four auxiliary colors (violet, brown, black and gray) that show integrative characteristics of the personality like sensitiveness, relaxation, coercion and numbness (**Table 1**).

The choice of colors in the test is made explicitly in four tables where the squares are colored directly with the eight colors or implicitly in other four specific tables where the squares are colored with a basic color shaded with one of the other basic colors. Globally, when the subject can choose all the colors in order of preference in the same table, basic colors usually appear in the first four selections while auxiliary colors are usually expected to fall within the last four selections. Only one table provides the choice of simple black and white shapes that correspond to basic and auxiliary colors (**Table 1**). Shapes represent the behavior that the subject implements in the context expressed by the color. If there is a contradiction between the choice of a favorite color and the corresponding rejected form or vice versa, then there is a behavioral mask that is a contrast between the inner emotional state and the behavior that the subject adopts to deal with it.

Specifically, the test is composed of four parts: **Gray table:** consists of five squares, three of different shades of gray, one black and one white. Subjects are asked to choose in order of preference three different squares: two preferred and one rejected. If the choice of each square fits with an expected result, this is an indicator of the anxiety in dealing with the requested task (i.e., state anxiety). **Eight color table:** consists of eight squares of different colors, four basic (blue, green, red, yellow) and four auxiliary (violet, brown, gray, black). Subjects are asked to choose in order of preference all eight colors. This choice is requested twice: the first time after the gray table, the second at the end of the test. The second choice is considered more reliable (Lüscher and Scott, 1969). The choice of the preferred color in the first position and the one rejected in the last are respectively considered in the second choice as an indicator of desired objectives and suppressed characteristics. The rejection of a basic color in the second choice is considered an indicator of the anxiety that the patient experiences in everyday life (i.e., trait anxiety). At the end of the second choice subjects are also asked to indicate the "combined color" that is the color that best fits with the favorite color and symbolizes the desire that the subject wants to achieve. **Form table:** consists of seven different black and white forms each one corresponding to a basic or an auxiliary color, except black. Subjects are asked to choose forms indicating which two they like most and which two they dislike most. Behavioral masks (i.e., contradictions between intentional situations and emotional needs) are obtained comparing the two preferred and two rejected forms to the two preferred and two rejected colors. **Basic color tables:** consist in one table of six pairs of squares of basic colors and four other tables (one for each basic color) of six pairs of squares of different shades of each basic color. Subjects are asked to choose their preference of one colored square for each pair in all tables. The four tables of shades of colors allow us to select implicitly basic preferred colors. A regular choice occurs when for every six pairs of choices in the first table the subject chooses one color once, another twice, and another three times. In the opposite cases we have an irregular choice. Psychological states (i.e., frustration, compensation, ambivalence and conflict) are also found on the basis of color choices in all five tables.

TABLE 1 | Lüscher color test's eight colors, the associated forms, and their meanings.

Colors		Associated form	Physiological meaning	Psychological meaning
Basic	1. Blue	A black circle on a white background	*Quietude*	*Membership*
	2. Green	A little dark square surrounded by a bigger one	*Constraint*	*Steadiness*
	3. Red	A dark-contour acute triangle	*Excitement*	*Activity*
	4. Yellow	A white circle on a dark background	*Relief*	*Openness*
Auxiliary	5. Violet	A rhombus with a dark contour and rotund sides	*Sensitiveness*	*Transformation*
	6. Brown	A sine curve on a dark background	*Relaxation*	*Well-being*
	7. Black	–	*Stasis*	*Coercion*
	0. Gray	A dark hexagon on a white background	*Numbness*	*Spacing*

From The Lüscher Color Test, modified (Lüscher and Scott, 1969).

Aims of the Study

The main aim of the study was to assess the emotional state of cognitively impaired patients through the color choice preference in a group of AD patients and compare it with a group of MCI patients and a control group.

Moreover, a secondary aim was to support Lüscher color test as a screening tool to approach emotional problems in cognitively impaired patients.

Statistical Analysis

A comparison of demographical and clinical features between the three groups was performed using one-way ANOVA followed by Bonferroni *post hoc* test. All dichotomous variables were compared using Pearson's χ^2 test. Frequency counts and percentages were calculated separately in each group for all Lüscher color test parameters.

Furthermore, to assess the association between these Lüscher color test parameters and the severity of the disease, measured with the MMSE, Spearman's Rho correlations were performed. Statistical significance was set at $p < 0.05$ and all analyses were performed using IBM SPSS v.22.

RESULTS

Seventy-one AD, 50 MCI and 68 controls, matched for age, sex, and education were enrolled. Mean age, sex distribution, education, and general cognitive level (MMSE) of each group are listed in **Table 2**. Disease duration was respectively of 3.87 ± 1.23 years in the AD group and 2.68 ± 1.12 years in the MCI.

Lüscher Color Test Analysis

Gray table: state anxiety was detected, respectively in 74.6% of AD patients, 84% of MCI patients and in 89.7% of controls. State anxiety positively correlated with the MMSE score ($r = 0.207$; $p < 0.05$), confirming that a higher score in the MMSE (i.e., control group) corresponds to higher presence of anxiety. **Eight color table:** the order of preference of the first choice of the eight basic and auxiliary colors is reported in **Table 3**. Cognitively impaired patients, especially AD ones, chose mainly auxiliary colors (violet and brown), while basic colors, especially blue, were chosen by controls. Auxiliary colors choice negatively correlated with the MMSE score ($r = -0.139$; $p < 0.05$), confirming that with a higher severity of disease (i.e., low MMSE score) auxiliary colors are the most chosen. The most rejected color was black in controls (41.2%) and MCI patients (40%) while the most rejected colors in AD patients were black (26.8%) and gray (21.1%). The rejection of basic colors as an indicator of trait anxiety was prevalent among MCI patients (78%) compared to AD patients (67.6%) and controls (67.6%). Green was the prevalent combined color in AD patients (35.5%) while blue was prevalent in MCI (38%) and controls (36%). No differences were found in each group between males and females in choosing preferred colors. **Form table:** the order of preference of the first choice of the seven forms and the prevalence of behavioral masks are reported in **Table 4**. Patients and controls predominantly chose forms corresponding to auxiliary colors, mainly brown and violet. Moreover, as auxiliary form in particular, AD also chose form #0, corresponding to gray. Behavioral masks were prevalent in the control group (27.9%) compared to AD (18%) and MCI (14.5%) patients. **Basic color tables:** the prevalence of irregular choices and psychological states in all groups are reported in **Table 5**. Irregular choices were mainly made by cognitively impaired patients, specifically AD (27.5%) and MCI (22%), compared to controls (11.8%); negative correlations were found between irregular choices and the MMSE score ($r = -0.14$; $p < 0.05$). Frustration and ambivalence were prevalent in controls (60.3 and 50%) compared to AD (54.9 and 29.6%) and MCI (46 and 38%) patients; significant differences between groups were found in the ambivalence ($p < 0.05$). Furthermore, positive correlations between the MMSE score and ambivalence were also found ($r = 0.181$; $p < 0.05$), confirming that a higher score in the MMSE (i.e., control group) corresponds to higher presence of ambivalence.

TABLE 2 | Demographic and clinical data of patients and controls.

	AD *n* = 71	MCI *n* = 50	Controls *n* = 68	*p*/Chi square
Age (years)	76.08 ± 7.08	77.28 ± 6.3	72.5 ± 8.41	0.013
Sex (male/female)	27/44	24/26	25/43	0.419
Education (years)	8.18 ± 4.4	8.52 ± 4.15	9.46 ± 3.59	0.168
MMSE	17.47 ± 4.9	26.3 ± 2.47	29.31 ± 0.92	<0.001*

**Statistically significant as $p < 0.012$ (corrected for multiple comparison).*

TABLE 3 | Eight colors first choice preference.

		AD (%)	MCI (%)	Controls (%)
Basic color	1. Blue	11.3	8	20.6
	2. Green	4.2	12	5.9
	3. Red	15.5	14	19.1
	4. Yellow	16.9	18	16.2
Auxiliary color	5. Violet	43.7	42	36.8
	6. Brown	4.2	4	0
	7. Black	1.4	2	1.5
	0. Gray	1.4	0	0
Global preference	Basic color	47.9	52	61.8
	Auxiliary color*	50.7	48	38.2

**Auxiliary color choice negatively correlates with the MMSE score ($p < 0.05$).*

DISCUSSION

Our results suggest that the emotional state of AD patients is generally different compared to normal subjects and that Lüscher color test could be a useful tool to evaluate it due to its simple and rapid administration. Moreover, as we have found in other simple projective tests (the tree-drawing test and the human figure-drawing test) assessing personality and

TABLE 4 | Forms first choice preferences and behavioral masks.

		AD (%)	MCI (%)	Controls (%)
Basic form	1 (Blue)	2.8	6	1.5
	2 (Green)	15.5	22	22.1
	3 (Red)	8.5	2	1.5
	4 (Yellow)	5.6	16	8.8
Auxiliary form	5 (Violet)	15	24	25
	6 (Brown)	33.8	24	36.8
	0 (Gray)	16.9	6	4.4
Global preference	Basic form	32.4	46	33.9
	Auxiliary form	65.7	54	66.2
	Behavioral masks	18	14.5	27.9

TABLE 5 | Basic colors choices and psychological states.

	AD (%)	MCI (%)	Controls (%)
Irregular choice*	27.5	22	11.8
Frustration	54.9	46	60.3
Compensation	45.1	42	44.1
Ambivalence#	29.6	38	50
Conflict	46.5	50	50

*$p < 0.05$). #$p < 0.05$).

affectivity in AD patients, our sample data of Lüscher color test show a sort of progressive coarctation of the cognitive and emotional life of these patients along the course of the disease (Stanzani Maserati et al., 2015, 2018). In fact, AD patients live with a feeling of personal change due to instability and emotional insecurity, experiencing physical discomfort and a bodily need of being welcomed in a favorable environment. They need calmness, serenity and absence of conflicts and tensions and aspire to a sensitive understanding by someone with whom they can be identified. This emotional state corresponds mainly to violet as prevalent first choice on the eight color table, to gray and black as rejected colors and to brown and gray as prevalent choice on the form table. The worse the degree of cognitive impairment, the greater the intensification of these needs and feelings. Moreover, the greater the severity of cognitive decay, the lower the psychic complexity (less behavioral masks and less occurrence of psychological states like frustration and ambivalence).

The analysis of color choice preferences in our sample provides a sort of "inside view" of patients suffering from AD, which is an experience of physical fragility and insecurity characterized by a significant need for a favorable environment and care (Kojima et al., 2017).

This subjective perspective is therefore different from a typical analysis of behavioral disorders in such type of dementia. In fact the use of projective techniques through the unconscious selection of external stimuli allows us to infer the internal experience of AD patients because they perform these types of tests differently from normal subjects since personality and affectivity, as background, include their cognitive functional aspects.

Differently from AD, MCI patients are more anxious even if they feel less fragile. Thus anxiety could probably be an expression of an aspecific warning signal relative to the perception of their cognitive change. Anxiety in fact is a typical behavioral symptom of this clinical condition whose predictive role in cognitive decline is still debated (Gallagher et al., 2017).

Regarding possible limitations of our study, we focused on anosognosia/metacognitive deficits, i.e., the inability to express a reliable judgment with respect to one's own state. In fact, it is known that AD patients, due to the progressive neurodegenerative disgregation of cognitive functions, are negatively influenced not only in the main cognitive domains like memory, executive, praxic, and language functions, but also in the self-awareness of their performance (Mograbi et al., 2009). Therefore, in AD patients an output bias could exist in performing the emotional color preference choice. In this regard, previous studies highlighted that, although self-awareness dysfunctions are described and could be part of the global AD pathology i.e., executive and/or mnemonic anosognosia, AD patients' emotional reactions are to be considered not biased by the neurodegenerative disorder despite other self-conscious deficits (Agnew and Morris, 1998; Mograbi et al., 2009; Shaked et al., 2014). In conclusion, patients with AD show on the emotional/pre-verbal side, a normal implicit awareness (Martyr et al., 2011; Mograbi et al., 2012; Mograbi and Morris, 2013). It is thus conceivable that Lüscher color test, by using colors and basing on a pre-verbal task, could be used as a tool suitable to explore the emotional state in cognitively impaired patients.

However, the validity and reliability of Lüscher color test is still debated (Kertzman et al., 2003). Some authors advocated the validity of the test (French and Alexander, 1972; Carmer et al., 1974; Rahn, 1976; Adels, 1978; Ledford and Hoke, 1981) or suggested a weak validity (Donnelly, 1974; Donnelly, 1977), while others showed no validity (Braün and Bonta, 1979; Stimpson and Stimpson, 1979; Corotto and Hafner, 1980; Holmes et al., 1984, 1986; Picco and Dzindolet, 1994). In particular, Holmes supposed a Burnum effect in the interpretation, which is the reason why the test's interpretative statements may appear valid, i.e., because they are so general that they could describe almost anyone (Holmes et al., 1986). Authors also showed that there is no relationship between Lüscher color test and the Minnesota Multiphasic Personality Inventory (MMPI) (Holmes et al., 1984; Kertzman et al., 2003). Donnelly, however, taking into account literature and personal data about the correlation between Lüscher color test and scores on the Taylor-Johnson Temperament Analysis (Donnelly, 1977), concluded that "Lüscher test is probably not valid in terms of specific personality descriptions" but that it "might be a useful tool in spite of the specific criticisms voiced" and that "the test may have usefulness as a quick indicator of emotional problems that are extensive enough to warrant further investigation" and this was the critical point of view to which we have referred in our work.

Regarding the use of the test in clinical pathology, previous studies evaluated the use of the color choice test in aging, in neurodegenerative diseases and in other medical conditions

(Strenski et al., 1970; Cohen and Hunter, 1978; Corotto and Hafner, 1980; De Leo and Magni, 1982; Holmes et al., 1985a,b; Kuloglu et al., 2002; Volpato, 2008; Zilio, 2013; Savio and Zanardo, 2015; Zanardo et al., 2017).

The psychiatric condition has been explored showing conflicting data since patient groups are often poorly described, not comparable, and relationships are weak (Strenski et al., 1970; Cohen and Hunter, 1978; Corotto and Hafner, 1980; De Leo and Magni, 1982; Holmes et al., 1985a,b; Kuloglu et al., 2002). In general, yellow (Holmes et al., 1985a) and red (Corotto and Hafner, 1980; Holmes et al., 1985a) have been described as preferred colors in groups of generic hospitalized psychiatric patients while green (Kuloglu et al., 2002) has been chosen first by both anxious or depressed patients and by psychotics that are also reported to prefer black (Strenski et al., 1970). Data concerning a supposed general preference for violet by psychiatric patients has not been confirmed (Holmes et al., 1985b) nor has the rejection of yellow by depressed patients (Cohen and Hunter, 1978; De Leo and Magni, 1982).

In a group of old aged normal cognitive subjects living in a retirement home, data from Lüscher color test showed a prevalent rejection of yellow as an expression of becoming withdrawn and gray as a need of protection (Zilio, 2013), while a group of parkinsonian patients expressed a preference for green in the attempt to control their condition and a rejection of blue and red as indicators of depression (Volpato, 2008). In our AD patients the feeling of fragility and the need of a sensitive understanding were prevalent thus expressing different existential illness conditions if compared to the group of parkinsonian patients. Probably different pathological conditions could specifically influence different color choice preferences.

Sex differences in color preferences have been also explored showing heterogeneous data (Braün and Bonta, 1979; Seefeldt, 1979; Stimpson and Stimpson, 1979; Hafner and Corotto, 1980; Silver and Mc Culley, 1988; Silver and Ferrante, 1995; Wijk et al., 1999a,b, 2002). In general, men choose blue and red more frequently while women choose yellow, black and violet (Silver and Mc Culley, 1988; Silver and Ferrante, 1995). The prevalent choice of yellow by females is frequently reported (Braün and Bonta, 1979; Seefeldt, 1979; Silver and Mc Culley, 1988) even if a prevalent choice of the same color by males compared to females has been described (Stimpson and Stimpson, 1979). Anyway, sex seems to be independent of color preference (Hafner and Corotto, 1980) and the rank order of color preferences is stable with age in males and females (Silver and Ferrante, 1995; Wijk et al., 1999b) as well as in AD patients (Wijk et al., 1999a, 2002). In our AD patients, no differences were found between males and females also in choosing preferred colors.

Finally, AD patients have more color vision deficiencies than healthy subjects (Pache et al., 2003), therefore it could be speculated that there is also a significant physiological influence on color choice. Although our study is not designed to clarify this issue, it should be taken into account that color vision deficiencies in AD are not specific (Pache et al., 2003) and that, when present, they are not as severe as in other types of neurodegenerative dementias like that with Lewy bodies (Flanigan et al., 2018). It is also known that color discrimination ability in AD patients is significantly better in the yellow and red area but it is also evident that the severity of dementia did not affect the ability to rank colors in order of preference (Wijk et al., 1999a) and that the preference order for colors remains relatively stable also in normal aging (Wijk et al., 1999b) since color perception is qualitative and well preserved throughout life despite older age and AD (Wijk et al., 1999b, 2002).

There are some limitations in this study. First, Lüscher color test is more suitable to explore emotional state and non-stable traits of personality. Another limitation of the present study is that no correlation has been performed between Lüscher color test scores and standardized anxiety and depression scales. Third, although all patients underwent a general cognitive assessment with the MMSE, a fully comprehensive neuropsychological battery had not been administered. Moreover, further follow-up studies are needed to better study changes in the color choice preference and physiological influences over time along with the progression of the disease and to explore the neuroanatomical association of the color choice preferences, using also magnetic resonance techniques, so as to confirm these data in larger and more homogeneous groups of cognitively impaired patients of different types.

CONCLUSION

Knowledge of the inner emotional life of Alzheimer's patients is mandatory to understand the subjective motivation and perspective of their behavior. However, AD cognitive deterioration does not often allow patients to adequately communicate their needs and existential perspectives, thus they are often not understood, which results in the development of behavioral disorders.

Therefore, the awareness of clinicians about the existential fragility and insecurity of such type of patients allows us to better manage their behavioral disturbances, their quality of life and that of their caregivers. Moreover, this strongly emphasizes the importance of a reliable and gentle care of demented patients and the social necessity of educated and empathic caregivers.

Lüscher color test, like other projective techniques, such as the tree-drawing test and the human figure-drawing test, allows us to approach the evaluation of these patients in a simpler and unconventional way and it could be considered as an appropriate screening tool to approach their emotional problems.

DATA AVAILABILITY

All datasets generated for this study are included in the manuscript and/or the supplementary files.

ETHICS STATEMENT

All subjects gave consent to personal data processing for research purposes and the protocol was approved by the Local Ethical Committee (v. 2.0 September 2017). All subjects gave their informed consent to the study according to the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

MSM: ideation, methodology, and drafting of the article. MM: statistical analysis and processing. FM: data collection and processing. RD'O, FO, RP, and MDM: data collection. CT: methodology and supervision. RLo and RLi: methodology and supervision. SC: methodology, supervision, and tutoring.

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Resting-State Functional Correlates of Social Cognition in Multiple Sclerosis: An Explorative Study

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Social cognition includes mental operations essential for functional social interactions, and several studies revealed an impairment of social cognition abilities in patients with Multiple Sclerosis (MS). These deficits have been related to global and focal gray matter atrophy as well as microstructural white matter damage. Although some studies reveal a correlation between social cognition and task-based functional magnetic resonance imaging (MRI), no studies to date have explored the association between brain resting-state functional connectivity (RS-FC) abnormalities and several measures of social cognition in MS. The aim of this explorative study was to assess the contribution of RS-FC abnormalities of major brain networks to social cognition in MS patients. Clinical, neuropsychological, and MRI data were collected from 41 non-depressed and cognitively preserved relapsing-remitting MS patients (mean disease duration = 8.8 ± 8.2 years; median Expanded Disability Status Scale = 1.5, range 0–6.5) and 25 matched healthy controls (HCs). The ToM Pictures Sequencing Task (TMPS) and the Reading the Mind in the Eyes Task were employed to evaluate social cognition. All participants underwent a structural MRI and RS functional MRI 3T protocol. Regional gray matter atrophy was measured, and FCs of the default mode (DMN), right and left fronto-parietal, executive (EN), salience, cerebellar, and limbic (LN) networks were evaluated by independent component analysis (ICA). Differences on TMPS were found between MS patients and HC (MS < HC). In the MS group, associations were found between right middle temporal gyrus FC (in the DMN) and reciprocity subscale of TMPS, posterior cingulate cortex (PCC) FC (in the DMN) and first-order false-belief subscale of TMPS, cingulate gyrus FC (in the EN) and TMPS as well as reciprocity subscale of TMPS, and right superior temporal gyrus (in the LN) and reciprocity subscale of TMPS. All detected RS-FC changes did not co-localize with regional gray matter atrophy. The results suggest an

association between social cognition and RS-FC changes of DMN, EN, and LN in MS. Future studies should further explore the possible adaptive or maladaptive mechanisms of these FC abnormalities in MS.

Keywords: multiple sclerosis, social cognition, cognition, resting state functional connectivity, MRI

INTRODUCTION

Social cognition includes mental operations essential for functional social interactions (Beer and Ochsner, 2006). A key aspect of social cognition is social understanding (Arioli et al., 2018), the cognitive ability to decode and attribute mental states such as goals or intentions, knowledge, belief, thoughts and emotions to oneself and others (Premack and Woodruff, 1978).

As regards the neural correlates of social cognition, a meta-analysis on task-based functional magnetic resonance imaging (fMRI) studies revealed a core network, including the medial prefrontal cortex and bilateral temporo-parietal junction, which are consistently activated independently from the type of the instrument employed to assess social cognition (Schurz et al., 2014). However, different cortical areas were found activated on the basis of specific tasks. For example, the above-mentioned meta-analytic study (Schurz et al., 2014) revealed that the dorsal/posterior parts of the temporo-parietal junction showed an increased connectivity during tasks that required processing of false-belief, whereas the ventral/anterior parts of the temporo-parietal junction were engaged for tasks that depicted rational actions or behaviors.

Social cognition deficits occur in several neurological diseases such as amyotrophic lateral sclerosis (Trojsi et al., 2017), Parkinson's disease (PD; Bora et al., 2015), behavioral-variant frontotemporal dementia (Henry et al., 2014) and multiple sclerosis (MS; Henry et al., 2009, 2011; Banati et al., 2010; Pöttgen et al., 2013; Bora et al., 2016; Cotter et al., 2016). In MS, it is unclear whether (cognitive and affective) aspects of social cognition are both impaired: some studies found that the two subcomponents are equally impaired (Raimo et al., 2017), while others revealed deficits only on a single subcomponent, either cognitive (Roca et al., 2013) or affective (Cotter et al., 2016).

The neural substrates of deficit of social cognition in MS have been explored by means of MRI in several studies, revealing an association between social cognition and different measures of brain damage (Mike et al., 2013; Batista et al., 2017a,b; Chalah et al., 2017). In more detail, a worse performance on tests assessing social cognition has been related to reduced total and regional gray matter (GM) volumes, especially in the cingulate, orbitofrontal, and cerebellar cortex, as well as in the insula and the amygdala (Batista et al., 2017a; Chalah et al., 2017; Ciampi et al., 2018). As for the relationship between social cognition and white matter (WM) damage, a lower performance in tasks assessing social cognition was associated with macrostructural (T2 lesion volume; Mike et al., 2013; Batista et al., 2017b; Chalah et al., 2017) as well as microstructural (normal-appearing WM) damage, especially within tracts of limbic pathways and callosal interhemispheric fibers (Batista et al., 2017b), which are involved in social and communicative abilities or emotional processing (Paul et al., 2007; Von Der Heide et al., 2013; Downey et al., 2015). Few studies have used task-based fMRI to verify whether impairment on social cognition abilities was associated with a decreased or increased activation of specific cerebral area, and found that impairment of ability to recognize emotional facial expression was associated with decreased activation of the insular and ventrolateral prefrontal cortex (Jehna et al., 2011) or with an increased activation of the anterior and posterior cingulate cortex (PCC), praecuneus and occipital fusiform gyri (Krause et al., 2009). However, these studies have the limitation of investigating only specific aspects related to social cognition, such as facial emotion detection.

To date, no resting-state (RS) fMRI studies have explored cognitive and affective ToM in MS. RS fMRI represents a unique method to investigate brain networks with minimal bias, and it has been employed in several studies in MS (Gallo et al., 2012; Filippi and Rocca, 2013; Sbardella et al., 2015; Bisecco et al., 2018; Rocca et al., 2018). In particular, using resting-state functional connectivity (RS-FC) eliminates the nuisance effect of performance variability present during task-based fMRI studies. Therefore, the aim of our explorative study is to fill the above-mentioned knowledge gap by assessing the contribution of RS functional connectivity (RS-FC) abnormalities to social cognition in patients with MS. Since some studies report an association between social cognition and cognitive abilities, both in healthy (Apperly et al., 2009; Wade et al., 2018) and in MS patients (Raimo et al., 2017), we explored RS networks mainly associated with high-level cognitive and/or social abilities: (1) the default mode network (DMN), which actively supports several aspects of cognition, like working memory, memory retrieval, or divergent thinking (Spreng, 2012; Murphy et al., 2018); (2) the right and left fronto-parietal network (FPN), involved in cognitive control and in allocating attentional resources (Marek and Dosenbach, 2018); (3) the executive network (EN), engaged in high-level cognitive functions such as goal-directed behavior, working memory, and cognitive control (Menon, 2011); (4) the salience network (SLN), involved in the detection of relevant stimuli in the environment and in the coordination of behavioral responses (Chand and Dhamala, 2016); (5) the limbic network (LN), as amygdala lesions or atrophy was found to be associated with impairment of social understanding (Shaw et al., 2004; Batista et al., 2017a); and (6) the cerebellar network (CN), which is implicated in social cognition and in higher abstraction mentalizing (Van Overwalle et al., 2014).

MATERIALS AND METHODS

Participants

Forty-one relapsing-remitting MS patients were consecutively recruited at the MS center of the Division of Neurology of the

University of Campania "Luigi Vanvitelli," in Naples (Italy); 25 Healthy controls (HCs) were recruited from a large HC database created in our Institution. As for the inclusion criteria, patients had to have a diagnosis of MS according to the revised McDonald criteria (Thompson et al., 2018) and a relapsing-remitting phenotype; moreover, they had to be relapse- and corticosteroid-free within the month prior to scanning. As for the HCs, no T2 hyperintense lesions had to be shown in the MRI scanning. Both MS patients and HCs had to be between 18 and 65 years old, with no history of psychiatric illness and without deficit of oral comprehension defined by an age- and education-adjusted score on the Token Test (Spinnler and Tognoni, 1987) < 26.25.

All participants signed an informed consent form, and the study was approved by the local Ethical Committee.

Clinical, Neurological, and Behavioral Assessment

All participants underwent a neurological, neuropsychological, and behavioral assessment. All patients underwent Expanded Disability Status Scale (Kurtzke, 1983) to assess the severity of physical disability in MS patients. Patients and HC underwent Symbol Digit Modalities Test (SDMT; Rao et al., 1991; Amato et al., 2006) assessing the information processing speed. SDMT has been recognized as the most sensitive test for screening cognitive impairment in MS (Van Schependom et al., 2014). Moreover, patients and HC completed the Italian version of the Beck Depression Inventory—II Edition (Beck et al., 1996; Sacco et al., 2016) to evaluate depressive symptomatology.

Social Cognition Abilities

Patients and HCs underwent the ToM Picture Sequencing Task (TMPS; Brüne, 2003) and the Reading the Mind in the Eyes test (RMET; Baron-Cohen et al., 1997; Vellante et al., 2013). The TMPS consists of six sequences of pictures (each sequence includes four cards) depicting stories of cooperation, deception, or cooperation of two characters in deceiving a third person. Cards were shown to participants in a non-logical order, and subjects were asked to order the cards in a logical sequence of events. The sequence ordered by the participant and the seconds taken to complete each task were registered by a trained psychologist. If the story was put in the wrong order by the participant, the psychologist rearranged the figures in the right order before proceeding with a questionnaire that evaluated various aspects of social understanding, such as the person's levels of belief and false-belief reasoning, which is based on the idea that an individual's belief may differ from the reality (Ward et al., 2013), and the three different levels of social understanding characterized by an increasing order of complexity: the first-order Theory of Mind (ToM; the ability to discriminate between a person's and others' beliefs and mental states), the second-order ToM (the ability to make inferences on other person's beliefs about the mental states of a third person; Miller, 2009), and the third-order ToM (the ability to infer the mental state of others in complex social interactions; Kumfor et al., 2017). Moreover, the TMPS evaluates the comprehension of basic (i.e., the understanding of the reality) and sophisticated cognitive capacities (i.e., the understanding of deception and the norm of reciprocity) related to social cognition (Mazza et al., 2012). Total score of TMPS ranges from 0 to 59, with higher scores indicating better performance.

The RMET consists of 36 pictures of people's eyes shown to the participants, surrounded by four words indicating mental states. Participants were asked to choose which word best described the mental state of the person shown in the picture. Total score ranges from 0 to 36, with higher scores indicating better performance.

MRI Acquisition

Brain MRI scans were acquired on a 3T GE Medical System (Milwaukee, WI, USA) scanner equipped with an eight-channel parallel head coil. The following images were acquired:

(1) Proton density (PD)/T2 weighted [dual-echo fast spin echo, repetition time (TR) = 3.080 ms, echo time (TE)1/TE2 = 24/127.5 ms, slice number = 44 (PD)/44(T2), matrix = 256 × 384, axial slices, field of view (FOV) = 240 mm, slice thickness = 3 mm, interslice gap = 0 mm]; (2) high-resolution 3D-T1 (magnetization-prepared fast spoiled gradient echo, TR = 6.988 ms, TI = 650 ms, TE = 2.85 ms, slice number = 166, matrix = 256 × 256, sagittal slices, flip angle = 8°, FOV = 256 mm, voxel size = 1 × 1 × 1.2 mm^3); (3) RS-fMRI consisting of 240 volumes of a repeated gradient-echo echo planar imaging T2*-weighted sequence (TR = 1.508 ms, axial slices = 29, matrix = 64 × 64, FOV = 256 mm, slice thickness = 4 mm, interslice gap = 0 mm). During the functional scan, subjects were asked to stay motionless, awake, and relaxed, and to keep their eyes closed.

Conventional MRI Analysis

The identification of T2 hyperintense lesions in MS patients was conducted on PD/T2 images by a single experienced observer (MC) blinded to the patients' clinical characteristics. The Medical Image Processing, Analysis, and Visualization (MIPAV) software (version 4.2.2[1]) was used to contour lesions and to compute T2 lesion volume for each patient. Normalized brain (NBV), WM (NWMV), and GM (NGMV) volumes were measured on 3D-T1 images using the SIENAx software, after T1-hypointense lesion refilling (Jenkinson et al., 2012).

RS-fMRI Analysis (Esposito et al., 2008; Bonavita et al., 2017)

Standard image data preparation and preprocessing, statistical analysis, and visualization were performed with the software BrainVoyager QX (Brain Innovation BV, Maastricht, Netherlands). Data preprocessing included the correction for slice scan timing acquisition, a three-dimensional rigid-body motion correction based on a six-parameter rigid body alignment to correct for minor head movements, and the application of a temporal high-pass filter with cut off set to three cycles per time course. Translational motion parameters were verified to be always less than one functional voxel for all included participants. Structural and functional data were coregistered

[1]http://mipav.cit.nih.gov

and spatially normalized to the Talairach standard space using a 12-parameter affine transformation. During this procedure, the functional images were resampled to an isometric 3-mm grid covering the entire Talairach box. Single-subject and group-level independent component analysis (ICA) were carried out on the pre-processed functional time series using two plug-in extensions of BrainVoyager QX, implementing fast ICA algorithm and the self-organizing group-level ICA algorithm, respectively. For each subject, 40 independent components, corresponding to one sixth of the number of time points, were extracted. All single-subject component maps from all subjects were then "clustered" at group level, resulting in 40 single-group average maps that were visually inspected for recognition of the main physiological RS components. The sign-adjusted ICA components of all subjects were then submitted to a second-level, multi-subject random-effects two-way ANOVA that treated the individual subject map values as random observations at each voxel (Esposito et al., 2008), cluster membership as one within-subject factor with 40 levels (corresponding to 40 group components), and subject group as one between-subject factor with two levels (corresponding to HC and MS patients). Starting from ANOVA, a single-group one-sample *t*-test was used to analyze in each group the whole-brain distribution of the main physiological and cognitive RS components: the DMN, left and right FPN (LFPN and RFPN), EN, SLN, LN, and CN components. The resulting *t*-maps were thresholded at $p = 0.05$ (Bonferroni corrected over the entire brain). From these, an inclusive mask was also created from the HC group maps and used to define a new search volume for within-network, two-group comparisons. The voxel-wise comparisons between the two groups were indeed performed with two-sample *t*-test over the search volume. All the comparisons were made with gender and age included as covariate of no interest. To correct the resulting t-maps for multiple comparisons, regional effects within the search volume were considered significant only for compact clusters after the joint application of a voxel- and cluster-level threshold. The cluster-level threshold was estimated non-parametrically with a randomization approach: starting from an initial (uncorrected) threshold of $p = 0.001$ applied to all voxels, a minimum cluster size was calculated that protected against false-positive clusters at 5% after 1,000 Monte Carlo simulations (Forman et al., 1995). Individual ICA z-scores from DMN, LFPN, RFPN, EN, SLN, LN, and CN regions identified in the above analysis were also extracted and used in linear correlation analysis in the MS patients and in the HC groups with several scores: RMET, TMPS total, TMPS first-order ToM, TMPS second-order ToM, and TMPS reciprocity score. For these regional analyses, we used a statistical significance level of $p < 0.05$ (uncorrected). ICA z-scores express the relative modulation of a given voxel by a specific ICA component and hence reflect the amplitude of the correlated fluctuations within the corresponding functional connectivity network.

Voxel-Based Morphometry Analysis (Good et al., 2001)

Voxel-based morphometry analysis was performed using SPM12 software (Wellcome Trust Centre for Neuroimaging, London, UK[2]) on 3D-T1 lesion-filled images. Images were bias-corrected, tissue-classified, and registered using linear (12-parameter affine) and non-linear transformations (warping) within a unified mode, with default parameters incorporating the DARTEL toolbox (Ashburner, 2008). Subsequently, the warped GM segments were affine-transformed into MNI space and were scaled by the Jacobian determinants of the deformations to account for the local compression and stretching that occurs as a consequence of the warping and affine transformation (modulated GM volumes). The modulated volumes were smoothed with a Gaussian kernel of 8-mm full-width at half maximum. The GM volume maps were statistically analyzed using the general linear model based on Gaussian random field theory. Regional differences in GM volume between the experimental groups (HC vs. MS patients) were assessed with total intracranial volume, age, and sex as covariates of no interest. Correlations between GM volume and RMET, total TMPS, TMPS first-order and second-order ToM, and TMPS reciprocity scores were assessed both in the MS and HC groups using multiple regression analysis with total intracranial volume, age, and sex as covariates of no interest. Statistical inference was performed at the voxel level, with an FWE correction for multiple comparisons. Clusters were considered significant at $p < 0.05$.

A conversion table between Talaraich and MNI space coordinates was added as **Supplementary Table S1**.

Statistical Analysis

A Kolmogorov–Smirnov test was used to verify normal distribution of demographic, clinical, and conventional MRI variables. Between-group comparisons were performed using the Mann–Whitney and chi-square tests, as appropriate. Correlations between scores on social cognition tasks and conventional MRI variables were assessed using Spearman's rank correlation coefficient. A $p < 0.05$ was considered statistically significant; however, a Bonferroni correction for multiple comparisons applied to 10 measures (Beck Depression Inventory—II Edition, SDMT, NBV, NGMV, NWMV, RMET, TMPS, first-order, second-order, and reciprocity scores of TMPS; $p = 0.005$) was performed (SPSS Statistics version 25.0).

RESULTS

Clinical/Demographic, Neuropsychological and Conventional MRI Data

Clinical, demographical, and MRI characteristics of HC and MS patients groups are described in **Table 1**. MS patients were cognitively preserved and did not report depressive symptoms. No differences were found between MS patients and HC on cognition and depressive symptomatology; as regards the MRI measures, MS patients had lower NBV, NGMV, and NWMV compared to HC (**Table 1**). Moreover, MS patients had a lower score than HC on the RMET and TMPS tests, second-order ToM subscale, and reciprocity subscale of TMPS (**Table 2**). After Bonferroni correction, differences between the two groups on

[2]http://www.fil.ion.ucl.ac.uk/spm

TABLE 1 | Socio-demographic and clinical characteristics of multiple sclerosis (MS) patients and healthy controls (HC) and group comparisons.

	MS patients (n = 41)	HC (n = 25)	p
Mean age (years, SD)	34.18 (10.27)	37.83 (11.95)	0.284
Sex (M/W)	14/27	7/18	0.504
Mean disease duration (years, SD)	8.8 (8.2)	–	–
Median EDSS (range)	1.5 (0–6.5)	–	–
Mean SDMT z score (SD)	0.955 (1.43)	1.39 (1.36)	0.194
Median BDI-II (SD)	7 (0–18)	4 (0–14)	0.077
Median T2 LV (mm^3, range)	1,883 (44–34,934)	–	–
Mean NBV (mm^3, SD)	1,510 (76)	1,569 (64)	**0.002**
Mean NGMV (mm^3, SD)	843 (50)	870 (47)	*0.027*
Mean NWMV (mm^3, SD)	667 (37)	698 (41)	*0.008*
Median RMET score (range)	24 (13–30)	26 (17–29)	*0.021*
Median TMPS total score (range)	47 (29–59)	56 (39–59)	**<0.001**
Median TMPS first-order ToM (range)	5 (2–5)	5 (3–5)	0.233
Median TMPS second-order ToM (range)	4 (2–5)	5 (3–5)	*0.009*
Median TMPS reciprocity score (range)	2 (1–3)	3 (2–3)	**<0.001**

p, probability value; EDSS, Expanded Disability Status Scores; SDMT, Symbol Digit Modalities Test; BDI-II, Beck Depression Inventory II; T2 LV, T2 lesion volume; NBV, normalized brain volume; NGMV, normalized gray matter volume; NWMV, normalized white matter volume; RMET, Reading the Mind in the Eyes test; TMPS, Theory of Mind Picture Sequencing Task; ToM, Theory of Mind. Significant values ($p < 0.05$) are reported in italic. Significant values after Bonferroni correction for 10 measures ($p < 0.005$) are reported in bold.

TABLE 2 | Associations between social cognition measures and clinical, neuropsychological, and MRI data in the MS sample.

	RMET total score	TMPS total score	TMPS–first-order ToM	TMPS–second-order ToM	TMPS–reciprocity score
Age	−0.024 (0.882)	−0.111 (0.496)	−0.107 (0.513)	0.020 (0.901)	0.150 (0.355)
EDSS	0.015 (0.926)	*−0.364 (0.019)*	−0.035 (0.828)	*−0.383 (0.013)*	−0.006 (0.972)
SDMT	0.257 (0.131)	**0.521 (<0.001)**	0.272 (0.109)	*0.396 (0.017)*	0.038 (0.827)
BDI-II	0.024 (0.891)	−0.183 (0.285)	0.240 (0.159)	−0.270 (0.111)	−0.009 (0.959)
T2 LV	−0.025 (0.880)	−0.222 (0.169)	−0.038 (0.814)	−0.253 (0.116)	0.153 (0.345)
NGMV	−0.052 (0.749)	0.150 (0.356)	0.126 (0.438)	0.137 (0.399)	−0.111 (0.495)
NWMV	−0.221 (0.170)	0.078 (0.632)	*0.328 (0.039)*	0.140 (0.388)	−0.026 (0.873)
NBV	−0.100 (0.539)	0.157 (0.334)	0.238 (0.139)	0.201 (0.215)	−0.083 (0.610)

RMET, Reading the Mind the Eyes test; TMPS, Theory of Mind Picture Sequencing Task; EDSS, Expanded Disability Status Scores; SDMT, Symbol Digit Modalities Test; BDI-II, Beck Depression Inventory II; T2 LV, T2 lesion volume; NGMV, normalized gray matter volume; NWMV, normalized white matter volume; NBV, normalized brain volume. Values are presented as rho (p). Significant values are reported in italic. Significant values after Bonferroni correction for eight measures are reported in bold.

NBV, total score on TMPS, and scores on reciprocity subscale of TMPS remained statistically significant. In the MS group, no association was found between RMET and clinical variables, whereas a strong association was found between TMPS and SDMT scores (rho = 0.520; $p < 0.001$); see **Table 2** and **Figure 1**.

RS-fMRI

Comparison of RS-FC between MS patients and HC: (1) DMN: MS patients showed a decreased RS-FC in the PCC and an increased RS-FC in the right middle temporal gyrus; (2) RFPN: MS patients showed an increased RS-FC in the right middle temporal gyrus; (3) LFPN: MS patients showed a decreased RS-FC in the left middle temporal gyrus; (4) EN: MS patients showed a decreased RS-FC in the right precentral gyrus and in the cingulate gyrus; (5) SLN: MS patients showed a decreased RS-FC in the right middle temporal gyrus; (6) LN: MS patients showed an increased RS-FC in the right and the left superior temporal gyrus; and (7) CN: no significant differences were found between HC and MS patients (**Figure 2**).

Correlations between RS-FC networks abnormalities and social cognition tasks in MS patients: (1) DMN (see **Figure 3**): positive association between RS-FC in the right middle temporal gyrus and score on reciprocity subscale of TMPS (rho = 0.3107, $p = 0.0480$); negative association between RS-FC in the PCC and score on first-order false-belief ToM subscale of TMPS (rho = −0.3318, $p = 0.0341$); (2) EN (see **Figure 4**): negative

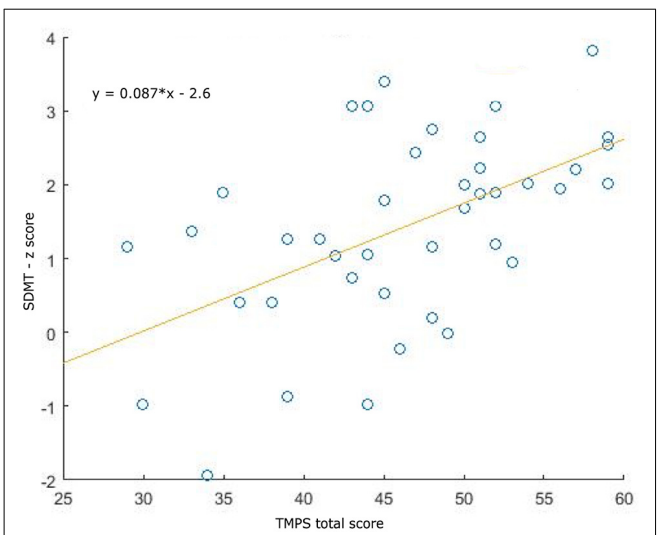

FIGURE 1 | Association plots between Symbol Digit Modalities Test (SDMT) and total Theory of Mind Picture Sequencing Task (TMPS) scores in the multiple sclerosis (MS) patients group.

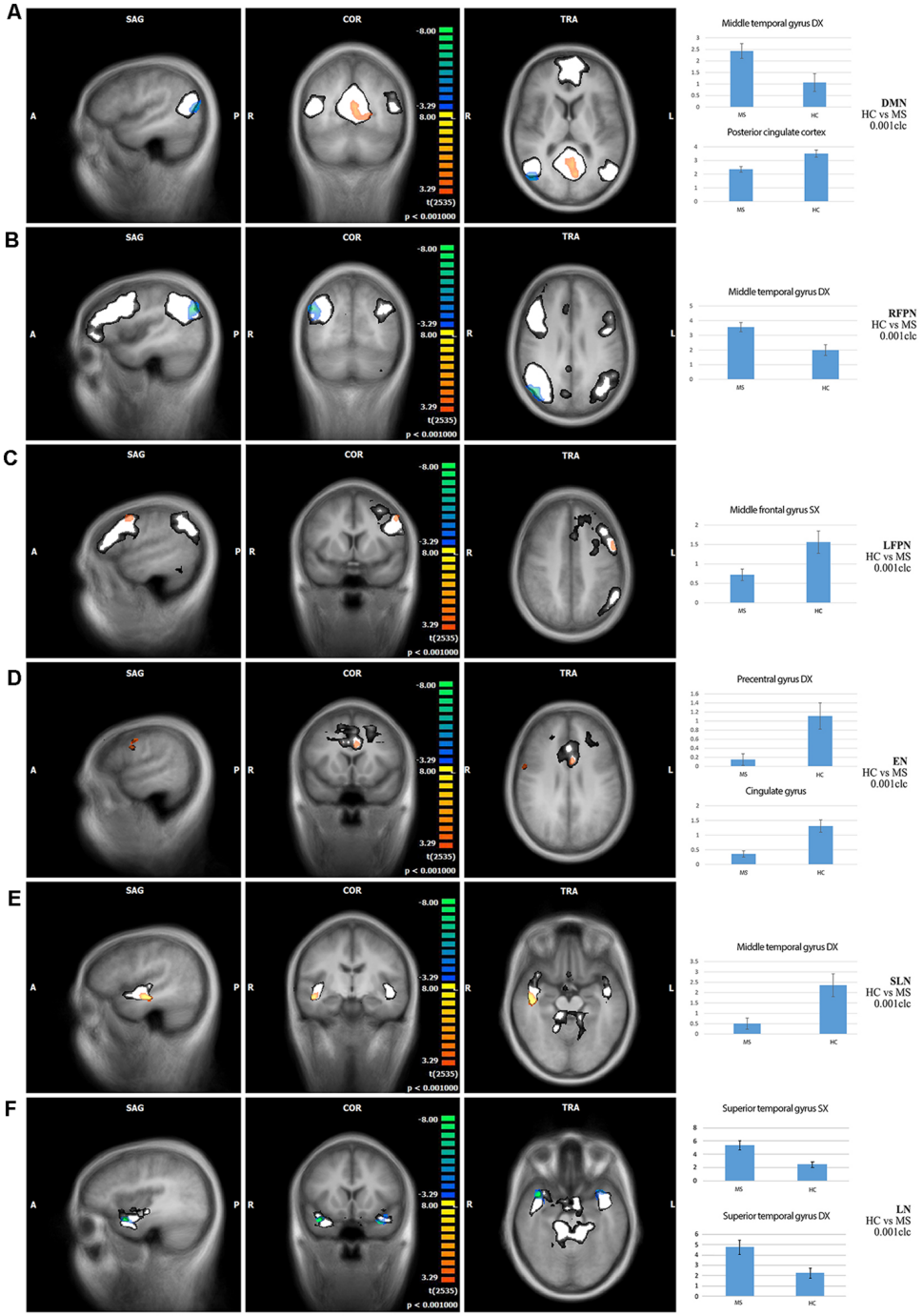

FIGURE 2 | Comparisons of resting-state functional connectivity between healthy controls (HCs) vs. MS patients (first three columns) and bar graphs showing independent component analysis (ICA) scores of highlighted clusters in HC and MS patients (fourth column) in **(A)** default mode network (DMN), **(B)** right fronto-parietal network (RFPN), **(C)** left fronto-parietal network (LFPN), **(D)** executive network (EN), **(E)** salience network (SLN), and **(F)** limbic network (LN). Color legend: hot colors: HC > MS; cool colors: MS > HC; white: explored functional brain network. A: anterior; P: posterior; L: left; R: right; S: superior; I: inferior; SAG: sagittal; TRA: transverse; COR: coronal. The clusters of significant differences ($p < 0.05$, corrected) are overlaid on three orthogonal slices of the averaged normalized anatomy and on the corresponding functional brain networks (in white).

association between RS-FC in the cingulate gyrus and total score on TMPS (rho = −0.3161, $p = 0.0441$); negative association between RS-FC in the cingulate gyrus and score on reciprocity subscale of TMPS (rho = −0.3640, $p = 0.0193$); (3) LN (see **Figure 5**): negative association between RS-FC in the right superior temporal gyrus and reciprocity subscale of TMPS

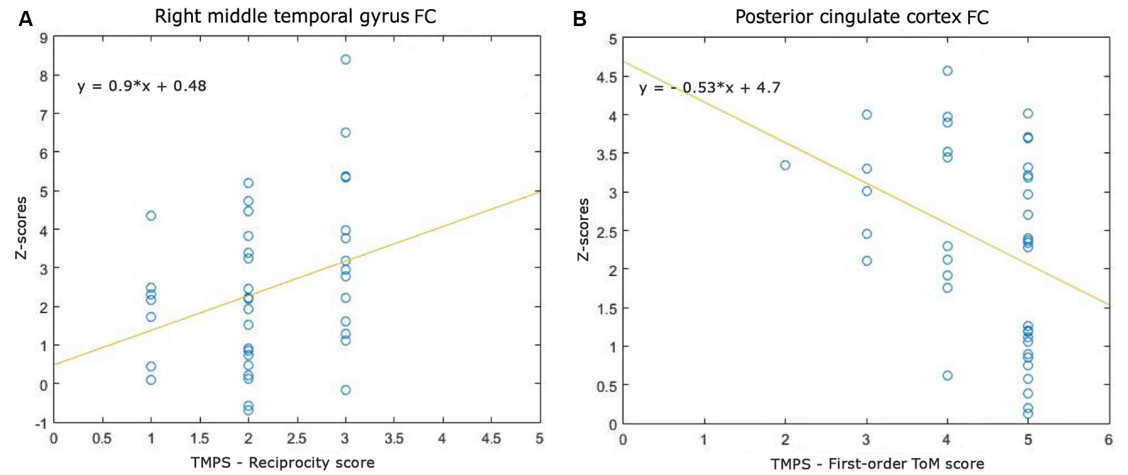

FIGURE 3 | Scatterplots of associations between resting-state functional connectivity (FC) of DMN abnormalities and ToM tasks in MS patients. **(A)** Association between right middle temporal gyrus FC and reciprocity score of TMPS; **(B)** Association between posterior cingulate cortex (PCC) FC and first-order ToM score of TMPS.

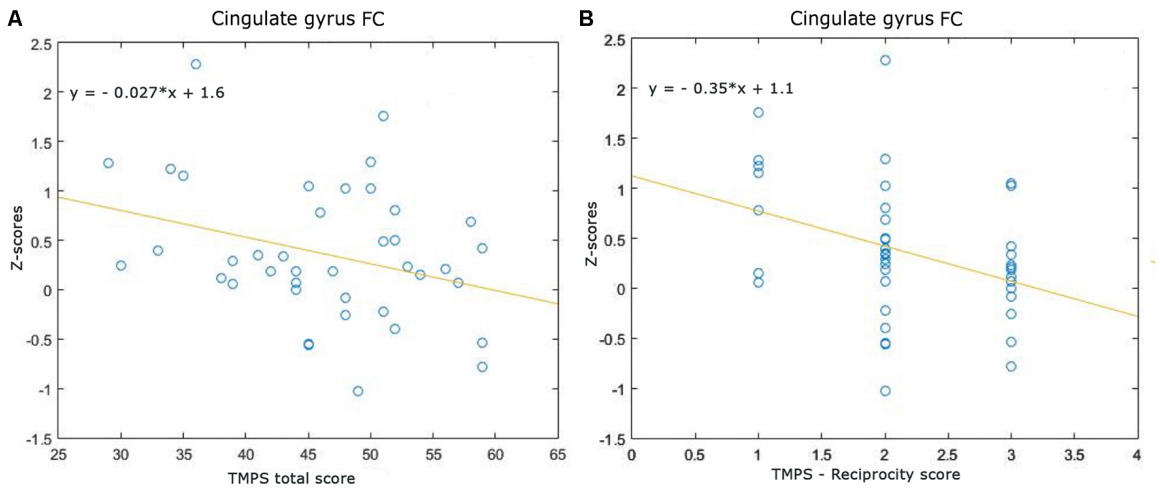

FIGURE 4 | Scatterplots of associations between resting-state functional connectivity (FC) of executive network abnormalities and social cognition tasks in MS patients. **(A)** Association between cingulate gyrus FC and TMPS; **(B)** association between cingulate gyrus FC and reciprocity score of TMPS.

(rho = −0.309, $p = 0.0493$; **Figure 4**). No correlations were found between social cognition tasks and RFPN, LFPN, and SLN RS-FC abnormalities. In the HC group, reciprocity subscale of TMPS was also negatively correlated with abnormalities in the right middle temporal gyrus in DMN (rho = −0.4668, $p = 0.0186$), while first-order ToM subscale of TMPS was positively correlated with FC in the right precentral gyrus in the EN (rho = 0.3958, $p = 0.0501$).

All detected RS-FC abnormalities did not co-localize with regional GM atrophy.

Voxel-Based Morphometry Analysis

MS patients, when compared to HC, showed significant regional GM loss in the following areas: the thalamus, bilaterally (right thalamus: $x = 11$, $y = -30$, $z = -5$, $K = 573$; left thalamus: $x = -8$, $y = -26$, $z = -5$, $K = 1{,}128$), and the superior frontal gyrus ($x = 35$, $y = 63$, $z = -9$, $K = 208$). No areas of regional GM volume reduction were found in HC when compared to MS patients. No correlations between social cognition tasks and regional GM volume were found in MS patients.

DISCUSSION

In the present cross-sectional study, we aimed to investigate the RSN abnormalities associated with social cognition deficits in MS patients. To our knowledge, this is the first work that used an RS-fMRI approach to explore the relationship between RSN abnormalities and multiple aspects of social cognition.

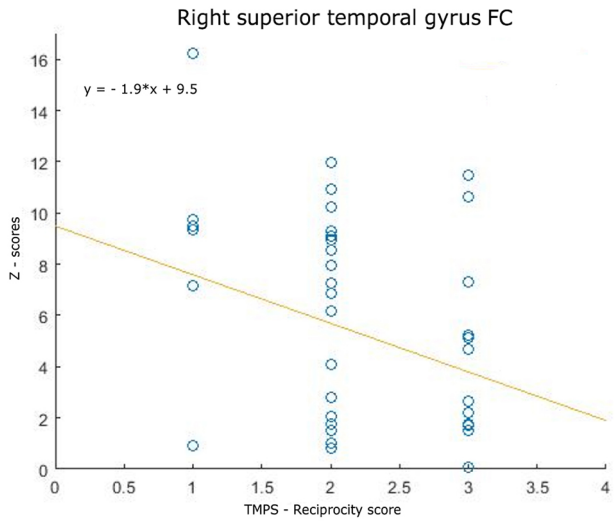

FIGURE 5 | Scatterplot of the association between resting-state functional connectivity (FC) of limbic network abnormalities (right superior temporally gyrus FC) and reciprocity score of TMPS in MS patients.

The results indicated a significant association between RS-FC abnormalities in the DMN, EN, and LN and poor performance on TMPS in MS. Only TMPS task was found to be strongly associated with SDMT, a cognitive task measuring processing speed and attention. These results partially replicate previous studies; for example, Raimo et al. (2017) found significant and strong associations with SDMT scores with several aspects of social cognition.

As regards the association between RS-FC and social cognition tasks, the results confirm that DMN is involved in social cognition abilities in MS, consistently with other previous studies with healthy subjects and with patients affected by neurological diseases, such as amyotrophic lateral sclerosis (Li et al., 2014; Trojsi et al., 2017). In more detail, we observed that more difficulties in understanding the concept of the social norm of reciprocity in interpersonal relationships were associated with reduced RS-FC in the right middle temporal gyrus, which belongs to DMN. Our results are in line with a recent meta-analysis including task-based fMRI studies on healthy subjects who showed an activation of the right middle temporal gyrus during the execution of social cognition tasks that assessed false beliefs and rational actions (Schurz et al., 2014). Moreover, the same association was found in our HC group, although with an opposite direction of correlation (a negative association in the HC group vs. a positive association in the MS group). This may suggest the presence of an attempt to compensate social cognition deficit in MS patients or a maladaptive mechanism: the possible disruption of parts of neural circuits could increase the FC of other brain areas that, in absence of lesions, show lower FC.

In the present study, we also observed a negative association between another node of the DMN, the PCC, and performance on first-order ToM: patients with an increased connectivity in this node performed worse on tasks that require differentiating between their own and others' mental states. PCC is involved in outcome monitoring and in social cognition as revealed in studies performed on HC and in patients with neurological diseases, such as amyotrophic lateral sclerosis (Maddock et al., 2003; Kable and Glimcher, 2007; Trojsi et al., 2017). Moreover, the involvement of PCC in social cognition in MS was also confirmed by a previous fMRI meta-analytic study where an activation of the PCC was described during the execution of non-verbal false belief stories tasks (Schurz et al., 2014). The negative association found in MS patients between PCC and first-order social cognition might imply a maladaptive attempt to compensate social cognition deficits in MS patients or an unbalancing in DMN network as counterpart of the middle temporal gyrus hyperconnectivity.

Another interesting finding of the present study was the association between a lower performance on TMPS, in particular on the reciprocity subscale, and an increased connectivity in the cingulate gyrus of the EN. The results might suggest a maladaptive role of EN abnormalities on social cognition in MS. Although in the literature there are no studies that associate the EN with social cognition, the cingulate gyrus—in particular the ACC—has been related to error detection, monitoring of conflict, cognitive control (Carter et al., 1998; Posner and DiGirolamo, 1998; Bush et al., 2000), and also cognitive flexibility, which has a relevant role in taking other people's perspective (Leber et al., 2008; Champagne-Lavau et al., 2012). Indeed, in our sample of MS patients, the increased connectivity of the cingulate gyrus may lead to difficulties in attribute mental states such as goals or intentions to others. These difficulties may be due to the damage of part of the brain network secondary to the diffuse presence of MS WM lesions.

Lastly, we observed an association between the right superior temporal gyrus in the LN and the reciprocity score of TMPS. The role of the right superior temporal gyrus in social cognition was confirmed in other studies; for example, Schurz et al. (2014) reported a consistent connectivity of the right superior temporal gyrus in several social cognition tasks, mainly related to false-belief reasoning, trait judgment, and social interactions. Moreover, abnormalities in the right superior temporal gyrus were found in a sample of children and adolescents with autism spectrum disorder, a neurodevelopment disorder characterized by impaired social cognition abilities (Jou et al., 2010). In MS patients, however, we found a negative association between the increased connectivity of the right superior temporal gyrus in the LN and the performance on reciprocity subtest of TMPS. As stated above, this may be due to the occurrence of compensatory processes to suppress social cognition deficits caused by GM and WM lesions or maladaptive mechanisms (Chalah and Ayache, 2017).

It should be noted that all the significant associations between abnormalities in RS-FC and social cognition tasks were mostly moderate, highlighting the complexity of the phenomenon we have explored. Since we have shown only the contribution of FC at rest, we cannot provide a final explanation for these results. We may argue that the social cognition deficits are probably due to the coexistence of structural (Mike et al., 2013; Batista et al., 2017a,b; Chalah et al., 2017) and functional

abnormalities. Moreover, other variables may moderate the relationship between abnormalities in RS-FC and ToM tasks, such as cognitive reserve, which is considered a protective factor against the impact of brain damage on specific cognitive abilities in MS patients (Santangelo et al., 2019). The study of such variables might prove an important area for future research.

With regard to the various components of social cognition assessed in this research, only the TMPS, that evaluates belief and false-belief reasoning and the comprehension of basic and sophisticated cognitive capacities, was related to RS-FC abnormalities of DMN and EN, while we did not find any significant associations between the RMET, evaluating the ability to understand others' emotional states, and RS-FC abnormalities of brain networks; differences in methodology (RS vs. task-based fMRI) and the low sample size of previous studies might explain these discrepancies (Krause et al., 2009; Jehna et al., 2011).

In our study, we did not find any significant association between global or focal GM atrophy and social cognition tasks, while previous studies did, evidencing a relationship between social cognition and GM atrophy in bilateral regions of the orbitofrontal cortex, insula, fusiform gyrus, praecuneus, cingulate cortex, and amygdala (Batista et al., 2017a; Chalah et al., 2017; Ciampi et al., 2018). We were not able to replicate the results of previous studies; this inconsistency may be explained by differences in the sample of MS patients, which differed for clinical variables, such as the phenotype or the cognitive status of the patients.

Social cognition is a broad construct that includes different cognitive processes related to social interaction (Beer and Ochsner, 2006). Several theoretical models have been proposed to describe the processes involved in social cognition and how these processes relate to each other; for example, according to Arioli et al. (2018), social cognition includes three main domains: social perception (the ability to distinguish between objects and persons), social understanding (the ability to decode others' behaviours) and social decision making (the ability to make decisions on the basis of others' behaviours). As for the relationships between processes, there are models that distinguish between cognitive ToM, affective ToM and empathy (Shamay-Tsoory et al., 2010), but there are also evidences of overlapping constructs and topographical convergences across brain activities related to these processes (Bzdock et al., 2012). These theoretical assumptions or evidences also reflect the difficulties in evaluating and differentiate between each single component of social cognition: for example, the RMET has been considered as a measure of ToM (Baron-Cohen et al., 1997; Vellante et al., 2013) or cognitive empathy (Warrier et al., 2017) by different authors.

Although the instruments that we employed in our study can be roughly included in the domain of social understanding, given the methodological difficulty to assess the single components of social cognition, it must be taken into account that some processes here assessed (i.e., cognitive empathy vs ToM) may overlap. Therefore, future studies could further expand our results by employing questionnaires and tools that measure multiple domains of social cognition and that are able to better discriminate between these processes.

This study is not exempt from limitations. First, we were not able to recruit an equal number of patients and controls (41 vs. 25, respectively). Moreover, when testing group differences between MS patients and HC on social cognition tasks, only total score on TMPS and score on the reciprocity subscale of TMPS remained significant after the Bonferroni correction. Nevertheless, we decided anyway to test the correlations of all social cognition tasks with RSN abnormalities because of the explorative nature of our study. In addition, since a too strict Bonferroni correction for multiple comparisons would have negatively influenced the explorative nature of the study, unadjusted p-values were considered. Moreover, while we employed two tests that evaluated social cognition in non-verbal modality, we could not assess the relationship between the RS-FC of cognitive-related brain networks and social cognition tasks in verbal modality. This issue should be investigated in future studies. Finally, our sample included MS patients with a medium disease duration, with no cognitive impairment, and with a relatively low lesion load; because of the nature of our cross-sectional study, we could not evaluate the evolution of the associations with time, in later stages of the disease. Future research should be conducted by taking into account the limitations and the methodological weakness of the present study; we believe that the use of a larger sample, employing statistical corrective measures to rule out the possible presence of a type 1 error, and using multiple psychological tests that are able to assess several components of social cognition and differentiate between the several processes that are part of social cognition might confirm and expand our novel findings.

In conclusion, the present study reinforces and expands the notion that patients with MS exhibit an impairment of social cognition abilities. Moreover, the performance on social cognition tasks (in particular those that assess social cognition) appears to be related to specific abnormalities in RSNs related to cognition, such as the DMN, the EN, and the LN. It must be emphasized, however, that the findings of our explorative study have to be treated with caution due to some methodological weaknesses (i.e., some data were not corrected for multiple comparison, different numbers of participants in the two groups). Future investigations should confirm our results by employing a larger number of patients, while also adopting a longitudinal design.

Among the subscales of TMPS, the reciprocity score was significantly associated to three nodes in three different brain networks (DMN, EN, and LN). The social norm of reciprocity plays a key role into maintaining cooperation among members of society; it is now considered a common feature of social cognition, since recent literature confirmed that social cognition is not only a process linked to "pure observation" of social situations, but it also includes elements of social interaction (Bratman, 2013). This component of social cognition seems to be particularly impaired in MS patients, as demonstrated in our study. Since social cognition abilities are necessary to maintain good social relationship, and MS patients need a good social support in order to reduce the risk of developing depression or anxiety (Schwartz and Frohner, 2005; Feinstein et al., 2013), our findings can have clinical implications. Indeed, a better

understanding of the mechanism subtending social cognition impairment in MS patients might prompt clinicians to identify patients at risk and provide them with specific and personalized psychoeducational programs to enhance or maintain their social cognition abilities and thus to help them to preserve their social relationships.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitato Etico Azienda Ospedaliera Universitaria Luigi Vanvitelli—AORN Ospedale dei Colli. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AG, GS, and AB conceived and designed the study. MA, SP, RC, and Ad'A collected clinical/neuropsychological data. MC collected MRI data. MA, FD, GC, and RD performed statistical and MRI analysis. AB and MA wrote the manuscript. AG, GS, and GT supervised the project. FE, SB, and FT contributed to the interpretation of the results and to the final version of the manuscript (provided critical feedback and revised the manuscript). All authors discussed the results and contributed to the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnbeh.2019.00276/full#supplementary-material.

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GENERAL COMMENTARY
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Response: Commentary: Metacognition and Perspective-Taking in Alzheimer's Disease: A Mini-Review

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INTRODUCTION

Impaired self-awareness is a frequent characteristic of dementia, particularly Alzheimer's disease (AD; Morris and Mograbi, 2013), leading to various negative consequences for the patients and their caregivers, such as reduced treatment adherence and higher caregiver burden (Seltzer et al., 1997; Patel and Prince, 2001; Bertrand et al., 2013). Lack of self-awareness is a complex phenomenon and its clinical presentation is heterogeneous (Clare et al., 2005). For example, it has been shown that people with AD (PwAD) may present impaired self-awareness for some deficits, but preserved awareness of other difficulties (Vasterling et al., 1995; Verhülsdonk et al., 2013; Bertrand et al., 2019). The Cognitive Awareness Model (CAM; Agnew and Morris, 1998; Morris and Hannesdottir, 2004; Hannesdottir and Morris, 2007; Morris and Mograbi, 2013) provides a neurocognitive explanation of lack of self-awareness, trying to account for the complexity of this concept.

Based on the framework developed by Stuss and Anderson (2004) to understand the structure of consciousness, Morese et al. (2018) pointed to the differences between the notions of anosognosia and self-awareness. The authors explain that awareness follows a hierarchical organization in which anosognosia is related to lower levels and self-awareness to higher levels. Whilst we agree that self-awareness and anosognosia can be distinguished (Mograbi and Morris, 2018), our view about the relationship between these concepts differs in relation to that proposed by Morese and colleagues.

The term impaired self-awareness has been employed in the seminal work of Prigatano to describe how awareness about self-ability, personal characteristics, and self-performance can be impaired in clinical populations (Prigatano, 2005). We believe that self-awareness refers to, as the term implies, awareness processes that take the self as an object (Morin, 2006), and it can be understood in even broader terms than those suggested by Prigatano, potentially also involving processes linked to knowledge about internal states (interoception), body ownership (proprioception, agency), identity (autobiographical memory), and monitoring/regulatory processes (metacognition, emotional regulation).

Anosognosia refers to awareness of having a condition (and, by extension, its symptoms and consequences; Mograbi and Morris, 2018), not necessarily being linked to lower-order processes.

In fact, it is likely that awareness about having a condition is influenced by higher-order factors such as culture (Mograbi et al., 2012, 2015), illness representations (Mograbi et al., 2012) and premorbid personality (Gilleen et al., 2012). It is possible that impairments in different self-awareness processes may lead to anosognosia (or loss of insight, as employed in the psychiatric literature) in clinical conditions. For example, impaired autobiographical memory may be linked to anosognosia in AD (Mograbi et al., 2009), whilst alterations in sense of agency may explain loss of insight in psychosis (Lysaker and Lysaker, 2010). As indicated above, metacognition can be seen as a self-awareness process, and its impairments may lead to specific forms of anosognosia.

CAM AND EXECUTIVE ANOSOGNOSIA

Empirical evidence has highlighted an association between frontal lobe dysfunction and reduced self-awareness in AD, both in studies using neuroimaging (Rosen et al., 2010; Zamboni et al., 2013) and studies employing neuropsychological tests of executive functions (Perrotin et al., 2008; Shaked et al., 2014). These data support the idea of a form of anosognosia linked to executive processes (executive anosognosia; Morris and Mograbi, 2013). In the CAM model, comparator mechanisms are responsible for monitoring of performance, comparing the actual performance with previous information about ability stored in a personal data base. The result of this comparison is passed to the metacognitive awareness system, leading to accurate self-awareness. So PwAD might present reduced self-awareness because the comparator mechanisms fail to detect the mismatches between the expected and the current experience. In other words, executive anosognosia, as proposed in the CAM, highlights the association between metacognition and anosognosia, with a deficit in metacognitive abilities leading to anosognosia.

APATHY AND ERROR MONITORING

Error monitoring is a prerequisite to develop awareness of performance. There is an association between error awareness and apathy in AD, with higher levels of the latter being related to poorer awareness in people with mild AD and MCI (Jacus, 2017). It is possible that this relationship reflects the importance of emotional processing in error monitoring (Mograbi and Morris, 2014). Emotional reactions mark instances of failed task performance with a level of personal significance, and the absence or diminution of error signals caused by apathy could thus be a leading cause of anosognosia in patients with neurodegenerative diseases, by preventing them to consider these events when evaluating their abilities (Rosen, 2011). In addition, apathy and anosognosia rely on shared neural networks. The anterior cingulate cortex (ACC) is a possible neural correlate of both phenomena, since it has been shown that cortical gray matter atrophy in the bilateral ACC is related to apathy severity in PwAD (Marshall et al., 2006, 2007). Furthermore, this region is the most likely generator of error related potentials like the error related negativity (ERN; Van Veen and Carter, 2002). Error-related activity has also been shown in limbic structures (Polli et al., 2009; Pourtois et al., 2010), suggesting that the amygdala may register motivational significance of motor actions, and the dorsal ACC could provide signals related to failure of cognitive control and behavioral adjustment (Pourtois et al., 2010).

CONCLUSION

In summary, apparently similar presentations of anosognosia, unawareness of having a condition and its consequences, can be linked to different impairments in self-awareness. For example, difficulties in metacognition may prevent detecting mismatches between expected and current performance, or impaired emotional processing may deprive errors of their affective signature, leading to limited awareness about performance and condition. This is precisely the notion described in the CAM, which tries to deal with heterogeneity of anosognosia in clinical groups, suggesting factors such as memory, executive functions, and top-down/bottom-up modulatory processes that can cause different forms of anosognosia. Future research should explore which self-awareness processes are particularly relevant in the context of specific conditions, investigating the relationship between different self-awareness components and how these relate to awareness of condition, considering the impact of the latter in clinical management of patients.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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frontiers in Behavioral Neuroscience

CASE REPORT
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Report of a Case of Creutzfeldt-Jakob Disease With an Unusual Clinical Presentation

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We describe the clinical features, neuropsychological tests, laboratory, electroencephalography (EEG), magnetic resonance imaging (MRI) and positron emission tomography (PET) findings of a 59-year-old woman who presented to our Centre for cognitive impairment since few months, with language disturbances, particularly anomia, dyscalculia, and memory loss. The clinical and neuropsychological features were non-specific and overlapping with those of other rapidly progressing neurodegenerative disorders. However, brain MRI played a pivotal role in the diagnosis, showing cortical diffusion restriction, particularly in the parietal lobes and posterior cingulum, with sparing of the perirolandic cortex, typical of Creutzfeldt-Jakob disease (CJD). Brain MRI abnormalities were visible since the first evaluation and remained stable at 2 and 6 weeks follow up. Basal ganglia and thalami were never involved. PET showed left lateralized reduced glucose metabolism, with partial overlap with MRI signal abnormalities. Despite MRI were strongly indicative of CJD, clinical, laboratory and EEG findings did not fulfill the diagnostic criteria for CJD which applied at the time of clinical assessment. Indeed, neither myoclonus, visual or cerebellar signs or akinetic mutism were present. Also, the characteristic periodic sharp wave complexes were absent at baseline EEG, and the CSF assay for 14–3–3 was negative. We, therefore, performed a real-time quaking-induced conversion (RT-QuIC) assay on a frozen sample of corticospinal fluid (CSF), which showed a positive result. RT-QuIC is a prion protein conversion assay that has shown high diagnostic sensitivity and specificity for the diagnosis of CJD. RT-QuIC has been recently incorporated in the National CJD Research and Surveillance Unit and Center for Disease Control and Prevention (CDC) diagnostic criteria for CJD. The fatal evolution of the disease brought the patient to death 13 months after symptoms onset. Pathology proved the diagnosis of sporadic CJD, subtype MM/MV 2C.

Keywords: Creutzfeldt-Jakob disease, sporadic, MRI, PET, diagnostic criteria, RT-QuIC

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INTRODUCTION

We describe a case of rapidly progressive dementia (RPD) that started with impairment of language skills and discuss the neuropsychological differential diagnosis. We outline the role of new diagnostic criteria for the diagnosis of Creutzfeldt-Jakob disease (CJD) that allow *in vivo* diagnosis of the disease even in cases with atypical clinical and electroencephalography (EEG) presentation, such as in this case.

CASE PRESENTATION

We report of a 59-year-old woman who developed, since December 2015, language abnormalities characterized by word retrieval difficulties and impairment in sentence production. These changes were reported to interfere with her job activity, with raising work-related stress and anxiety. In the following 6 months, she developed difficulties in calculation abilities, impairment of time perception and short-term memory loss. The social entourage had perceived that something was wrong, especially since spring 2016, when she was referred to a local neurologist and a mini-mental state examination (MMSE) was performed with a normal score (30/30). After 9 months from symptoms onset, she was considered unable to work. She was referred to our neurological outpatient service and hospitalized. Neurological examination in December 2016 showed moderate aphasia with some difficulties in the denomination. No pathological abnormalities were found in the neurologic exam of cranial nerves, strength, tone, reflexes, coordination, sensory function, and gait. A neuropsychological evaluation was conducted during the hospitalization with an initial informal discussion followed by a detailed neuropsychological examination using a battery of tasks designed to evaluate global cognitive functioning (Mini-Mental Status Examination, MMSE), language (Boston Naming test-short version, Phonemic and Semantic Fluency test), short term and working memory (forwards and backward Digit and Corsi span), anterograde verbal episodic memory (Story Recall test), anterograde visuospatial memory (Rey-Osterrieth Complex figure test Recall), attention and processing speed (Trail Making Test), executive function [Frontal Assessment battery (FAB)] and visuospatial skills (Rey-Osterrieth Complex figure test Copy). A detailed language assessment was also conducted through the Neuropsychology Exam for Aphasia (ENPA). At the time of the evaluation, the patient was alert and oriented in all domains, engaged in the examination but mildly anxious. She exhibited partial insight about her declining abilities, claiming that these were due to work-related stress. We perceived a lack of emotional insight and concern over her status. In the spontaneous speech, she showed difficulty in language production, with impaired word-retrieval and use of passe-partout words. There was no evidence of a primary impairment of comprehension. The language was characterized by a lack of focus, tangential and ambiguous speech. The neuropsychological evaluation outlined impairment across multiple domains (**Table 1**). She scored 23/30 at MMSE, showing a rapid deterioration compared to the test performed 6 months before, in June. Her performance was particularly poor in short and long verbal memory tasks. She was also impaired in the executive domain, with difficulty accessing mental lexicon and carrying out mentally effortful tasks such as calculation, mental manipulation, task-set inhibition and cognitive flexibility. Visuospatial long-term memory was less affected than verbal memory. Other measured abilities appeared to be preserved, including graphomotor skills and visuospatial abilities. The investigation of speech and language functions (**Table 2**) showed prominent abnormalities in two specific aspects of language processing: verbal fluency (Letter and Category subtasks) and spontaneous speech (Spoken Picture Description). Connected speech was compromised due to frequent pauses for word retrieval and difficulty in discourse organization. We did not find selective impairments on comprehension, denomination, repetition, reading, and writing. Laboratory tests were in range except for a slight increase in ammonia and amylase (non-specific findings); slight hypovitaminosis D and subclinical hyperthyroidism (with normal autoimmune screening with anti-TPO, anti-thyroglobulin, anti-TRAK). No further abnormalities were present in electrolytes, glucose, PCR, VES, sidero-vitamin levels (including B1 e B12). The autoimmune and infectious screening was negative.

We performed an extensive panel to search for paraneoplastic antibodies with negative results. Moreover, chest and abdomen CT scan with iodinated contrast were unremarkable. CSF examination was in range. CSF protein 14–3–3 was negative. The dosage of protein TAU and phospho-TAU was normal (TAU 284 ng/L—ref. <360 ng/L; p-TAU 30 ng/L—REF <60 ng/L), while Aβ42 was slightly reduced (Aβ42 367 ng/L—ref.>, 450 ng/L). Electroencephalogram (EEG) at baseline showed non-specific findings, with intermittent slight slow-waves abnormalities, mostly in the left frontal, central and temporal regions. Brain magnetic resonance imaging (MRI) showed bilateral and diffuse supratentorial cortical diffusion restriction, more evident in the parietal lobes and posterior cingulum, with sparing of the peri-rolandic cortex. No clear cortical signal abnormalities were visible on T2 weighted or T2-fluid-attenuation-recovery (FLAIR) images and no enhancement was visible after contrast media administration. Brain MRI abnormalities were visible since the first evaluation. Basal ganglia and thalami were never involved (**Figure 1**). Abnormalities remained stable at 2 and 6 weeks follow up MRI exams (not shown). FDG-PET ([^{18}F]-fluoro-2-deoxy-D-glucose positron emission tomography) showed left lateralized reduced glucose metabolism in temporal, parietal and frontal lobes, partially overlapping with the cortical diffusivity abnormalities seen on MRI. No involvement of subcortical structures was present (**Figure 2**). MRI findings were strongly indicative of CJD. However clinical, laboratory and EEG findings were not sufficient to fulfill the diagnostic criteria of CJD which applied at the time of clinical assessment (Vitali et al., 2011). Indeed, neither myoclonus, visual or cerebellar signs or akinetic mutism were present; periodic sharp wave complexes were not visible at baseline EEG and the CSF assay for 14–3–3 was negative. We, therefore, performed a real-time quaking-induced conversion (RT-QuIC) assay on a frozen sample of corticospinal fluid

TABLE 1 | Neuropsychology tests panel.

Domain of function	Task	Raw score	Adjusted score	Cutoff	Equivalent score
Global cognitive functioning	Mini-Mental State Examination (MMSE)	23/30	21	24	
Language	Boston Naming Test	13/15	12	11	2
	Phonemic fluency	15	17.50	17.35	1
	Semantic fluency	25	27	25	1
Attention and processing speed	Trail Making Test, Part A (seconds)	42	25	93	4
	Trail Making Test, Part B (seconds)	313	255	282	1
	Trail Making test, B-A (seconds)	271	230	186	0
Memory	Digit Span forward	4/9	4.13	4.26	0
	Digit span backward	3/8	3.19	2.65	1
	Corsi span forward	3/9	3.15	3.46	0
	Corsi span backward	0/8	-	3.08	0
	Story recall test	3/28	2.50	8.00	0
	Rey-Osterrieth Complex figure test (ROCF)—Recall	8.5/36	12	9.47	2
Executive function	Frontal Assessment battery (FAB)	10/18	10.34	11.60	0
Visuocostructional skills	Rey-Osterrieth Complex figure test (ROCF)—Copy	36/36	-	28.88	4

Performance on neuropsychological testing presented as raw scores, adjusted scores (for age and education) and equivalent scores. Equivalent score (Capitani and Laiacona, 1997) is a 5-point scale where neuropsychological scores are standardized after adjustment for age and education. ES = 0 indicates a pathological performance. ES = 1 a borderline performance. ES ≥ 2 a normal performance. Neuropsychological assessment results are organized by domain of function.

(CSF), which showed a positive result. Notably, CSF was clear, protein and white blood cell levels in CSF were in range, respectively 271 mg/L (range 200–400) and 0,7/μl (normal value <5/μl). In the following months, the patient experienced a rapid worsening of symptoms, with symptomatic epilepsy. A detailed neuropsychological follow-up could not be repeated. Neither myoclonus, tremors or involuntary movements were present during the course of the disease. Notably, a long-term EEG monitoring, performed in February 2017, showed most evocative findings, with single triphasic waves in both waking and sleeping status compatible with mild encephalopathy and slight phasic periodism during the night. The patient died in May 2018 after the recurrence of an epileptic seizure. She developed pneumonia probably due to bronchoaspiration with consequent respiratory failure. Pathology proved the diagnosis of sporadic CJD, subtype MM/MV 2C.

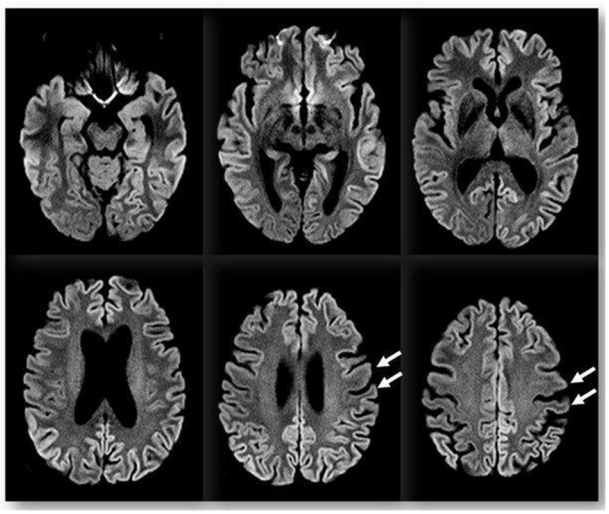

FIGURE 1 | Brain magnetic resonance imaging (MRI). Diffusion-weighted imaging (DWI) with *b* value of 1,000 s/mm^2 showing bilateral and diffuse supratentorial cortical diffusion signal changes with a restriction on ADC map (not shown) and slight left lateralization. The peri-rolandic cortex is spared (arrows). There is no involvement of subcortical structures.

DISCUSSION

This is a case of RPD induced by CJD which exhibited unusual clinical and EEG manifestations, yet typical MRI findings, which may be relevant to physicians to consider the CJD etiology in similar clinical pictures. RPD refers to a condition characterized by a quick decline in more than one cognitive domain with functional disability in a short time (Geschwind, 2016). The differential diagnosis of RPD includes many treatable conditions that our patient multimodal work-up allowed to rule out. Among these, paraneoplastic autoimmune encephalopathies, infections, toxic or metabolic conditions, neoplasms, and other conditions such as dural arteriovenous fistula (DAVF) that sometimes manifest as RPD (Geschwind, 2016).

In the differential diagnosis, we considered an atypical presentation of primary progressive aphasia (PPA) since language skills were involved from the beginning of the disease. The clinical profile of PPA is a gradually progressive deficit in language function with relative sparing of other intellectual functions (Mesulam, 2003; Gorno-Tempini et al., 2011). Among the different forms of PPA, the cognitive profile of our patient resembled more that found in logopenic progressive aphasia (LPA). LPA is characterized by word-finding difficulty with frequent pauses in spontaneous speech, impaired single word retrieval and naming, difficulty in repeating sentences, phonological errors and confrontation naming. Comprehension, motor speech and word repetition are spared. The language profile of our patient was not fulfilling the criteria for the other forms of PPA: in the non-fluent agrammatic aphasia

TABLE 2 | Neuropsychological exam for aphasia (ENPA).

Task	Sub-task	Raw Score	Adjusted score	Cut-off	Interpretation
Repetition	Words	10/10	–	8.8	-
	Not-words	5/5	–	2.0	-
	Phrases	3/3	–	3.0	-
Reading	Words	10/10	–	6.4	-
	Not-words	5/5	–	4.0	-
	Phrases	2/2	–	1.3	-
Writing	Words	8/10	7.4	6.3	-
	Not-words	3/5	2.3	1.4	-
	Phrases	2/2	–	0.6	-
Denomination	Nouns/oral	10/10	–	8.2	-
	Nouns/writing	5/5	–	2.7	-
	Verbs/oral	8/10	7.5	6.1	-
	Verbs/writing	3/5	2.6	3.0	-
	Colors/oral	5/5	–	4.0	-
Comprehension	Words/hearing	20/20	–	18.4	-
	Words/visual	19/20	18.8	17.0	-
	Phrases/hearing	12/14	11.9	11.6	-
	Phrases/visual	12/14	11.6	11.3	-
Words generation	Letter F	5	4.1	5.7	*
	Letter A	6	5.1	4.8	-
	Letter S	2	1.1	5.8	*
	Animals	10	9.2	10.3	*
	Objects	11	8.1	8.5	*
Spoken picture description		–	–	–	Frequent pauses for word-finding, impaired connecting speech, a problem with discourse organization*

*Performance on language testing presented as raw scores, adjusted scores (for age and education) and interpretation of the results. – Indicates a normal performance; *Indicates a pathological performance.*

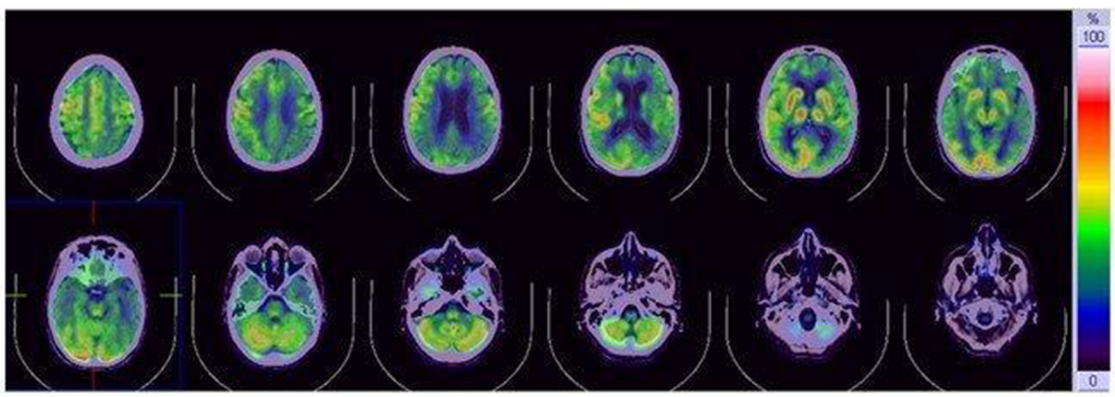

FIGURE 2 | [^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET). FDG-PET reduced glucose metabolism in the temporo-parietal and frontal lobe, with slight left lateralizatio. No involvement of subcortical structures is present.

and semantic aphasia. The first condition is characterized by disturbances of language production, distorted articulation (apraxia of speech), syntactic simplification with telegraphic language, without a deficit in word comprehension. The second condition, also named semantic PPA, is characterized by severe anomia, impaired word comprehension with loss of meaning of the words, gradual disintegration of semantic knowledge about people and objects, with preservation of the phonological and syntactic aspects of language (Gorno-Tempini et al., 2011). Consistent with our language assessment, the patient could repeat word, not-words and sentences, but produced a reduced output, clearly showed by impaired performance on fluency tasks and spoken picture description, demonstrating an executive derangement in language tests as well as in other executive tasks (Trail Making Test, Part B, digit span backward). This is in line with a recent report that outlined that language disorders in prion diseases represent a dynamic aphasia in the context of a prominent dysexecutive syndrome (Caine

et al., 2018). PET findings could be compatible with LPA even though hypometabolism was found to extend beyond the temporoparietal areas. However, the rapid evolution of global cognitive impairment was not supporting this hypothesis.

The possibility of an Early-onset Alzheimer's disease (EOAD) was also considered. EOAD manifests in younger subjects <65 years and is characterized by impairment in language, visuospatial and behavioral executive domains with sparing of episodic memory, which is typically involved in late-onset Alzheimer's disease (LOAD; Palasí et al., 2015; Mendez, 2019). EOAD patients have a more aggressive clinical course (Koedam et al., 2008; Stanley and Walker, 2014), and age-related psychosocial needs (Rosness et al., 2010). Decreased CSF level of Ab42 could support the hypothesis of Alzheimer's disease however tau and phospho-tau were not elevated. Also, FDG_PET uptake was decreased beyond the temporoparietal cortex.

In light of the characteristic of MRI findings, the diagnosis of CJD was considered. CJD, although rare, is the most common human prion diseases, a group of lethal transmissible neurodegenerative diseases, related to the conversion of a normal cellular protein, the prion protein (PrPC), into a misfolded form (PrPSc) which accumulates in neuronal cells leading to intracellular spongiform changes and neuronal loss (Prusiner, 1998). Human prion diseases occur in sporadic, genetic and acquired forms. Sporadic CJD (sCJD) is the most common form and is related to the spontaneous conformational conversion of PrP^{C}. Genetic forms, caused by mutations in the gene PRNP encoding for PrP^{C}, include familial CJD (fCJD), Gerstmann-Sträussler-Scheinker syndrome (GSS) and fatal familial insomnia (FFI). The acquired forms, resulting from the human-to-human transmission, include kuru and iatrogenic CJD (iCJD). Kuru, related to cannibalism, is now considered to be extinct. ICJD has been reported to occur by transmission *via* contaminated neurosurgical instruments such as intracerebral EEG needles, human dura mater grafts, inoculation with human pituitary hormones or corneal transplantation. A further iatrogenic form, variant Creutzfeldt–Jakob disease (vCJD), results from bovine to human transmission of the agent of bovine spongiform encephalopathy (BSE); a human-to-human transmission may also occur.

According to the molecular classification proposed by *Parchi e Gambetti* (Parchi et al., 2012), different molecular subtype of sCJD are distinguished based on the PRNP gene codon 129 genotype, homozygous or heterozygous for methionine (M) or valine (V), and the pathologic prion protein (PrP^{Sc}) type, that is classified as type 1 or type 2 depending on the size and electrophoretic mobility at Western blot of the protease-resistant core fragment (PrPres). Six phenotypes are therefore distinguished: MM1, MM2, MV1, MV2, VV1, or VV2. MM2 can be further divided into two subgroups based on histopathological criteria: MM2C, cortical form, with predominant cortical pathology and MM2T, thalamic form, with typical atrophy of thalamic and inferior olivary nuclei. The MV2 group has also been divided into two distinct subtypes based on pathological criteria MV2C (MV2 cortical type) and MV2K (MV2 kuru plaque-type). Since both MM1/MV1 and MM2C/MV2C share the same clinicopathological features, they have been merged into single entities, MM/MV1 subtype and the MM/MV2C subtype. In conclusion, six different subtypes are distinguished in the current classification of sCJD: MM/MV1, MM/MV2C, MM2T, MV2K, VV1 or VV2 (Parchi et al., 2012).

CJD brain MRI abnormalities typically involve the cortex and the basal ganglia (putamen and caudate), with diffusion restriction variably associated with T2 and FLAIR hyperintensity. Cortical involvement may be focal or diffuse, symmetric or asymmetric; the perirolandic cortex is usually spared. Thalamic involvement (unilateral or bilateral) has been described in cases of variant-CJD but can be found in sporadic forms as well. Thalamic signal abnormalities are known as MRI "hockey stick sign," since they are located in the pulvinar and dorsomedial thalamic nuclei, resembling the shape of a hockey stick. Diffusion restriction in the cerebellum has been reported in atypical cases (Fragoso et al., 2017). Similar MRI abnormalities may be found in hypoxic/anoxic brain injury, encephalitis, metabolic conditions such as hepatic encephalopathy or hypoglycaemic encephalopathy, and status epileptics, therefore MRI finding must be interpreted in the appropriate clinical setting.

To date, a diagnosis of "definite CJD" can be made just upon neuropathologic examination, with prion protein identification by immunochemistry or Western blotting. An *in vivo* diagnosis of "probable CJD" has been previously based on the WHO diagnostic criteria established in 1998 (WHO, 1998), with the following revisions in 2009 by the European MRI-CJD Consortium (Zerr et al., 2009) and in 2011 by the University of California, San Francisco (Vitali et al., 2011). According to WHO revised criteria a diagnosis of possible CJD was possible in the presence of progressive dementia plus two other clinical findings among myoclonus, pyramidal/extrapyramidal symptoms, visual/cerebellar dysfunction, and akinetic mutism, plus EEG evidence of periodic sharp wave complexes (PSWCs) or elevated CSF 14.3.3 protein or typical MRI findings, such as high-signal intensity on either FLAIR or DWI in both the putamen and the caudate nucleus or at least two cerebral cortical regions, from either the temporal, occipital, or parietal cortices, not including frontal or limbic regions. The National CJD Research and Surveillance Unit (NCJDRSU) in 2017 (Unit NCR and S PROTOCOL, 2017) and the Center for Disease Control and Prevention (CDC) in 2018 (Diagnostic-Criteria, 2018) have introduced new diagnostic criteria incorporating the use of a novel ultrasensitive seeding assay, the real-time quaking-induced conversion assay (RT-QuIC). This assay can detect the amplified pathological prion protein in the CSF or the olfactory mucosa with very high sensitivity and specificity (Bongianni et al., 2017; Foutz et al., 2017). The assay is based on the ability of the misfolded pathological prion protein (PrPSc) to induce conversion of the normal prion protein (PrP) to the misfolded form, with subsequent protein aggregation. The formation of aggregates can be monitored in real-time using a fluorescent dye. These new criteria now allow a diagnosis of "probable CJD" just in the presence of progressive neuropsychiatric disorder and positive RT-QuIC in CSF or other tissues, extending the diagnosis to cases with atypical clinical presentation and non-supportive EEG and/or MRI findings. Notably, EEG PSWCs are found in approximately 73% of patients with sCJD, usually in

the late stage of the disease while MRI abnormalities are found in about 83% of patients. Protein 14–3–3 has been reported to have a good sensitivity for CJD (up to 85–95%), however, it is not specific (Zerr et al., 2009).

The interpretation of the RT-QuIC assay is affected by the presence of raised red and white cells counts and elevated total protein concentrations in the CSF. Red cells in CSF samples inhibit the RT-QuIC response, with fewer replicates and longer reaction times. A cut-off of $<1{,}250 \times 10^{6/L}$ red blood cells is recommended. High CSF total protein concentrations of >1.0 g/L and raised white blood cells may result in an RT-QuIC response with a high and fluctuating baseline that can be misinterpreted as a positive RT-QuIC result. CSF samples for RT-QuIC analysis are required to be clear, with a white cell count of $<10 \times 10^{6/L}$ and a total protein concentration of <1 g/L. CSF RT-QuIC is not affected if CSF samples are stored at room temperature or 4°C for up to 8 days and is not affected by repeated freeze and thaw cycles. RT-QuIC can be run on CSF samples but also olfactory neuroepithelium obtained by nasal brushing (Green, 2019). RT-QuIC has demonstrated high diagnostic value but has limited prognostic value since different sCJD subtypes generate very similar RT-QuIC reaction products (Piconi et al., 2019).

Other biochemical analysis methods have been developed for the diagnosis of CJD. Among these, Sodium Phospho-Tungstic Acid (NaPTA) precipitation/western blotting and Conformation Dependent Immunoassay (CDI) that, so far, have not been tested for use in routine diagnostics or screening, and Protein Misfolded cyclic amplification (PMCA) that is less sensitive for sCJD PrPSc (Franceschini et al., 2017).

The role of positron emission tomography (PET) in CJD is not well elucidated compared to other neurodegenerative diseases. A left-lateralized frontal and parietal hypometabolism, as we found in our patient, has been shown in a cohort of CJD patients (Renard et al., 2017). PET abnormalities do not have a strict anatomical correlation with MRI abnormalities and may precede them. Basal ganglia hypometabolism is not commonly detected (Mente et al., 2017).

In conclusion, in our case, the complementary examinations carried out, and in particular, the RT-QuIC test in CSF, was fundamental to make the correct diagnosis and thus differentiate between the possible etiologies of RPD.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article.

ETHICS STATEMENT

Diagnostic work-up and case report descriptions were conducted according to the principles expressed in the Declaration of Helsinki, the institutional regulation and Swiss laws and guidelines. Written informed consent for the publication of the content of this case report was obtained from the patient's daughter after her death.

AUTHOR CONTRIBUTIONS

EPro, SR, and IB wrote the manuscript, made table and figures, reviewed the literature. EPro interpreted brain MRI results. LS performed neurological evaluations of the patient. SR reviewed the neuropsychological and language evaluations of the patient. LS and EPra performed the final manuscript review.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychology

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Improving Self-Awareness of Motor Symptoms in Patients With Parkinson's Disease by Using Mindfulness – A Study Protocol for a Randomized Controlled Trial

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Objective: This study aims to increase self-awareness in patients with Parkinson's disease (PD) using a newly developed mindfulness-based intervention, tailored for the specific needs of PD patients. Its impact on self-awareness and patients' daily lives is currently being evaluated.

Background: Recently, the phenomenon of impaired self-awareness for motor symptoms (ISAm) and some non-motor symptoms has been described in PD. ISAm can negatively influence patients' daily lives, e.g., by affecting therapy adherence, and is therefore the main focus of this study. The main goal is the development of IPSUM ("Insight into Parkinson's Disease Symptoms by using Mindfulness"), a PD-specific intervention for increasing patients' mindfulness and thereby reducing ISAm.

Methods: The effectiveness of IPSUM is evaluated by comparison of an intervention group with a waitlist-control group. A pre-post design with an additional 8-week follow-up measurement is applied, resulting in three measurement points: before, directly after and 8 weeks after completing the intervention protocol. In total, up to 180 non-depressed PD patients without severe cognitive impairment (non-demented) will be included. The primary outcome is a quantitative score for measuring ISAm. Secondary outcome measures are affective changes, neuropsychological performance and self-awareness of cognition. At pre- and post-measurement an fMRI scan is performed to connect behavioral and neurobiological findings. At post- and follow-up-measurement each patient will take part in a semi-structured interview to explore IPSUM's impact on self-awareness and patients' everyday lives.

Results: The conception of the intervention protocol is finished, the resulting 8-week program is presented in detail. It has successfully been tested in the first group of patients, their feedback so far was quite promising. Recruitment is ongoing and a first interim analysis will be performed once 30 patients have completed IPSUM.

Conclusion: For the first time, the intervention protocol of IPSUM has successfully been tested in a group of PD patients. As the study goes on, more quantitative data is collected for statistical analyses to evaluate its effectiveness. More qualitative data is collected to evaluate feasibility and effectiveness. We hope for this intervention to be capable of reducing the patients' ISAm and improving their quality of life on many levels.

Keywords: self-awareness, anosognosia, Parkinson's disease, mindfulness, quality of life, randomized controlled trial, intervention protocol

INTRODUCTION

Parkinson's disease (PD) is one of the most common neurodegenerative disorders. Neural degeneration and loss of dopaminergic cells in the substantia nigra cause a lack of dopamine which ultimately leads to impaired motor functioning (Lill and Klein, 2017). Cardinal motor symptoms of PD include bradykinesia, rigidity and resting tremor (Postuma et al., 2015). As drug treatment commonly consists of dopamine replacement therapy, levodopa-induced dyskinesia might evolve over time (Rizek et al., 2016). Though PD is mainly classified as a movement disorder, the frequent occurrence of a wide range of non-motor symptoms has been recognized in recent years. They include sleep disturbances, autonomic dysfunction (e.g., constipation), hyposmia and psychiatric symptoms like depression, anxiety, hallucinations or impulsivity (Postuma et al., 2015).

The phenomenon of anosognosia for hemiplegia following a right hemisphere stroke is well known. The term anosognosia refers to a complete lack of self-perceived neurological or neuropsychological deficits. A partial absence of this ability is defined as impaired self-awareness (ISA) (Prigatano, 2014). Though rarely considered in the past, more recent research describes the phenomenon of impaired self-awareness for motor impairment (ISAm) in non-depressed, non-demented patients with Parkinson's Disease (for an overview see Maier and Prigatano, 2017). ISA is associated with lower therapy adherence, as well as higher patient mortality and caregiver burden and is therefore of high clinical relevance (Prigatano, 1999; Koltai et al., 2001; Appelros et al., 2007; Turró-Garriga et al., 2013).

ISAm in PD patients has mostly been studied for levodopa-induced dyskinesia (LID) ISAm for hyperkinetic movements has also been described for other diseases such as Huntington's disease and schizophrenia (Vitale et al., 2001; Emsley et al., 2011; Sitek et al., 2014). Depending on the used measurement method, the prevalence of ISAm for LID in PD was found in up to 91% of patients with dyskinesias (Vitale et al., 2001; Maier et al., 2015). ISAm-LID in PD is associated with higher disease duration (Amanzio et al., 2010; Maier et al., 2016), higher levodopa equivalent daily dose (Amanzio et al., 2010; Maier et al., 2016) and predominantly left-sided symptoms (Pietracupa et al., 2013). Positron emission tomography using ^{18}F-Flourodeoxyglucose (FDG-PET) has shown a positive correlation between ISAm-LID and higher glucose metabolism in brain areas which are considered important for the development of LID; mainly in the left putamen, the left supplementary motor area and the left pre-supplementary motor area (Maier et al., 2016).

On the other hand, ISAm for hypokinetic movements (resting tremor and bradykinesia) is prevalent in patients with and without dopaminergic medication (ON- and OFF-state). ISAm for hypokinetic movements (ISAm-Hypo) was found in 42–54% of patients in the ON-state, and in 24–55% of patients in the OFF-state (Maier et al., 2015, 2016). Maier et al. (2016) report a positive correlation of ISAm for hypokinesias in the ON- as well as the OFF-state, but no correlation between hypokinetic movement severity and the severity of ISAm-Hypo. Concerning dopaminergic states, ISA scores in the OFF state have been associated with left-sided disease onset and worse left-sided symptoms, while in the ON-state no findings could support this relationship.

There are two theories surrounding the underlying mechanisms of ISA. It is suggested that the underlying mechanism for ISAm-Hypo might differ from the mechanism for ISAm-LID (Maier and Prigatano, 2017). For once, similar to ISA in other diseases like traumatic brain injury and Alzheimer's Disease, right hemispheric dysfunction may cause ISAm in PD (Prigatano, 2014; Shany-Ur et al., 2014). Examining glucose metabolism in the FDG-PET study Maier et al. (2016) have found a significant association between ISA scores in the OFF-State and hypometabolism in the right inferior frontal gyrus. They also report a tendency for significance in the right insular cortex. Both regions have not only been linked to anosognosia for hemiplegia in stroke patients (Kortte et al., 2015; Moro et al., 2016), but also to ISA of overall functional competency in dementia (Shany-Ur et al., 2014). The right inferior frontal gyrus and the right insula are part of a brain network which has been associated with motor response inhibition and action monitoring and might therefore be affected in PD patients with ISAm (Fotopoulou et al., 2010; Moro et al., 2016).

Contrary to the theory of right hemispheric dysfunction, it is hypothesized that ISAm-LID emerges as a consequence of dopaminergic overstimulation (Vitale et al., 2001; Amanzio et al., 2010, 2014). While dopamine replacement therapy compensates the lack of dopamine in mesocorticolimbic pathways, and therefore enhances executive functioning, medial-prefrontal ventral-striatal circuits might be overstimulated as they are less affected by dopamine depletion (Maier and Prigatano, 2017). This might result in impaired executive functioning like attentional set shifting, response inhibition and performance monitoring. Amanzio et al. (2011) suggested that a dysfunction of the cingulate cortex, which is typically involved in action and performance monitoring, contributes to the phenomenon of ISA. Although ISAm-LID has been associated with lower cognitive

performance by some researchers, contradictory findings have not shown any correlation of ISAm-LID and cognitive or executive performance in neuropsychological tests (Maier et al., 2012, 2016; Pietracupa et al., 2013).

Despite the growing research interest in ISA for motor symptoms in PD, it is worth mentioning that ISA might also exist in regards of cognitive impairment (ISAc), mainly for memory and executive impairment (Kudlicka et al., 2013; Lehrner et al., 2015). Pillai et al. (2018) conclude that impaired self-appraisal for cognitive functioning is equally likely to occur in PD patients with mild cognitive impairment (MCI) and patients with amnestic MCI, which often progresses to Alzheimer's Disease. Orfei et al. (2018) have highlighted the importance of the general level of cognitive functioning. They found higher anosognosia in PD patients with dementia and multi-domain MCI compared to PD patients with single-domain MCI or normal cognitive functioning. Interestingly, greater anosognosia might also be associated with depression and lower executive functioning. It has to be noted though, that other researchers have not found any evidence for ISAc in PD (Starkstein et al., 1996; Sitek et al., 2011, 2013; Koerts et al., 2012). In their review, Maier and Prigatano (2017) have suspected the use of different methods to assess ISAc, sample differences, as well as the potential importance of a present cognitive impairment to be reasons for these conflicting results. Future research should therefore comprise extensive neuropsychological test batteries and imaging data to get further insight into the phenomenon of ISAc. It is worth mentioning that newer research has already taken some of these aspects into consideration (Orfei et al., 2018; Pillai et al., 2018).

To study anosognosia for memory impairment in Alzheimer's Disease Vannini et al. (2017) calculated an anosognosia index to quantify the discrepancy between subjective and objective memory scores. Using this method, they found decreased memory awareness in patients with amnestic mild cognitive impairment in comparison to a healthy control group. Among others, they also reported an association between lower memory awareness and reduced glucose metabolism in the posterior cingulate cortices and the hippocampus. Maier et al. (in preparation) applied a similar method to study differences of cognitive awareness between PD patients with and without MCI and healthy controls. For PD patients as a whole, they found an association between higher impairment of awareness and reduced metabolism in FDG-PET in the anterior and mid-Cingular cortices. Specifically, for PD patients with MCI they report the same association in the mid-Cingular cortex as well as the right superior temporal area and parts of the adjacent insular cortex. Taking neurobiological findings of ISAm and ISAc in consideration, the cingulate gyrus, as well as the (right) insula seem to play an important role regarding the general development of impaired self-awareness.

The concept of mindfulness originated in Buddhism, but has grown in popularity in western civilization and scientific research for several years (Kabat-Zinn, 2013; Fox et al., 2016). It has been formerly described as "paying attention in a particular way: on purpose, in the present moment, and non-judgementally" (Kabat-Zinn, 2004, p. 4). Mindfulness can be understood as a kind of personality trait, which can be improved by regular formal or informal mindfulness practice (Keng et al., 2011). While formal practice involves meditation or yoga practice, informal practice comprises all sort of daily activity which is performed while maintaining the described mindful attitude (Kabat-Zinn, 2013; Schug, 2016).

In general, mindfulness is strongly associated with variables of psychological health like quality of life, feelings of vitality and autonomy or optimism (Brown and Ryan, 2003; Rasmussen and Pidgeon, 2011). On the other hand, it is negatively associated with depression, social anxiety or other psychiatric symptoms (Brown and Ryan, 2003; Baer et al., 2006; Dekeyser et al., 2008; Cash and Whittingham, 2010; Rasmussen and Pidgeon, 2011). For more detailed information see Keng et al. (2011). Similar results have been reported for meditation practice alone, which is an essential part of most intervention concepts. While meditation practice seems to reduce negative emotions, like anxiety and stress, it might also enhance cognitive performance of attention and self-reflection (Sedlmeier et al., 2012). Further studies also hint at possible positive implications of mindfulness training on attention and possibly working memory and executive functioning (Chiesa et al., 2011).

Other studies also suggest positive implications in regards of body awareness. For example, early qualitative studies indicate a more positive self-representation and acceptance toward oneself as well as higher responsivity and intensity of body and emotional perception caused by regular yoga practice (Emavardhana and Tori, 1997; Daubenmier, 2005; Impett et al., 2006; Dittmann and Freedman, 2009). Additionally, long-term meditators showed an improved awareness and interpretation of body states (Tang et al., 2015), a higher coherence of emotional perception and physiological arousal, as well as more sensitivity for body sensations (Sze et al., 2010). In a study conducted by Fox et al. (2012), meditators reported more intense body sensations after completing a guided body scan meditation (in which the meditator focuses his/her attention systematically on different parts of the body) compared to a control group.

These behavioral findings regarding self-awareness and perception are also reflected on a neurobiological level. Early findings have suggested that meditators, compared to matched controls, display higher cortical thickness in the right prefrontal cortex and right insula. These areas have been associated with attention, introspection and processing of sensory stimuli (Lazar et al., 2005). In addition to higher cortical thickness, in a meta-analysis considering 21 studies, Fox et al. (2014) identified differences in volume and density of gray and white matter in various regions. Regions linked to self-awareness include the bilateral insula, somatomotoric cortices, the rostrolateral prefrontal cortex, and the anterior and mid-cingulate cortices. These regions have been mostly associated with abilities of introspection, metacognitive and body-oriented perception and self-regulation. According to the authors, especially changes in the area of the insula are central to general meditation practice, independently of the type of meditation practiced (Fox et al., 2014, p. 61). Although most studies have focused on cross-sectional comparisons between long-term meditators and novices, it is assumed that the effects regarding areas like the prefrontal cortex, the cingulate gyrus and the insula might be

just as significant after only 8 weeks of mindfulness training (Gotink et al., 2016).

In a clinical context, many psychological mindfulness-based interventions exist. The most popular and most cited program is called Mindfulness-Based Stress Reduction (MBSR), which was developed by Jon Kabat-Zinn to improve stress and pain management in patients with chronic pain (Kabat-Zinn, 1982). In fact, the effects of MBSR and other mindfulness-based interventions have been studied in various physical chronic diseases, like Multiple Sclerosis, chronic pain or cancer. For those patient groups, positive effects have been found especially in regards of quality of life, stress and fatigue (Ott et al., 2006; Grossman et al., 2010; Rosenzweig et al., 2010). Larouche et al. (2015) have suggested that mindfulness-based interventions might slow down cognitive decline in patients with Alzheimer's Disease.

In PD, some studies have already investigated the effects of mindfulness interventions in pre-post-designs. Participating in an intervention has led to an increase of mindfulness *per se*, an improvement of quality of life, as well as a reduction of negative emotions like depression, anxiety and stress (Pickut et al., 2015; Advocat et al., 2016; Cash et al., 2016; Dissanayaka et al., 2016). Cognitive functioning might also be positively influenced as improvements of attention, mental flexibility and self-reported ability of speaking have been reported (Cash et al., 2016). The only neurobiological study in a PD population investigating mindfulness was published by B. A. Pickut et al. (2013) who found an increase of gray matter density in the right and left hippocampus and part of the right amygdala. However, the authors postulate the need for more studies to clarify the neurobiological changes caused by mindfulness training in PD. Moreover, McLean et al. (2017) criticized methodological flaws for most behavioral studies, too. Hence, they have not been able to conduct a meta-analysis regarding the impact of mindfulness in PD patients and also emphasize the need for more studies of high quality. In addition, Rodgers et al. (2019) recently conducted a pilot trial to test the efficacy of a modified protocol of mindfulness-based cognitive therapy (MBCT) for reducing depression. For patients participating in a 6-week MBCT intervention, they report a significant reduction in depressive symptoms. Though no reduction of anxiety or improvement of quality of life was found, the results of this study suggest that mindfulness-based interventions can potentially be helpful to fight depression in PD patients.

To the best of our knowledge, so far, no study has investigated the effects of mindfulness on ISA in PD patients. The aim of this study is to get better insight into the effects of mindfulness training on impaired self-awareness in PD. Therefore, we present IPSUM, a protocol for a newly developed mindfulness-based intervention to increase self-awareness in PD. IPSUM, an acronym for "Insight into Parkinson's Disease Symptoms by using Mindfulness," is an 8-week intervention, whose development has been influenced by existing mindfulness-based programs as well as previously reported experiences with mindfulness interventions in groups of PD patients. IPSUM is innovative because (1) it is tailored for the specific needs of PD patients (2) educates about the use and practicability of mindfulness specifically in PD and (3) has a larger focus on the aspect of self-awareness and its implications for daily living compared to other mindfulness interventions. It takes into account the specific needs and impairments of PD patients, such as a reduced attention span, impaired executive functioning and lesser mobility.

We expect this new intervention to increase mainly impaired self-awareness for motor symptoms, but also to affect cognitive ISA. Based on the described general mindfulness literature, we assume several factors involved for mindfulness training to be an effective way to increase self-awareness in PD patients. For once, training the ability to describe one's own perception (instead of judging it) might affect the patients' view on their own body (Daubenmier, 2005). As they start being more focused on the present moment (e.g., during mindfulness meditation and yoga exercises), they also should be more aware of their body movements and posture as well as other internal sensations (including their thoughts and emotions). Achieving and maintaining this perceptional shift might be facilitated by increasing acceptance toward themselves and their disability, regular attention training in form of mindfulness meditation and improved emotion regulation of unpleasant emotions (Cayoun, 2005; Tang et al., 2015). As described earlier, neurobiological studies reported structural changes of brain regions associated with abilities of introspection, meta-cognitive and body-oriented perception and processing of sensory stimuli (Lazar et al., 2005; Fox et al., 2014). Therefore, we expect neurobiological changes caused by regular mindfulness training to strongly support the training of self-awareness. As the cingulate gyrus and the insula have shown to be central to ISAm and seem to be influenced by mindfulness practice, we are particularly interested in those areas.

In addition, as it seems typical for mindfulness interventions, we hope to find an increase of several aspects of emotional well-being (e.g., quality of life) while reducing negative emotions like depression, anxiety or stress and other PD-related non-motor symptoms (e.g., apathy or impulsivity). As mindfulness-related research has indicated, an increase of cognitive performance in dimensions that are impaired in PD, mainly attention and executive functioning, might also be possible. As neurobiological research for this specific field is practically non-existent, we also plan to perform resting-state fMRI and structural MRI scans to link behavioral and neurobiological data. To get more detailed information about changes relevant for the patients' everyday life, a short semi-structured interview is planned.

METHODS

Patients with idiopathic PD (diagnosed according to the Movement Disorder Society PD criteria (Postuma et al., 2015) are recruited from the Department of Neurology, University Hospital Marburg, Germany. Up to 180 patients between 45 and 85 years of age will be included.

Exclusion criteria are depression [Beck Depression Inventory-2 – BDI-II score >19 (Beck et al., 1996; Hautzinger et al., 2006)], dementia [Parkinson Neuropsychometric Dementia Assessment – PANDA score <15 (Kalbe et al., 2008)] and a

clinical diagnosis of additional severe neurological or psychiatric disorders. Patients with an advanced disease stage [i.e., Hoehn and Yahr scale, stage 5 (Hoehn and Yahr, 1967)] are excluded as they are not expected to be able to perform practical exercises during the intervention. Additionally, patients with prior regular experience in meditation or yoga are excluded as this study seeks to examine mindfulness novices. As this study seeks to improve an impaired self-awareness, patients must show signs of ISAm. This is checked by using a short screening tool. For all patients, antiparkinsonian medication is registered and has to be unchanged for at least 2 weeks prior to baseline measurement. Furthermore, patients' eligibility to undergo an MRI scan is checked (though this is no exclusion criterion). The study has been approved by the local ethics committee of the University Hospital Marburg (Study number: 119/18) and registered at the German Clinical Trials Register (DRKS00015807). All patients have to give written informed consent prior to participation.

Study Design

To evaluate the effectiveness of IPSUM on ISAm an adaptive pre-post-design is applied. First, eligible patients are randomized into an intervention group and a waitlist control group. After approximately eight to twelve patients have been successfully recruited, they are randomized by a computer program. Patients of the intervention group are measured at three points in time: before, directly after and 8 weeks after the intervention has ended. As stated before, the intervention takes place between the first two measurements and continues for 8 weeks. Patients of the control group are measured at the same time intervals, but do not take part in the intervention and are therefore treated as usual. For ethical reasons those patients can participate in the intervention after the study has ended. **Figure 1** gives an overview of the course of the study.

At all three points in time ISAm is evaluated. Additionally, patients complete several questionnaires for emotional well-being. Cognitive functions are assessed using an elaborate neuropsychological test battery. Up to 30 patients will undergo a resting-state fMRI and structural MRI scan. Patients who have completed the intervention protocol can take part in an interview to report possible changes in their everyday life. For clarification, **Figure 2** gives an overview of the tests performed at each measurement point. All patients, independent of their study group, complete all tests in the same order. For some neuropsychological tests parallel forms are available. For those tests, the applied version at each time point is randomly selected after a patient's group assignment. It has to be noted, that all measurements are performed during the medication ON-state. Hereafter, primary and secondary outcomes, as well as all measurement procedures are further elaborated.

Outcome Measures

The main goal of this study is to increase self-awareness for motor symptoms. Therefore, the primary outcome for efficacy testing is a global ISAm-score. To be precise, mainly its change from baseline to post-intervention assessment is analyzed to evaluate the effectiveness of IPSUM. Changes of ISAm from baseline to follow-up are considered as a secondary outcome.

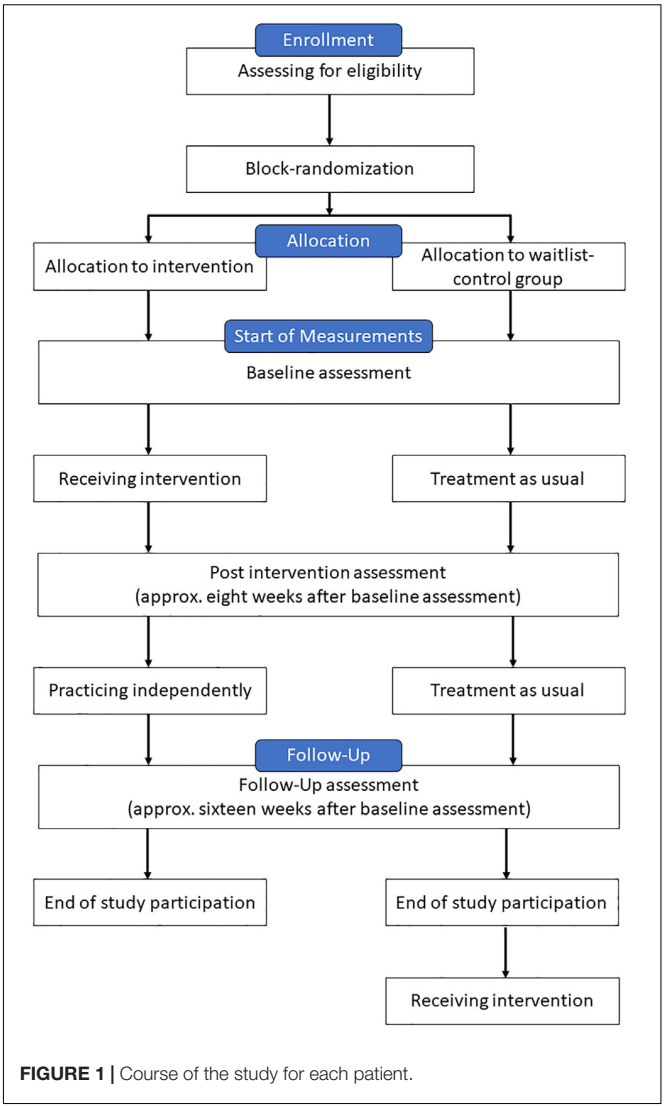

FIGURE 1 | Course of the study for each patient.

However, we determined several other secondary outcomes like general neuropsychological test performance, the congruence between neuropsychological test performance and subjective daily life impairment (ISAc) and the congruence between objective neuropsychological test performance and subjective test performance (metacognition). Also, changes of several PD related symptoms (depression, apathy, impulsivity, sleeping problems) and affective states (stress, anxiety, quality of life, mindfulness) are analyzed. The aforementioned secondary outcomes comprise all changes from baseline to post measurement as well as changes from baseline to follow-up measurement. Additionally, structural neurobiological changes in the Insula and Cingulate Cortices, as well as any kind of reported subjective changes during the semi-structured interview are also considered when IPSUM's effectiveness is evaluated.

Motor ISA-Assessment

A common method to evaluate self-awareness is by comparing self and outside assessments. In this study we use the recently

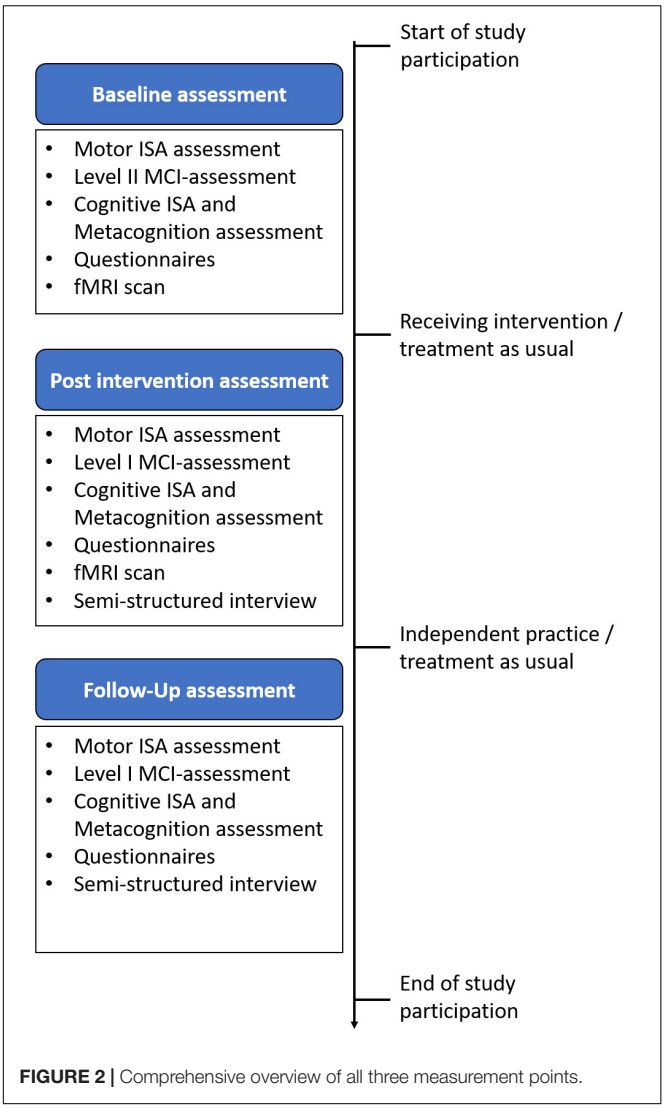

FIGURE 2 | Comprehensive overview of all three measurement points.

developed and validated measurement method by Maier et al. (2015). The patient is shown several video clips where a healthy person demonstrates various movements. The task for the patient is to repeat the movement him/herself as seen in the video clip. The following 15 symptoms are examined:

1. Sitting on a chair: resting tremor (left and right hand), dyskinesia.
2. Right hand pronation-supination: speed and amplitude of movement, dyskinesia.
3. Left hand pronation-supination: speed and amplitude of movement, dyskinesia.
4. Arising from a chair: resting tremor (left and right hand), dyskinesia.
5. Walking down an aisle: resting tremor (left and right hand), dyskinesia.

The symptoms are distributed across the four subscales dyskinesia, resting tremor right hand, resting tremor left hand and bradykinesia. Following each task, the patient rates his/her performance on a dichotomous scale whether the movement was impaired or not. Regarding the perception of a symptom, in total each patient answers 15 questions with either yes or no. The whole procedure is recorded by video. Later, independent raters evaluate the movements as well. In case of any discrepancies – if the patient does not see any impairment, although the raters do – an impaired self-awareness is noted. For each symptom, irrespective of the patient's awareness, they also rate its severity according to UPDRS-III (values range 0–4; 0 = normal/absent; 1 = mild; 2 = moderate; 3 = severe; 4 = unable to perform). This procedure allows the calculation of two independent scores: one score for overall motor impairment severity and a second score for ISAm severity. While the motor impairment score is calculated by summing up all motor severity ratings, the ISAm score is calculated by summing up all motor severity ratings of the potential 15 discrepancies. Hence, both scores can vary between 0–60. In the medication ON-state the ISAm global score can also be divided into subscores for impaired self-awareness for hypokinetic symptoms (ISAm-Hypo for tremor and bradykinesia) and hyperkinetic symptoms (ISAm-LID).

Assessment of Cognitive Performance, Cognitive-ISA and Metacognition

Each patient's cognitive performance is evaluated at baseline measurement. To identify patients with mild cognitive impairment (MCI), MCI-Level II-Assessment is applied. To the best of our knowledge, no established neuropsychological test battery exists to perform level II testing. Therefore, we have compiled a test battery ourselves, while also taking into account the guidelines of diagnostic criteria for MCI in PD (Litvan et al., 2012). To differentiate between single- and multiple domains of PD-MCI, for research purposes it has been strongly recommended to use two different neuropsychological tests for each cognitive domain. **Table 1** specifies the neuropsychological tests used for this purpose.

For time-economic reasons and to minimize patient strain, full MCI-Level II-Assessment cannot be performed during post- and follow-up measurement. To investigate the effects of mindfulness on cognitive performance regardless, one test for each domain

TABLE 1 | Overview of the applied neuropsychological test battery.

Domain	Test I	Test II
Attention/Working memory	TAP: Sustained attention	WMS-R: Digit span forward/backwards
Executive Functioning	RWT: Alternating semantic verbal fluency	Trail Making Test A + B
Language	WAIS-IV: Similarities	WAIS-IV: Vocabulary
Memory	VLMT	ECFT-MI: Recognition Trial
Visuospatial Ability	WMS-R: Spatial Span forward/backward	ECFT-MI: Matching Trial

ECFT-MI: Extended Complex Figure Test – Motor Independent Version (Fastenau, 1996); RWT: Regensburg verbal fluency test (Aschenbrenner et al., 2001); TAP: test battery for attention (Zimmermann and Fimm, 2002); VLMT: Verbal learning and memory test (Helmstadter et al., 2001); WAIS-IV: Wechsler Adult Intelligence Scale – Fourth Edition (Wechsler, 2008); WMS-R: Wechsler Memory Scale-Revised (Härting et al., 2000).

is applied at these time points. For this purpose, tests listed in the column "Test I" are used. Each patient also completes the Montreal Cognitive Assessment [MoCA (Nasreddine et al., 2005)]. As mentioned before, some neuropsychological tests offer parallel versions. To minimize training effects caused by performing the same test more than once, the applied test version of the Regensburg verbal fluency test, the Verbal learning and memory test and the MoCA is chosen randomly for each patient. It is possible that the same test version is assigned to a patient more than once. In addition, neuropsychological data is used to evaluate two kinds of cognitive awareness. For one, self-awareness for performance level in daily life and secondly, metacognition for cognitive performance in neuropsychological tests.

Impaired Self-Awareness of Cognition

To investigate impaired self-awareness of cognition (ISAc), subjective cognitive impairment in everyday life is compared with the more objective performance in neuropsychological tests. Subjective cognitive impairment in general is assessed by using the Cognitive Failures Questionnaire [CFQ (Broadbent et al., 1982)]. Additionally, for impairment of executive functions the Dysexecutive Questionnaire [DEX (Wilson et al., 1998)] is applied. Higher scores reflect higher subjective impairment in both questionnaires. For further statistical analysis, questionnaire and neuropsychological test raw data is transformed into standardized z-scores to allow better comparison. A delta score is calculated by subtracting subjective scores from objective scores. Beforehand, depending on the analytical objective, the transformed values of all neuropsychological tests are either summed up for reflecting general cognitive performance, or only verbal fluency performance is taken into account to reflect executive cognitive performance. Impaired self-awareness of cognition occurs if objective neuropsychological test performance appears to be worse than subjective impairment in everyday life. This is reflected by a positive delta score. A similar method has been used before to study anosognosia of memory deficits in Alzheimer's Disease (Vannini et al., 2017).

Metacognition

In addition to comparing subjective cognitive performance in daily life, we also plan to compare the patients' objective cognitive performance (according to normative value) to their estimated performance in neuropsychological tests. Therefore, each patient is asked to rate his/her performance compared to a healthy person of the same age, right after completing a neuropsychological test. On a 5-point Likert scale, the patient rates whether his/her performance is equal to the performance of the upper 20, 40, 60 or lower 20 or 40 percent of people the same age. By doing so, the patients are required to observe themselves from a metacognitive perspective. If the patients rate their own performance better than their objective test performance, the ability of metacognitive observation might be impaired.

Questionnaires

To evaluate the effects of IPSUM on emotional well-being as well as other non-motor symptoms of PD, all patients are asked to complete several questionnaires. All questionnaires are filled out at all three measurement points. PD related symptoms of interest are depression [BDI-2], Apathy [Apathy Evaluation Scale – AES (Marin et al., 1991)], Impulsivity [Questionnaire for Impulsive-Compulsive Disorders in PD – QUIP (Probst et al., 2014)] and Sleeping Problems [Parkinson's Diseases Sleep Scale-2 – PDSS-2 (Trenkwalder et al., 2011)]. Furthermore, to study changes of emotional well-being, experienced stress [Perceived Stress Questionnaire-20 – PSQ-20 (Fliege et al., 2005)], state and trait anxiety [State-Trait Anxiety Inventory – STAI (Spielberger, 2010)] and quality of life [Parkinson's Disease Quality of Life – PDQ-39 (Berger et al., 1999)] are assessed. Data about subjective cognitive impairment in general [CFQ] and specifically for executive function [DEX] is needed to evaluate ISAc, as described above. Since this study intends to evaluate the effects of a mindfulness based intervention, trait mindfulness [German Version of the Five Facet Mindfulness Questionnaire – FFMQ-D (Marin et al., 1991; Michalak et al., 2016)] is also assessed.

Imaging

Eligible patients are asked to undergo an optional MRI scan during baseline and post measurement to study potential neurobiological changes induced by the intervention. Additionally, the neurobiology of ISAm and ISAc can further be studied. The MRI protocol comprises a T1-weighted structural scan for morphometric analysis, a blood oxygen level-dependent (BOLD) resting state time series to analyze functional connectivity, as well as a diffusion-weighted sequence for tractography. Scans will be acquired on a 3T Siemens Trio MRI scanner. Currently up to 30 patients (15 per group) are planned to participate in the imaging measurement of this study.

Semi-Structured Interview

Up to this date, the applied quantitative measurement of ISAm has not been used for longitudinal studies. Therefore, it is uncertain if the instrument is sensitive to changes over time. Because of that, every patient who successfully completed the intervention protocol can take part in a semi-structured interview focusing on the possible changes they noticed over the last weeks (**Supplementary Table S1**). This also includes possible side effects caused by the intervention. The interview takes place during post- and follow-up measurement. By collecting qualitative data, we hope to get a more detailed insight into changes induced by mindfulness, especially in regards of self-awareness, and their relevance for the patient's everyday life. Additionally, feedback regarding the intervention itself can be collected to further improve the training protocol in the future.

Intervention Protocol

IPSUM is an 8 weeks long, group-based intervention which seeks to improve mindfulness and self-awareness of motor symptoms in patients with PD. In this study, all training sessions are held by a psychologist (main author T.B.). The concept is designed for groups of 4–8 patients and consists of 8 weekly sessions of approximately 2 h of duration. The main topic of a session differs from week to week. **Table 2** gives an overview of all weekly topics.

While each session's general topic is different, various recurring elements can be highlighted. For once, each week contains of a short theoretical input which fits the weekly topic.

TABLE 2 | Session Overview.

Week	Topic	Main goal
1	Introduction to the concept of mindfulness	Understanding the general concept in theory and by practice
2	The power of breathing	Understanding that we can only control our behavior (e.g., by experiencing the importance of breathing)
3	Thoughts and appraisals	Introduction to the concept of defusion from one's own thoughts and appraisals and the importance of observing them
4	How to deal with emotions	Learning about the purpose of pleasant and unpleasant emotions and ways of self-care
5	Stabilization of mindful practice	Repetition of previously gained knowledge as well as solving current problems with daily practice
6	Mindfulness and stress resilience	Learning about the use of mindfulness techniques in regards of stress reduction
7	Moving meditation	Performing the complete sequence of sitting yoga composed of movements learned during the training
8	Closing session: A new beginning	Evaluation of the whole training participation and to find solutions for persisting problems of mindful practice to facilitate independent practice after the intervention has ended

To account for possible impairment of attention, concentration or general cognition, this aspect will not exceed a duration of 15 min. A practical exercise which builds on the theoretical input is performed.

Secondly, patients practice guided mindfulness meditation in a group setting. To prevent patients from falling asleep or cancel meditation practice, various elements of gentle movement and muscle tensing and releasing are included. Additionally, some basic yoga movements are taught. To account for the impaired mobility of patients with PD, sitting yoga on a chair is practiced. At the end of the intervention each patient will have learned a simple yoga sequence which they can also perform at home. As the ability to describe one's own experience (instead of judging it) is central to the concept of mindfulness, this part is extended by a small sensory exercise. Here, patients are handed a different object each week (e.g., wool or a heat pad) and are asked to describe it as detailed as possible using all five senses. As noted in a previous study of a mindfulness intervention with PD patients, patients find it helpful to focus on external stimuli instead of internal sensations alone (Birtwell et al., 2017).

Previous research also has shown that the time invested for mindfulness practice is of high importance. Therefore, each week patients are asked to practice body scan and mindfulness meditation at home using an audio CD with guided instructions. Since all participants are meditation beginners and also might have attentional deficits, practice time is raised each week, up to 30 min a day. To support the implementation of mindfulness into the patients' everyday life, they are also asked to perform an informal mindfulness exercise which changes weekly, e.g., mindful walking or mindful eating. If possible, the time used for mindful practice should be noted in a journal for future analyses.

Starting in week two, each session will begin with a reflection of the week before. Here, the patients get the opportunity to talk about their experiences with the previous week's homework and possible difficulties they might have encountered. The group setting is expected to be quite helpful for sharing common experience among the patients and getting support to overcome possible problems that may arise during daily practice. At the end of each session, each patient receives a brief written summary containing all relevant information of the theoretical input to allow reviewing specific details of the newly learned information as needed and to support independent practice at home. To continue mindfulness training at home, patients are asked to further practice 30 min of daily mindfulness meditation in addition to improving their informal mindful practice. To ensure compliance, patients are asked to note down all performed mindfulness exercises in tables contained in their written summary for another 8 weeks.

Planned Statistical Analyses

The results of a power analysis suggest, that a total of up to 166 patients (83 patients per group) might be needed to detect a significant effect. By applying a group sequential study design the number of patients needed is raised to 180 to allow for interim analyses to be performed after including 60 and 120 patients, respectively. To the best of our knowledge the motor ISA-Assessment has not been applied in a longitudinal study design. Depending on the results of these interim analyses or due to economic reasons, the study might be stopped beforehand.

Demographic and baseline characteristics will be compared using *t* tests or other non-parametric methods, if necessary. To analyze most of the primary and secondary outcomes, performing repeated-measures mixed model analyses of covariance will be essential. Independent variables will be group (intervention and waitlist) and time (pre, post and 8-week follow-up) and also their interaction. Baseline measure, the amount of medication (levodopa equivalent daily dose) and depression scores will be included as covariates. To specifically analyze ISAm scores, which are the main outcome, and to determine their degree of objectiveness, inter-rater reliability will be computed for each measurement point in time.

In order to get more insight into possible mechanisms of mindfulness, ISA and their connection to each other, several moderation and mediation analyses are planned. For example, we expect the number of completed training sessions, motor symptom severity and patients' general cognitive performance level to be possible moderating factors affecting mindfulness scores itself and/or the relationship between mindfulness and ISA. Among others, mediating factors considered will be cognitive performance of sustained attention and questionnaire scores of negative emotions like anxiety and depression. Of course, neurobiological changes will be included as well.

When the effectiveness of a treatment is evaluated, the question of how to deal with dropout patients has to be

considered. If a patient cannot conclude his or her study participation, the reason and time of drop out will be documented. To still be able to include as many patients as possible in the analyses, the intention-to-treat analysis is preferred. For missing values, missing at random-analyses will be performed. In case of positive results, maximum likelihood methods will be applied. Data will be analyzed using SPSS, version 26.0 (IBM Corp., Armonk, NY, United States). To analyze qualitative data collected during semi-structured interviews, qualitative content analysis will be used (Mayring, 2015).

Imaging fMRI data will be analyzed using SPM12 (Penny et al., 2007). Functional connectivity of the left and right anterior insula and the anterior cingulate – central nodes of the salience network which have repeatedly been described to be altered following mindfulness interventions – will be analyzed by comparing pre to post measurements within and between groups, focusing on connectivity with the medial prefrontal cortex and the default mode network (Kilpatrick et al., 2011; Doll et al., 2015). Voxel-based morphometry will be applied to perform pre-post between-group comparisons of gray matter density in the same regions. Diffusion MRI will be used to analyze training effects on fractional anisotropy of the anterior-superior parts of the corona radiata and corpus callosum, following results reported after a similar intervention in healthy subjects (Tang et al., 2010). Neural correlates of impaired self-awareness (motor and cognitive) will be assessed based on previous findings in FDG-PET, with the cingulate gyrus and right insular cortex as regions of interest in morphometric and functional connectivity analyses.

DISCUSSION

The phenomenon of anosognosia has been described for various neurological diseases. Recently a less extreme version, the phenomenon of impaired self-awareness, has been observed in non-demented, non-depressed patients with PD. While it has been mostly reported for motor symptoms, it might also occur for cognitive or other non-motor symptoms. Based on scientific research, mindfulness training is suggested as a possible therapy concept. However, existing mindfulness interventions often do not consider the specific needs of patients with PD, e.g., decreased mobility or attention deficits. Therefore, we developed IPSUM, a new mindfulness-based intervention. IPSUM does not only consider the special needs of PD patients, but also has a larger focus on the aspect of self-awareness compared to other mindfulness interventions. While its feasibility and effectiveness in regards to impaired self-awareness of motor symptoms are the primary objectives of this study, we also want to evaluate changes of cognitive performance and self-awareness, as well as other non-motor symptoms and emotional well-being. As some patients undergo an fMRI scan, we hope to get better insight into the neurobiological changes caused by mindfulness training in PD patients with impaired self-awareness. Additionally, to evaluate the feasibility of IPSUM and to investigate the impact of mindfulness on the patient's daily life, a semi-structured interview is conducted.

The Need for a Tailored Mindfulness Intervention Protocol

As stated before the concept of MBSR has been widely applied and studied in a variety of patient groups. Indeed, previous studies, which focused on the effects of mindfulness in PD, have administered the MBSR program or a variation of it. We intended to create a new intervention protocol to meet the specific needs of PD patients, which are mostly elderly people, many of whom have never heard of the concept of mindfulness, and usually do not have any prior experience with yoga, meditation and/or mindfulness exercises. Considering those needs has led to another mindfulness concept which mainly differs from the MBSR concept in three ways.

For once, the main goal is different. While MBSR mainly deals with pain and stress, IPSUM seeks to improve self-awareness of motor symptoms which are very specific for and almost exclusively occur in PD. Using the IPSUM protocol, it is expected to achieve some sort of stress reduction, too, as the practiced exercises are partly overlapping (e.g., mindful meditation, body scan). However, the instructions in IPSUM often remind the patient to focus on specific motor symptoms and their observation, if a symptom is present indeed. The repetitive focus on motor symptoms is expected to increase the patients' awareness for their symptoms and thus fulfill the main goal.

Secondly, to consider possible problems of executive functioning (e.g., problems with planning) a general structure is persistent throughout the entire intervention to provide some sort of orientation for the patient. For example, for each day another suggestion for informal mindful practice is given. Additionally, the patient is not explicitly asked to practice without guided instructions (which they would be asked to do in MBSR). However, he or she still has the option to do so, if he or she wants to.

Thirdly, general session duration is shorter and all parts of a session usually do not last longer than 15 min because of possible attention problems. During the weekly session small movement breaks are implemented to increase the patients' vigilance. Homework practice duration is gradually increased to allow for an early sense of accomplishment despite possible cognitive impairment. The duration interval then is gradually increased to up to 30 min of practice per day. In contrast to the MBSR concept, the IPSUM protocol does not include a 6 h "day of mindfulness" at all as this might be too demanding.

Given these reasons, we felt the need to conceptualize a tailored mindfulness protocol for patients with PD.

Strengths of This Study

This study is conducted with the expectation of further insight into the phenomenon of impaired self-awareness in PD and its relation to practiced mindfulness. Therefore, in the following the study's strengths are highlighted.

For once, this is the first project to study the relationship between self-awareness and mindfulness in PD which also

collects longitudinal quantitative and qualitative behavioral and neurobiological data. Though the planned sample size of up to 180 patients is quite large, it has to be noted that the study might be stopped beforehand due to economic reasons or a lack of eligible patients. However, sample sizes of other studies were much smaller (usually around 10 to 15 patients with one study including around 60 patients). Despite a small sample size, they also found significant effects for mindfulness related aspects (Advocat et al., 2013; Pickut et al., 2013; Cash et al., 2016; Dissanayaka et al., 2016; Birtwell et al., 2017). Additionally, similar to other studies the interventional effect is compared to a waitlist-control group but not an active control group. The planned training duration of 8 weeks are standard and, based on described literature, should be adequate to achieve significant changes. If a significant impact is found in this sample, an active control group and longer time intervals between measurements should be considered for further evaluation of the training protocol.

A main part of this study is the evaluation of ISAm, which is done by using a psychometric evaluated tool developed by Maier et al. (2015). This method is similar to the evaluation of ISAm in previous studies (Maier et al., 2016). In our study, however, it is for the first time assessed with repeated measurements. Also, we only assess ISAm during the medication ON-state, but not in the OFF-state. Not taking their medication would be another heavy strain for each patient, and we therefore decided to refrain from OFF-state evaluation of ISAm. Additionally, the ON-state is more accurate in reflecting the patient's daily life situation. As we also focus on the implications of mindfulness in everyday life during an interview, we get the opportunity to combine qualitative and quantitative data. Future studies might also focus on the evaluation of OFF-state ISAm. As this is also the first time this method is used in a longitudinal study, its sensitivity to change is still unknown.

The measurement of cognitive performance is quite comprehensive as a full MCI-Level II-Assessment is applied at baseline. Though this test battery is self-compiled, it does meet established criteria for the diagnosis of MCI. However, due to time-economic reasons and patient strain the full test battery cannot be applied at post- and follow-up-measurement. Instead one neuropsychological test for each domain is assessed to make sure changes of cognition can be investigated. Regarding the evaluation of ISAc, it has to be noted that the described analyses are not validated, but have been used before (Vannini et al., 2017).

CONCLUSION

In conclusion, we expect this study to prove the feasibility and preliminary effectiveness of IPSUM, a newly developed mindfulness-based group intervention for the specific needs of PD patients, by increasing self-awareness of motor and cognitive symptoms and also increasing the patient's quality of life on many levels.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Local Ethics Committee of the University Hospital Marburg. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TB, CE, and FM contributed to the conception and design of the study. TB developed the intervention protocol with support of AG. TB wrote the first draft of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2020.00743/full#supplementary-material

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BRIEF RESEARCH REPORT
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Take the First-Person Perspective to Become Dementia-Friendly: The Use of 360° Video for Experiencing Everyday-Life Challenges With Cognitive Decline

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The current spread of dementia is engendering an emergency that is not limited to the medical issues but also involves its social dimension. Accordingly, it is necessary to promote a perspective change about the disease that supports a more inclusive view of people with dementia. To ensure this, Dementia-Friendly Communities (DFCs) have recently been developed. Nonetheless, it is not always effortless to deal with people with dementia in an inclusive way because of misconceptions about how they perceive everyday contexts and react in everyday situations. We asked 170 individuals (aged between 13 and 75) to "put themselves in the shoes of a person with dementia" for a few minutes, facilitating this through the use of a 360° video, and to try to experience how activities such as going shopping feel from the first-person perspective. Before and after the experience, participants expressed their opinions about the needs and the autonomies that are deemed to be granted to a person with dementia. The results revealed changes to social perspective after having experienced firsthand what living with dementia could be like. A deeper comprehension of what it is like to live with dementia appeared to be gained, and participants' beliefs about the needs and daily autonomies of those with dementia were modified after the experience. It is possible to conclude that, through the change of perspective, people are more willing to be inclusive toward people with dementia, as is wished for in the DFC approach, although a wider formative intervention on how to be really inclusive still seems to be required.

Keywords: Dementia-Friendly Community, dementia needs, ViveDe, 360° video, first-person experience

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INTRODUCTION

The latest research developments on dementia have shown that there are still no unequivocal data about the causes of this disease (Kapasi et al., 2017). Nor is there an efficacious therapy to stem the cognitive impairments and psychological alterations that the various forms of dementia involve (Watt et al., 2019). Therefore, person-centered approaches (Kitwood, 1997), both for diagnosis and treatment, still seem to be among the most valuable solutions for people with dementia. Moreover, it is necessary to consider that, to date, one of the arrangements that is most effective in dementia treatment is to maintain a high quality of life for people already suffering from this illness (Landeiro et al., 2018).

Consequently, in parallel with research on maximizing the effects of prevention strategies (Hodes et al., 2019) and to support an early diagnosis (Paulsen et al., 2013), Dementia-Friendly Communities (DFC) are springing up all over the world (Alzheimer's Disease International, 2016; Lin, 2016) Dementia-Friendly Communities are communities of citizens, not exclusively personally involved in dementia healthcare and/or relatives to people suffering from dementia, which promote inclusive lifestyles to people affected by this disease. Their main goal is to maximize the autonomy of the person with dementia within the urban context (Smebye et al., 2016) through improving their quality of life, extending their residence at home as far as possible, and maximizing their network of social relations. Worldwide DFCs are proposing educational projects in schools, organizations, and groups of individuals in order to support them in understanding, respecting, and supporting people who live with dementia. The development of DFCs tends to counteract, above all, the institutionalization of people who still have a less severe form of dementia (not such as to completely degrade their daily self-government), minimizing the effort required to ensure that their essential needs are met, which is often delegated too early to a caregiver. Dementia-Friendly Communities are connected in an international DFC network, even though each country and each specific community finds its own way to becoming Dementia-Friendly. The main cornerstones of DFCs are to remove obstacles to inclusion in society, to prevent stigma and fear about dementia in the general population, and to avoid under-estimation of the capabilities of people with dementia by professionals, stakeholders, and any community member.

Despite this effort, the concrete actions that support the community of citizens in becoming Dementia-Friendly clash daily with the misconception of dementia (Swaffer, 2014), which finds its prototypical representation in "ageism" (thinking that dementia is a pathology exclusive to elderly people), in "nihilism" (thinking that it is not possible to do anything for people with dementia if you are not a professional), and also in "ignorance" (thinking that dementia destroys the ability to understand the environment and to have goal-directed behaviors from its first diagnosis). In addition, the main resistance to becoming truly inclusive toward a person with dementia comes from the difficulty of understanding from a third-person perspective what underlies the observable unusual behaviors of a person with dementia within that person (these behaviors are often interpreted as not dependent on the disease). In particular, because dementia mainly affects the person's cognitive and emotional capacities, which by their nature are not detectable by an external observer (Zahavi, 2008), people tend to not fully understand some behaviors a person with dementia generally shows (such as, for example, time-space disorientation or mood alteration) during a daily relational situation (such as encountering a casual acquaintance or taking part in a meeting).

To overcome these issues, approaches that encourage a change of perspective have recently been adopted. For example, the Virtual Dementia Tour® has been widespread in the United States for many years; this is mainly aimed at caregivers and family members of people with dementia, showing them how some sensory and motor limitations can compromise the ability to solve simple problems (Beville, 2002). Though there are some doubts as to its evidence-based efficacy (Merizzi, 2018), the results of related studies show that there might be a change in the management of the patient by the caregivers after this experience.

With the objective of providing the general public with the opportunity to experience dementia from the inside through the use of new technologies, in Italy, the ViveDe project was developed by the Dementia-Friendly research group at the University of Bergamo[1]. The main goal of the project is to use virtual reality eyeglasses to present several everyday situations that people with dementia can face in everyday life through the use of 360° videos that are explorable on the x/y axis. Thus, even a member of the public who is not familiar with dementia has the possibility to take a first-person perspective on dementia during a daily activity and to experience how living with dementia might be (Morganti, 2019).

In this research, we aim at investigating if the ViveDe approach is useful for paving the way to becoming Dementia-Friendly. Our main hypothesis is that, after the ViveDe experience, which forces them to assume the first-person point of view, participants will change their social perspective on dementia, abandoning the stigma and reflecting on the role that they might have in promoting the autonomy of people living with dementia. Specifically, our research hypothesis will be that, after the experience with the immersive 360° video, the participant will modify their opinions about:

1. What the prerogatives of people with dementia are:
   (a) The need for continuous assistances after the dementia diagnosis.
   (b) The possibility of having a large amount of autonomy in daily activities.
   (c) The exclusive role of professionals in supporting dementia people.
2. What the demands of people with dementia are, in terms of those expressed by Maslow (1943):
   (a) To have basic needs (physiological and safety) granted.
   (b) To have psychological needs (social belonging and esteem) granted.
   (c) To have self-actualization needs granted.
3. What the possibilities of becoming Dementia-Friendly are through
   (a) Improved knowledge about dementia.
   (b) Modification of the perceived difficulty of being a friend to a person with dementia.

METHODS

Participants

All participants were volunteers attending a public event in which the VideDe project was presented.

[1] http://www.vivede.it

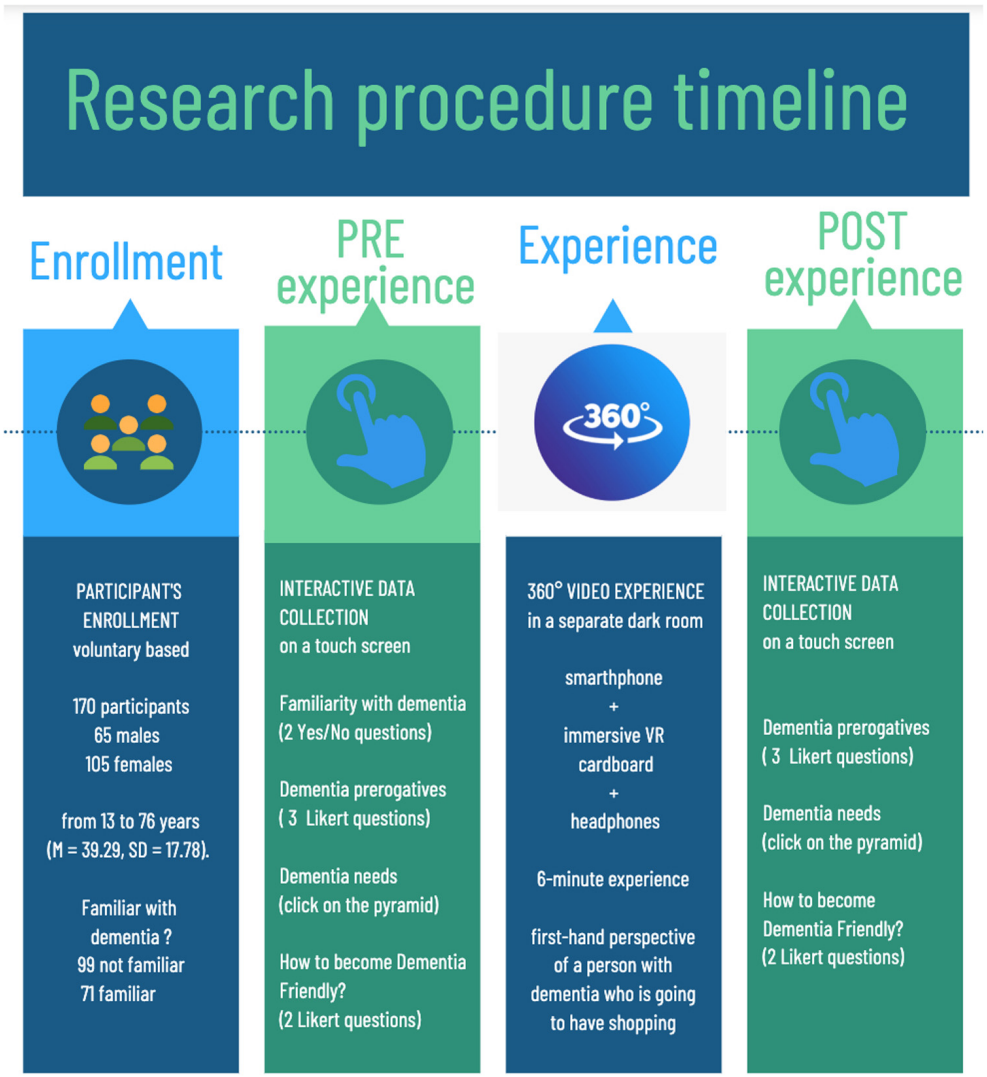

FIGURE 1 | Research procedure timeline.

In total, 170 (65 males and 105 females) took part in the experiment, with ages ranging from 13 to 76 years (M = 39.29, SD = 17.78). Additionally, 99 participants declared that no relative of theirs was diagnosed with any form of dementia, whereas the remaining 71 did have such a relative.

Procedure

After having signed an informed consent form, participants entered the experimental setting and were guided by an experimenter to answer the questions described in the following paragraph, which were depicted on a touch-screen device. Participants were then taken into a separate room, where a brief video on how to interact with a 360° video was presented. After this explanation, participants could start their immersive experience with a 6-min ViveDe video under the supervision of one experimenter. Once the virtual experience was over, participants were again requested to provide answers to the same questions as were provided before the experience on the touch screen. The entire procedure (including the informed consent phase) took approximately 20 minutes. The experiment timeline is depicted in **Figure 1**.

Interactive Data Collection

Data were collected in an anonymous form through the use of an interactive table placed at the entrance of the experimental setting. By clicking on the touch screen, participants provide to the experimenter information about their age and familiarity with dementia (Do they work with dementia? Are they relatives of people with dementia?).

Moreover, in order to explore the research hypothesis, on the interactive table participants have to:

1. Answer three questions to provide their opinions about the prerogatives of people with dementia. The questions are

answered on a five-point Likert scale. The questions are about:

(a) Assistance: Do you think that people with dementia need to have continuous familiar assistance during everyday activities?
(b) Autonomy: Do you think that people can continue to autonomously meet their personal needs (such as going out to purchase goods or doing their housekeeping) just after a dementia diagnosis?
(c) Institutionalization: Do you think people with dementia have to immediately ask for support from institutional welfare (such as nursing homes and/or professional caregivers) after their first diagnosis?

2. Click on a pyramid image that represents the five levels of individual needs defined by Maslow (1943) in order to answer the question, "Which needs do you consider as essential to be warranted to a person with dementia?" The needs depicted are (from the bottom to the top of the pyramid): physiological, safety, social belonging, esteem, and self-actualization. A brief description of the needs according to Maslow's definitions is provided on the screen in order to avoid misunderstanding.
3. Answer two questions to provide their opinion about the perceived difficulty of becoming Dementia Friendly, in particular in terms of taking care of people diagnosed with dementia ("Please indicate on the depicted line a point that corresponds to how demanding you think it is to live with a person with dementia") and in terms of the knowledge on dementia they believe they have ("Please indicate on the depicted line a point that corresponds to your knowledge on what dementia is"). The questions are answered on a 10-point Likert scale (1 = minimum, 10 = maximum).

The Immersive Experience

After the touch-screen phase, participants were conducted to a separate dark room within which they had the ViveDe experience. The experience was made possible through the use of the Homido virtual reality Headset V2 (a commercial device for smartphones with 100° FOV lenses, farsightedness and nearsightedness settings, and IPD and immersion adjustment[2]) and a set of headphones. Participants immersively experienced a 360° video downloadable on their smartphone from the www.vivede.it website. The video provides a six-minute experience of a person with dementia doing their daily shopping at the neighborhood bakery and greengrocer. In the video, a typical daily situation is represented (e.g., other customers at the same store being in a hurry while several cognitive impairments are experienced by the person with dementia in managing money or remembering the list of goods that have to be bought). A video snapshot is provided in **Figure 2**; the Italian version of the video is available at https://youtu.be/A15h8_UHWE4.

The 360° video is fully explorable on the *x*/*y* axis. The video provided to participants is from a first-person perspective (i.e., participants can perceive the entire scene as if they are in the shoes of a person with dementia). Moreover, the participants can hear firsthand the voice of a person with dementia as if it is their "thoughts." The video, like the others developed in the ViveDe project, is the upshot of a previous research phase in which people with dementia, caregivers, and urban communities were involved in providing qualitative and quantitative information about how difficult is it to face everyday challenges when living with dementia (Morganti, 2019).

FIGURE 2 | A ViveDe 360° video snapshot.

Design

The only factor was "Time." All participants filled the questions before and after the ViveDe experience. The dependent variables were:

(a) Prerogatives of people with dementia. Three questions measured on a five-point Likert scale (1 = not agree, 2 = slightly agree, 3 = partially agree, 4 = mainly agree, and 5 = totally agree) exploring the perceived need for assistance in dementia patients, the perceived right for autonomy, and the perceived need to be relocated to specialist health and social structures.
(b) Demands of people with dementia. The eight clusters reported in **Figure 3** originated from the perceived need for each of the five levels of Maslow's pyramid (physiological, safety, belonging, esteem, and self-actualization), which the participant either selected or not as being required by people with dementia;
(c) Possibility of becoming Dementia-Friendly. The perceived knowledge of the respondent about what dementia is and their perception of the difficulty of living with a person diagnosed with dementia, on a Likert scale ranging from 1 to 10, with no specific label.

DATA ANALYSIS

The hypotheses concerning participants' opinions about the prerogatives of people with dementia and participants' opinions about the perceived difficulty of becoming Dementia-Friendly were explored by using SPSS 22 statistical software.

To explore participants' opinions about the individual demands of people with dementia, analyses were conducted

[2]http://www.homido.com

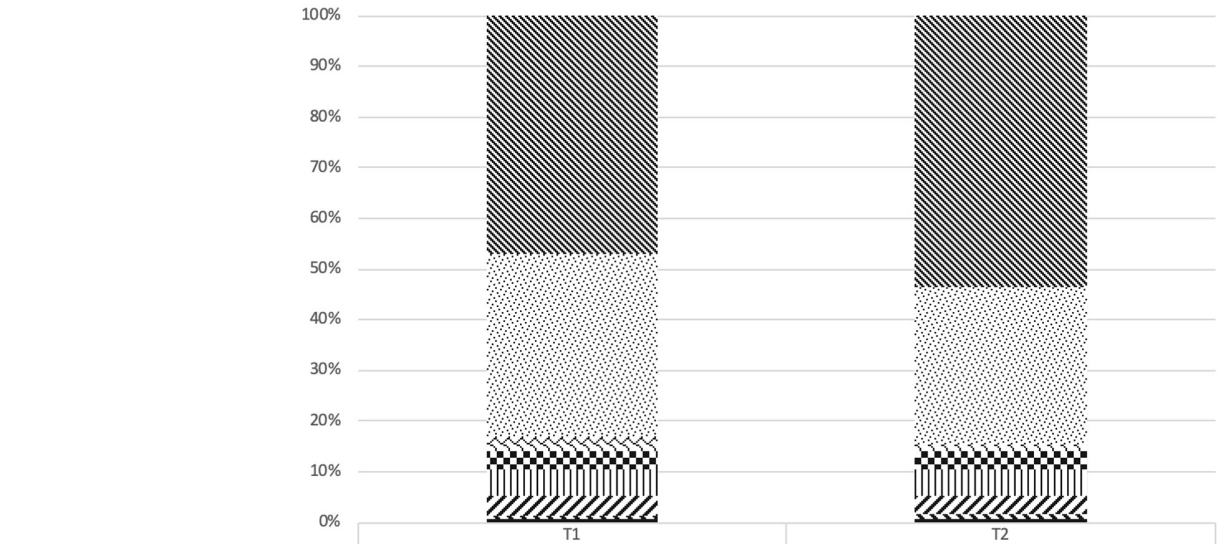

FIGURE 3 | Relative percentage of the eight clusters at T1 and T2.

using Sleipner 2.1, which is a statistical package used for typological analyses and for studying individual development, that is, stability vs. change (Bergman and El-Khouri, 2002). An individual in one cluster is said to be "stable" if s/he shows a tendency to re-emerge in a similar cluster at a later time; on the contrary, "change" refers to a tendency to re-emerge in a different cluster. According to Bergman et al. (2003), individual stability is related, but not equivalent to, structural stability. In the present case, individual stability was evaluated by performing Fisher's hypergeometric distribution test in single cells in the cross-tabulation of eight possible clusters at Time 1 (T1, pre-experience) and Time 2 (T2, post-experience). These clusters were obtained as follows.

The five levels of Maslow's pyramid of needs were grouped into three possible levels: a base level (basic needs) including physiological needs and safety, a second level (psychological needs) including social belonging and esteem, and a third level (self-actualization needs) focusing on self-actualization only (Maslow, 1943, 1954). If a participant selected at least one of the two variables of the basic needs level (physiological needs and safety), it was concluded that such a participant believed that the basic needs were believed to be an important need for a person with dementia. Code "2" was assigned in this case. On the other hand, if none of the two needs was selected, it was believed that the participant believed that the basic needs were not relevant for people with dementia, and code "1" was employed. The same applied for psychological needs. Concerning the third level, which focuses on self-actualization, it was assessed only whether the participant reported that people with dementia have (coded as 2) or do not have (coded as 1) a need for self-actualization. Consequently, eight possible configurations/clusters were possible, which are reported in **Figure 3**.

The analysis was conducted using the EXACON module of Sleipner, which produces a contingency table for two categorical variables, in our case, cluster membership at T1 and T2. The EXACON procedure focuses on cell-wise analysis of types based on exact tests. Specifically, a type is said to occur in a cell if the observed frequency is much larger than the expected frequency and the associated hypergeometric probability is low; that is, we observe a significantly larger frequency than we expect to observe by chance alone. In the opposite case, an antitype is said to occur. In other words, this analysis evaluates the T1-to-T2 sequences of clusters for perceived needs to verify whether these sequences occur differently than expected by chance.

RESULTS

Prerogatives of People With Dementia

Before running any analysis, correlations among the three questions were evaluated. As **Table 1** shows, there were several significant correlations, suggesting that answers to one question have a relationship with answers to other questions. For this

TABLE 1 | Descriptives for answers of the three questions on assistance, autonomy and institutionalization and correlations among answers to the three questions.

	M (SD) pre-experience	*M* (SD) post-experience	*t*-test (169)	Assistance post-experience	Autonomy post-experience	Institutionalization post-experience
Assistance pre-experience	3.68 (0.76)	3.82 (0.87)	−1.66	–	−0.58**	0.10
Autonomy pre-experience	2.86 (0.92)	2.34 (0.88)	5.89***	−0.16*		−0.11
Institutionalization pre-experience	3.39 (0.94)	3.06 (1.15)	3.35**	−0.33**	−0.06	–

*The correlations under the diagonal are for the pre-experience answers and those in the upper triangle are for the post-experience answers. *p < 0.05, **p < 0.01, **p < 0.001.*

reason, a MANOVA was conducted with Time (T1, pre-experience vs. T2, post-experience) as the factor and answers to questions 1–3 (assistance, autonomy, and institutionalization) as dependent variables. There was a significant multivariate effect, $F(3, 167)$, Wilks' $\lambda = 14.10$, $p < 0.001$. At a univariate level, the effect for the question concerning assistance was not significant, $F(1, 169) = 2.77$, $p = 0.09$, partial $\eta^2 = 0.02$. On the contrary, the effect was significant for autonomy, $F(1, 169) = 34.65$, $p < 0.001$, partial $\eta^2 = 0.17$, and for institutionalization, $F(1, 169) = 11.25$, $p < 0.01$, partial $\eta^2 = 0.06$. As **Table 1** shows, participants reported similar levels of perceived need for assistance at T1 and T2, whereas they reported lower needs for autonomy and institutionalization at T2 compared to T1.

Demands of People With Dementia

Figure 3 reports the relative percentage of the eight clusters at T1 and T2. The analyses showed that there were 12 significant cells. Of these, four cells revealed that more participants than expected re-emerged in the same cluster at T2. In particular, this happened for cluster 3, $p = 0.02$, cluster 4, $p < 0.01$, cluster 7, $p < 0.001$, and cluster 8, $p < 0.001$. Four cells show that more participants than expected re-emerged in a different cluster at T2. This happened, for example, for changes from cluster 2 to cluster 3, $p = 0.03$, for changes from cluster 3 to cluster 5, $p < 0.01$, for changes from cluster 5 to cluster 3, $p < 0.05$, and for changes from cluster 6 to cluster 8, $p < 0.05$. Four cells show that fewer participants than expected re-emerged in a different cluster at T2. This happened for example for changes from cluster 3 to cluster 8, $p < 0.05$, for changes from cluster 7 to cluster 8, $p < 0.001$, for changes from cluster 8 to cluster 3, $p = 0.02$, and for changes from cluster 8 to cluster 7, $p < 0.001$.

These results illustrate that: (a) the majority of participants tended to recognize that all of the three levels of needs described by Maslow's pyramid should be granted to people with dementia and (b) there is a general trend to "move up" toward the higher level of needs represented in the pyramid from pre- to post-experience.

Possibility of Becoming Dementia-Friendly

The correlation between the question about the perceived difficulty of taking care of people diagnosed with dementia and the question about perceived knowledge about dementia was explored. Such a correlation was not significant before the ViveDe experience, $r = 0.13$, $n = 170$, $p = 0.09$. The correlation post-experience was significant, $r = 0.19$, $n = 170$, $p = 0.01$. Due to this last correlation, a MANOVA with Time (T1, pre-experience vs. T2, post-experience) as the factor and perceived difficulty and perceived knowledge as dependent variables was run. There was a significant multivariate effect, $F(2, 168)$, Wilks' $\lambda = 53.88$, $p < 0.001$. At a univariate level, the effect for knowledge was significant, $F(1, 169) = 107.64$, $p < 0.001$, partial $\eta^2 = 0.39$. Participants increased their perceived knowledge from $M = 4.71$ (SD = 2.08) pre-experience to $M = 6.06$ (SD = 2.08) post-experience. In contrast, the change in perceived difficulty from pre-experience, $M = 7.94$ (SD = 1.66) to post-experience, $M = 8.04$ (SD = 1.64) was not significant, $F(1, 169) = 0.60$, $p = 0.43$, partial $\eta^2 = 0.00$.

DISCUSSION AND CONCLUSION

The results showed that the ViveDe experience had an impact on how participants considered dementia. Although the idea of needing assistance is not changed by the first-person experience, it significantly reduces the idea that assistance should be delegated to welfare professionals (such as hospitals or nursing homes). We could consider this as a greater positive disposition toward the autonomy of a person with dementia, but we see, however, that this was not confirmed by the analysis. The disposition toward autonomy, though it changes significantly, appears to become more negative. This result is apparently not consistent with the assumptions but can be understood in the light of the firsthand experience provided by ViveDe 360° video.

Precisely because, in an everyday life situation considered to be simple to manage (like buying bread and fruit in a neighborhood shop), the participants felt like they were not able to complete the task without the collaboration of others (the shop managers and the attending customers), a "stereotyped" idea of autonomy materialized from the experience of "frustration" in autonomy. This was to such an extent as to lead participants to change their opinion toward the conception of autonomy to become more restrictive. Therefore, though, on the one hand, this fact confirms the transformative potential of the immersive experience, it also leads us to expand the educational pathways about conceptions of autonomy and the effort required to give assistance to people with dementia within a really inclusive urban community. Indeed, in a Dementia-Friendly perspective, citizens are informed and trained about inclusive behaviors that can best support the autonomy of

the person with dementia by avoiding the spontaneous errors of interaction that the participants probably experienced within the video.

This finding appeared to be confirmed by the answers to the knowledge/difficulty questions, in which participants after the experience significantly changed their evaluation of what they knew about dementia but not on the estimated difficulty of being Dementia-Friendly. ViveDe video appears to be successful in being informative about how people with dementia live and how they experience the urban surroundings, but the participants did not receive any new insights into how to supportively interact with and on how to include people with dementia in a daily situation. This suggests the direction in which the interactive dimension of the next ViveDe videos has to be more carefully developed.

Finally, one of the clearest unexpected findings was provided by the positioning on Maslow's needs pyramid both pre- and post-experience. Not only did the majority of the participants "recognize" that people with dementia have the right to have their basic needs (such as physiological and safety) fulfilled – by highlighting the "welfare" nature of the caregiving relationship – but it appears clear that the participants recognized from the beginning that they also have the higher-level needs (such as social belonging, esteem, and self-actualization) that are generally the needs of any person, regardless of illness. Probably, precisely because the sampling of the participants was on a voluntary basis and the ViveDe experience was proposed indiscriminately to a wide audience, the individuals who participated in the experience did so already thinking that people with dementia have a wide range of needs. In addition, after the ViveDe experience, the urge to consider the needs of a person with dementia appeared even stronger in our participants. In fact, they significantly revised their choices by adding the needs at the higher positions in the pyramid, even when they had not done so previously.

In conclusion, our participants showed they took part in the research with an already assimilated idea of "being a person with dementia" (as advocated by Kitwood's perspective) and were predisposed, before the ViveDe experience, to be in some way Dementia-Friendly. Moreover, having the opportunity to understand what it could mean to be in that situation by taking a firsthand perspective on dementia enabled participants to revise some opinions about the challenges and skills that an observer generally tends to attribute to a person with dementia when watching a daily interaction from a third-person perspective. This perspective change definitely produced new familiarity with dementia, but it also raised new questions about what daily practices are more suitable to being faced by a person with dementia. Our participants, in fact, significantly modified their understanding of dementia but not their estimation of the difficulties of becoming inclusive toward people with dementia. It must be borne in mind, however, that one important limitation of this study was the lack of a control group and/or a longitudinal measure; hence, the results must be taken with caution. Concerning the former, it is possible that a control group would not be of much help to understand the change of perspective, as control participants would just answer the same questions twice in a very short time-window. As far as the latter, future research should also explore how the change in perspective is affected after longitudinal and repeated exposure to the experience. Future studies could have different aims: to evaluate whether longer exposures to the experience may reinforce its positive effect, as suggested by Zajonc (2001) and to verify whether information that explicitly clashes with one's previous knowledge can modify previous beliefs (Ecker et al., 2010; Lewandowsky et al., 2012).

Furthermore, the findings presented in this study, even if it could be considered as one of the first significant results in this field, still leave open the question of how to strongly convey a social perspective change that really takes us in the direction of the construction of a stable Dementia-Friendly Community. We acknowledge that ours was a temporally circumscribed intervention, but it had a high experiential and transformative potential. Unfortunately, we cannot measure this change through follow-up monitoring of our participants or explore whether their future actions changed toward being more Dementia-Friendly when they returned home. Thus, although it has shown to be effective, the ViveDe experience still needs a *post hoc* focus on how to convey effective community change that directs toward full inclusion of people with dementia.

DATA AVAILABILITY STATEMENT

Data access is restricted to protect confidential information about a personal point of view on dementia that can be erroneously considered outside the research context. To access the dataset contact the corresponding author. Data will be available on request with the permission of the third party.

ETHICS STATEMENT

This study involving human participants was reviewed and approved by University of Bergamo. Written informed consent to participate in this study and for the publication of any potentially identifiable images or data included in this article was provided by the participants.

AUTHOR CONTRIBUTIONS

FM ideated the research. FM, PS, and NP conducted the experiment. FM and NP wrote the manuscript. FM, NP, and AG collaborated on data analysis. All authors contributed to the article and approved the submitted version.

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An Emotional Agent for Moral Impairment Rehabilitation in TBI Patients

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The ability to identify the emotions of others is a key component of what is known as social cognition. Narratives exploit this mechanism to create an emotional bond with the characters and to maintain the engagement of the audience throughout the story. In this paper, we illustrate a case study in emotion understanding in stories that exploits a computational agent to explore emotion impairment in a group of traumatic brain injured people. The study focuses on moral emotions, aiming to investigate the differences in moral functioning that characterize traumatic brain injured patients. After comparing the understanding of the moral and emotional facets of the agent's behavior in traumatic brain injured patients and in neurologically intact controls, slight–yet meaningful–differences were observed between the two groups. We describe the test methodology and results, highlighting their implications for the design of rehabilitation applications based on virtual agents.

Keywords: narrative, emotion understanding, moral emotions, social cognition, traumatic brain injury, computational models, models of emotion

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1. INTRODUCTION

Emotions play a crucial role in stories, as stated by scholars for centuries, from philosophy (Aristotle, 2013) and psychology (Bruner, 1991) to narratology (Giovannelli, 2009). In Plato's Ion, the rhapsode Ion describes his ability to evoke emotional states in the audience: "For I look down upon them [the spectators] from the stage and behold the various emotions of pity, wonder, sternness stamped upon their countenances when I am speaking." (Plato and Jowett, 1924 as cited in Damiano et al., 2019). In narratives, emotions, and moral emotions in particular, take a leading role in engaging the audience, ensuring their involvement throughout the plot, from rise to climax to resolution (Olson, 1961; Giovannelli, 2009).

The ability to read and understand the emotions of characters is crucial to grasping the meaning of a story. Such ability relies on what is known as *social cognition*. Social cognition (Cassel et al., 2019) is an umbrella term indicating a set of processes from the ability to read social cues both from the self and from others and understanding emotions, beliefs, and behavior to the capability of generating appropriate responses to social cues. Traumatic brain injuries (here TBI), like other neurological conditions, lead to impairments in social cognition (Bibby and McDonald, 2005) as well as in controlling behavior and properly displaying emotions (Roberts et al., 2019).

Several studies point toward a relationship between social cognition and social behavior following TBI (Milders, 2019). Although addressing social impairments is a fundamental step

toward full recovery (Kelly et al., 2017), testing tools for social cognition after TBI are often underutilized in clinical practice (Kelly et al., 2017).

Here, we investigate the perception of emotions in narrative scenarios by TBI individuals involved in effective cognitive rehabilitation but yet impaired, to some extent, in their moral and emotional functioning (i.e., inability to empathize, difficulties in understanding their own emotions, etc.). More specifically, we focus on the understanding of narrative situations involving moral emotions. In fact, authors have claimed that moral impairments following TBI should gain more attention in research (McDonald, 2013), as moral capabilities greatly affect the quality of life of patients and of their caregivers (Saint-Jean et al., 2019). The use of narrative scenarios is two-fold: on the one side, thanks to the universally acknowledged capability of narrative to convey values in a compact and effective form for human cognition (Bruner, 1991), they represent a suitable format for presenting moral dilemmas to the patients; on the other side, these scenarios can afford the creation of applications for training and rehabilitation that prompt the patients to reason about the emotions of characters in fictional stories. Our work leverages a computational agent model to explore the difference in the understanding of moral actions and emotions in narrative scenarios among TBI patients and neurologically intact individuals.

Aimed at generating human-like, believable behaviors, computational agents rely on cognitively inspired architectures where emotions and deliberation affect each other to replicate the complex interaction of rational and emotional components in humans (Marsella et al., 2010; Lisetti and Hudlicka, 2014). Since the output of the agent can be compared with the predictions of the audience about what the character will feel and do, virtual agents provide a stable, verifiable framework for the design and the implementation of experiments in story understanding.

In addition, the agent can afford the design of characters who behave and feel according to specific psychological theories or can be set to standard functioning to support the creation of rehabilitation applications (Habonneau et al., 2012; Chauveau et al., 2018).

In order to study the moral emotional impairment of TBI patients through stories, this study employs narrative scenarios whose characters are replaced by a computational agent that encompasses moral values and emotions, the *Moral Emotional Agent* or *MEA* (Battaglino et al., 2013).

Our methodology, previously sketched in Ceccaldi et al. (2016), is aimed at comparing the differences in the understanding of emotions, focusing on moral emotions between traumatic brain injured patients and neurologically intact controls. Drawing from the experiments described by Battaglino and Damiano (2014a), where the emotions generated by the agent were compared with the emotions ascribed to the narrative character by the human users, we compare the emotions generated by the agent with those identified by the test and control groups to investigate the differences between the two groups. The results confirm the role of emotions in the understanding of narratives and highlight the impairment of TBI patients in the understanding of moral emotions. The advantage of our approach is two-fold: on the one side, new testing scenarios can be easily generated by submitting new plots to the computational agent; on the other side, the agent can be straightforwardly employed to implement virtual characters to train the patients through stories. Differently from abstract dilemmas, stories possess the unique quality of engaging the audience, and this provides a natural candidate for creating effective training tools. This is also in line with the use of virtual characters in applications for health care and medicine, where the affective dimension has been recognized as a main requisite for establishing successful and effective relationships with the patients (Calvo et al., 2014).

1.1. Related Work

Behavioral consequences of traumatic brain injury can be a greater burden for caregivers of brain damaged individuals than physical consequences of the injury (Bornhofen and Mcdonald, 2008). Despite being relatively well documented, the impairments underlying the negative social outcomes occurring after TBI are far from being fully understood (Milders et al., 2008). Moreover, there is currently a lack of diagnostic tools to assess the changes in social behavior and cognition (Cattran et al., 2016). The tools proposed in the literature have addressed several aspects of this area while also leveraging different testing tools and methodologies, such as emotion recognition (in terms of facial expressions), theory of mind, sensitivity to social cues, complex language (inference, humor), empathy, understanding of paralinguistic cues, social interaction and social anxiety (Cattran et al., 2016). A thorough review of testing tools for social cognition after TBI goes beyond the scope of this study. Most used testing methodologies have been recently described by Milders (2019). Nonetheless, works on emotion understanding in stories might help the reader better fathom our study on narrative scenarios. The Emotional Inferencing From Story (EIST) proposed by Neumann et al. (2015) assesses the ability to understand emotions of others from contextual cues. The purpose is to measure emotion understanding when non-verbal cues are unavailable; to do this, patients were presented with short stories and asked to evaluate how the character in that story was feeling. When compared with neurologically intact individuals, TBI participants scored significantly lower, showing EIST validity in assessing impairments following TBI. Similarly, Saint-Jean et al. (2019) illustrate how social cognition deficits in TBI patients can be effectively assessed through narrative scenarios. For instance, they describe the social problem solving task, a test made up of 10 written stories depicting a character facing a social problem. In the test, participants had to detect and understand the problem and to identify its key components. Furthermore, the task required them to propose solutions to the problem or to evaluate solutions that were already presented in the scenario. Patients scored significantly lower than healthy controls in the social problem task. What is more, when it comes to training such ability to understand the emotional content of stories, research has shown that it did positively impact social behavior according to caregivers' ratings (Radice-Neumann et al., 2009). Radice-Neumann et al. trained TBI patients to infer emotions from contextual cues portrayed in stories, and to make connections

between these stories and personal events. The training relied on short stories; while reading the scenarios, participants also had to take contextual cues of emotional features (i.e., characters' wants, expectations, and behavior) into account and relate the story to personal lives. After reading each scenario, participants were asked to select the strongest emotion they believed the character was feeling. Feedback was given for incorrect responses. When the correct option was provided, participants were asked why it was correct, how they would have felt in that situation, if they ever found themselves in similar circumstance and to state a life event that had made them experience that emotion. The training resulted in participants being more comfortable in reporting their emotions and better able to handle their emotions in challenging situations. Caregivers of participants reported improvements in attitude and ability to communicate feelings.

2. MODELING STORY CHARACTERS WITH THE MEA AGENT

In the last decade, the use of virtual agents in health care has been explored in different domains, spanning from nursing (Bickmore et al., 2012) and counseling (LeRouge et al., 2015) to training of people with autism (Burke et al., 2018) and assistance to elderly and cognitively impaired people (Yaghoubzadeh et al., 2013; Chauveau et al., 2018). Virtual agents can be implemented on different devices in an non intrusive way, thus guaranteeing portability and continuity in therapies, and can be personalized to meet the needs of specific patients or groups of patients. In particular, the integration of an affective component in virtual agents has attracted the attention of scholars, since it opens to the creation of empathetic virtual agents, more natural and believable in the interaction with the user (Lisetti and Hudlicka, 2014).

2.1. The MEA Model

The core reference model for creating virtual agents is provided by the widely acknowledged Belief Desire Intention (BDI) model (Bratman, 1987; Cohen and Levesque, 1990). The BDI model, informed on Dennet's notion of "intentional stance" (Dennett, 1987), is suitable to simulate the intentions behind the behavior of human agents, and as such can be effectively employed to create virtual agents that interact with human users. Following this model, the MEA agent (Battaglino et al., 2013) features a set of goals, or *desires*, composing the motivational component of the agent; the *beliefs* of the agent are formed by a representation of the world, continuously updated through perception, and by the knowledge about how actions can be planned and executed in the world to achieve the agent's goals; the agent's commitment to execute action plans bridges the gap between the agent's abstract goals and its practical *intentions*. The MEA model integrates in the BDI model an emotional component based on the cognitive theory of emotions proposed by Ortony et al. (1988) (here OCC). In MEA, a goal is associated with an *importance of success* and an *importance of failure*, and with three different set of conditions: *adoption conditions*, *success conditions*, and *failure conditions*. A goal becomes an *active intention* when the agent believes that one of the adoption conditions of a goal is true in the world; at this point, the agent starts the deliberation phase, trying to find plans to achieve the goal's *success conditions* and dropping those that have been achieved or whose *failure conditions* have become true. Psychology shows that decision-making relies on preferences that vary with the subjective utilities of anticipated outcomes, weighted by their probabilities (Angie et al., 2011) and that decision-making and moral judgment are related to how people combine desires, personal values, and expectation to choose a course of action. So, the agent, after devising a set of plans to achieve its goals, ranks them by combining the achievement of goals (measured through their *importance of success* and the *importance of failure*) with a measure of its own emotional well-being (*Expected Emotional Reward, EER*) and becomes committed to the plan with the best trade-off between positive and negative emotions, then starts to execute it. After monitoring the effects of the execution on the state of the world (the plan might have succeeded or not, other events may have occurred), the agent eventually updates its beliefs and emotional state accordingly.

A characterizing feature of the MEA model is given by the explicit acknowledgement of *values* in the appraisal of emotions. Values (or "standards" in OCC terms) are the moral drive of the agent (Fraassen, 1973; Dehghani et al., 2008), which binds its behavior to a moral dimension and enables it to morally appraise the behavior of self and others, thus eliciting moral emotions. In the MEA agent, each value holds a *priority* that indicates the importance of the value for the agent, and a set *violation conditions*. When one of the violation conditions of a value is true in the state of the world, the value is *at stake* and will originate a goal to bring it back to balance. In the reasoning cycle of MEA, the appraisal of emotions occurs twice: the first time, during the deliberation phase (*Anticipatory Emotional Appraisal*), to assess the consequences of the agent's options on the agent's emotional state; the second time, after assessing the changes occurred in the world (*Emotional Appraisal phase*), to generate the agent's actual emotional state, according to the following schema:

1. **Value Monitoring**: If the agent believes the condition of a value to be true in the current situation, then the value is *at stake*.
2. **Goal Formation**: Goals whose adoption conditions hold in the belief base are adopted and become *active intentions*; they include value-based goals, motivated by the values at stake.
3. **Emotional Anticipatory Appraisal**: After computing the *expected emotional reward* (EER) of every goal from its associated plans, the agent chooses the optimal plan; in this phase, the agent "feels" only anticipatory emotions.
4. **Execution**: The agent starts the execution of the next action of the chosen plan.
5. **Monitoring**: The agent appraises the world and updates her beliefs about it, including the status of its goals and values.
6. **Emotional Appraisal**: depending on the updates observed in the state of the world (goals achieved or failed and values re-established or at stake) the agent feels certain emotions.

Consider, for instance, an agent who desires a chocolate treat, but hasn't got one. Having learnt that another agent has a chocolate candy (adoption condition), the goal to eat the chocolate candy

becomes the agent's active intention (*Goal formation*). So, the agent starts planning how to achieve her goal, eventually devising two plans: asking the other agent to give her the candy, or stealing the candy. The agent appraises the effect of each plan on her goals and values, and ranks the plans according to their expected emotional reward (*Emotional Anticipatory Appraisal*). Depending on the goal and value structure of the agent (whether she is inclined to follow the rules, optimistic about others, etc.), the ranking of plans will vary. Eventually, the agent selects a plan and executes it (*Execution*), monitors its effects (*Monitoring*) and feels emotions based on its outcome: gratitude, anger, disappointment, satisfaction, etc. (*Emotional Appraisal*). When the reasoning cycle starts again, the agent might realize one of her values to be at stake (*Value Monitoring*): for example, because she has put at stake her honesty due to her desire for chocolate.

2.2. Emotional Appraisal in MEA

The reference theory of emotions in the MEA agent is the OCC theory (Ortony et al., 1988), chosen for its capability to match the emotional range of characters in the perception of the audience (Lombardo et al., 2015). In the OCC model, events are appraised based on the their desirability for the agent's goal, self, and others' actions are appraised based on their compliance with the agent's moral standards, objects are appraised based on the agent's specific attitudes toward them.

Following the general framework established by Gratch and Marsella (2004), the generation of the emotional states in MEA is a two-step process:

First, the appraisal generates a set of *appraisal variables*, such as the desirability and probability of an event, each associated with some intensity; in the *affect derivation* process, emotional states are activated based on the appraisal variables. In practice, when an agent's goal is achieved (or not achieved), the appraisal process generates a *desirability* variable (or an *undesirability* variable); when an agent's value is put at stake (or brought back to balance) by the execution of some action, the appraisal process generates a *blameworthiness* (or *praiseworthiness*) variable; the probability that an event occurs or that a agent's plan succeeds generates a *likelihood* variable. Based on the appraisal variables, the affect generation process generates emotions according to the following rules (see **Figure 1**):

- **Joy** (or **Distress)** if a *desirable* (or *undesirable*) appraisal variable is generated;
- **Pride** (or **Shame)** if *praiseworthy* (or *blameworthy*) appraisal variable is generated and the responsibility is *self-caused*;
- **Admiration** (or **Reproach)** if *praiseworthy* (*blameworthy*) appraisal variable is generated and the responsibility is *other-caused*.

When the same situation is appraised as both an action and a non-intentional event, appraisal variables for both values and goals are generated, thus eliciting compound emotions: Gratification (Joy and Pride), Gratitude (Joy and Admiration), Remorse (Distress and Self-Reproach), Anger (Distress and Reproach). If a *likelihood* appraisal variable has a high (or low) value, Hope (or Fear) are generated. The *intensity* of emotions depends on the multiplicative relationship between the importance of values and goals, the effort (i.e., the length of the plan) and the probability of success of the plan.

As a consequence of the anticipatory emotional appraisal, the behavior of the agent is compelled by its moral values through anticipatory emotions, a feature that makes it especially suitable to model moral dilemmas in stories (Williams, 2006), where introspection plays a prominent role. Also, the agent model guarantees that the dynamics of the agent's deliberative and emotional processes can be traced and exposed to the users, in line with the requisite of transparency and explainability required by the principles of trustworthy AI [1].

For example, consider again the agent who desires chocolate, but can only steal it from another agent or ask for it. Assuming that stealing puts the agent's honesty at stake, the agent's behavior depends on the anticipatory emotional appraisal: if honesty is of minimal importance for the agent (i.e., it has a low priority), negative emotions such as the shame generated by the act of stealing, or the fear to fail a risky plan, will be largely compensated by the satisfaction of eating the candy, and agent will end up stealing; on the contrary, if honesty is very important for the agent (i.e., it has a high priority), the expectation of shame will retain her from stealing, unless she is really hungry. Notice that even if the agent eventually decides to steal, this won't stop her to feel shame, possibly with a low intensity, and mixed with satisfaction or disappointment depending on whether she actually obtained the chocolate candy.

2.3. Validating the MEA Model

In order to validate the MEA model, Battaglino and Damiano compared the behavior and the emotions generated by the MEA agent with the predictions of human participants in a set of narrative scenarios (Battaglino and Damiano, 2014a,b). Following the suggestions of a drama expert, the scenarios for both experiments were taken from well-known literary works, thus lifting the experiment design from the task of inventing new and potentially controversial narrative situations. The original experiments included two tests, structured as simple games. The Actor Studio (Battaglino and Damiano, 2014a) test was designed to validate the role of emotions in the agent's deliberation: given the character's scale of moral values, participants were asked what course of action the character would choose, and what emotions she/he would feel, as if they were practising at the well-known "Actor's Studio" following the Stanislavski's acting method. In order to bypass the participants' previous knowledge of the literary works, the scenarios were re-written with different characters and actions but keeping the interplay of characters' goals and values unmodified. The test included 3 narrative scenarios (see **Appendix 1.1**) where the main character's options (plans in agent's terms) were generated by the MEA agent given the character's goals and values (see section 2.1). After receiving a description of the character's goals and values, each participant was asked to choose the most suitable option for the character.

[1] https://ec.europa.eu/info/sites/info/files/commission-white-paper-artificial-intelligence-feb2020_en.pdf

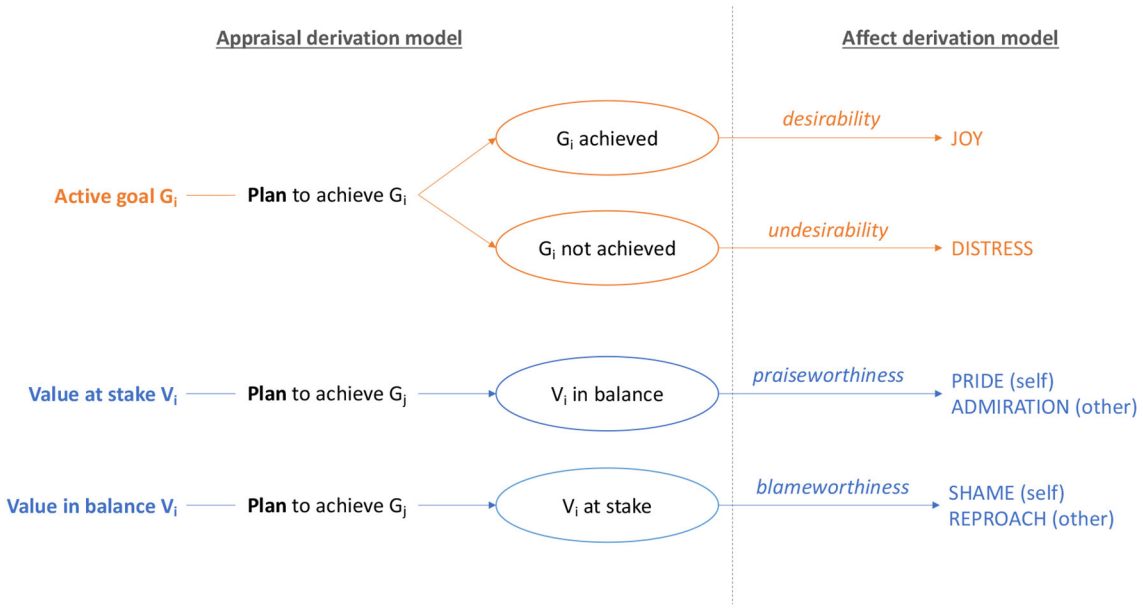

FIGURE 1 | Emotional appraisal and affect generation in the MEA model. Other appraisal variables (importance of goals, priority of values and plan length) do not determine the affect type, but only the intensity, and are not represented in the figure.

The Audience Studio (Battaglino and Damiano, 2014b) test was aimed at validating the interplay of values and emotions in the agent: all participants were exposed to the same characters' behavior with two different conditions—with and without moral emotions—and had to assess their adequacy, as if they were assessing the performance of actors interpreting the characters. The test included 4 narrative scenarios (see **Appendix 1.2**) where the main characters were implemented by the MEA agent (Battaglino et al., 2013; Cristina, 2015). Differently from the Actor Studio, where alternative options were generated to create the user choices, in this test only the actual behavior of the character in the literary work was generated, with and without value-based emotions. Since the participants' knowledge of the characters' actions was not relevant here, the original characters and actions were maintained.

The results, discussed in Battaglino and Damiano (2014a,b), showed that the expectations of the testers matched the predictions of the model: for the Actor Studio, the participants attributed to the character the course of behavior and the emotions predicted by the model (Battaglino and Damiano, 2014a); for the Audience Studio, the emotional states including moral emotions were evaluated as more complete and believable (Battaglino and Damiano, 2014a,b).

3. EXPERIMENTAL METHODOLOGY

In this study, both tests described in Battaglino and Damiano (2014a) were used to explore emotion understanding in narrative in TBI patients. In previous studies, the expectations of neurologically intact individuals on characters' behavior and emotions have been demonstrated to match predictions made by modeling characters as MEA agents (Battaglino and Damiano, 2014a,b). Therefore, this study could leverage such testing tools to compare MEA agents' behavior and emotions with TBI participants' expectations and predictions.

3.1. Participants

The clinical sample was recruited from "Puzzle" rehabilitation center in Turin (Italy)[2].

The clinical sample was made up of 14 TBI individuals (mean age 40.3), involved in neuropsychological rehabilitation at the center from 1 to 13 years (mean 5.5). Being in its exploratory phase, our study involved an heterogeneous sample, with participants having different cognitive profiles and clinical histories, with lesions being localized mostly (but not exclusively) in the frontal area. However, they were all recruited according to their ability to execute the testing procedures, to read and to verbally understand the scenarios thoroughly, along with having difficulties in social cognition (e.g., emotion understanding, empathy). In fact, only the patients that were deemed able to complete the tasks by the center neuropsychologists were invited to participate. Moreover, prior the experiment, each participant had the possibility to familiarize with the experimenter and with the testing procedure, to avoid stress and discomfort. As completing the task required full recovery of specific cognitive abilities (i.e., linguistic and narrative abilities to read and understand the plot), recruiting participant was challenging, resulting in a small sample. Before starting the tests, two TBI patients with a cognitive profile similar to that of participants took part in the study in order to test if their cognitive

[2]Puzzle rehabilitation center is an Italian leading facility for neuropsychological recovery after traumatic brain-injury (www.centropuzzle.org/).

impairments (i.e., reading difficulties, attention deficits) would result in the task being too difficult or impossible to complete. Secondly, the methodologies were slightly adapted to the needs of the participants; for example they were made shorter (as patients were very slow in reading, often taking longer than 60 minutes for each test). After this, the Actor Studio and the Audience Studio testing methodologies were presented to a new sample made of TBI patients and healthy controls, in order to compare the groups. The control group was a convenience sample including neurologically intact individuals (i.e., people that declared to the experimenters never suffering from TBI), matching each patient for age and gender.

3.2. Actor Studio Testing Methodology

The experiments were conducted online. For each scenario (see **Appendix 1.1**), a short text introduced the character and her/his values, then the narrative situation was illustrated. **Figure 2** shows a screenshot of the page in which the narrative scenario is illustrated. The character's scale of values was presented to the participant not in a numerical format, but with a figurative scale, in order to make the priorities of the values as clear and understandable as possible. The task of identifying the expected course of action and emotions for the character was presented to the participants as a game: participants were asked to pretend they were practicing identification in an acting class, trying to adopt the point of view of the characters as actors following the Stanislavski's acting method. By pressing the "play" button (bottom of the page, **Figure 2**), the two alternative actions generated by the MEA agent were presented to the participant, who then had to indicate a set of possible emotions (taken from the set of the 12 emotion types included in the MEA model, see section 2.2).

3.3. Audience Studio Testing Methodology

The experiment was conducted online. It was made up of the 4 narrative scenarios illustrated in **Appendix 1.2**, taken from well-known literary works (namely Hamlet, The Count of Montecristo, Thérèse Raquin, and The Vicomte of Bragelonne). After a brief description of the narrative situation, participants were presented with a dialogue between the characters involved in the scenario. The dialogues were extracted from movies or books for more immediacy. After this, characters' emotions were described through text labels (e.g., "Hamlet feels reproach toward Ophelia"). Participants were then asked to select, from a list, those emotions they would feel in a similar situation (again, the set of 12 emotions from OCC model). Differently from the Actor Studio, subjects had to evaluate both the emotions of the protagonist and of the other character. Whereas, the Actor Studio testing methodology allowed scores for each scenario to be related to the same participant, the results for the Audience Studio methodology could only be measured separately for each scenario. Although simplified to meet the needs of TBI patients, the Audience Studio testing procedure took more time than the Actor Studio to be completed. Scenarios are in fact longer to be read and understood and the testing procedure also contains items we eventually decided not to take into account (e.g., the participants' evaluation of the characters' attitude and behavior). For this reason, TBI participants were sometimes unable to complete the testing procedure all at once, as their daily schedule in the rehabilitation center only allowed them to participate in the testing for about 45–50 min. Therefore, some participants completed the test through several sessions, resulting in scores being impossible to be related to the same participant. Regrettably, the system did not record the experiment time, thus causing sessions taking place on the same day to be indistinguishable.

By contrast, the Actor Studio methodology required the participants to choose a nickname for their performance. This, along with the testing procedure being simpler and therefore shorter, allowed every single session data to be related to its tester and with the right scenario. The aforementioned characteristics of the testing methodologies allowed us to compare scores between groups for both methodologies, but a deeper analysis of the scores and of their correlation with the clinical data was possible only for the Actor Studio test.

4. MEASURES AND RESULTS

This section illustrates the measures employed to compare the performance of the two groups along with the results, discussed in section 5.

4.1. Measures

Data were analyzed through SPSS Statistics 24 (IBM). Sample size was $n = 13$ for TBI patients and $n = 11$ for the control group (as a consequence of participants drop-out). One neurologically intact participant was not included in the analysis, as his scores were significantly lower than other participants' (i.e., Action score and Emotion total score both for moral and non moral emotions being equal to 0). Participants' responses were turned into scores in order to perform comparisons between groups. As mentioned before, for the Audience Studio methodology only, scores were measured separately for each scenario.

For both methodologies, scores were calculated as follows:

- Emotion total score (ETS): score = 1 each time participants would choose the same emotion predicted by the MEA model;
- Moral emotion score (MES): score = 1 each time participants would choose the same emotion predicted by the MEA model; only for moral emotions, being them admiration, contempt, gratification, gratitude, pride, shame, anger, blame;
- Non moral emotion score (N-MES): score = 1 each time participants would choose the same emotion predicted by the MEA model; only for non moral emotions, being them joy, sadness, hope, and fear;
- Error total score (ERTS): score = 1 each time participants both would choose an emotion in disagreement with MEA model and would miss indicating those predicted by the model;
- Moral emotion error score (MERS): score = 1 each time participants both would choose an emotion in disagreement with MEA model and would miss indicating those predicted by the model; only for moral emotions;
- Non moral emotion score (N-MERS): score=1 each time participants both would choose an emotion in disagreement

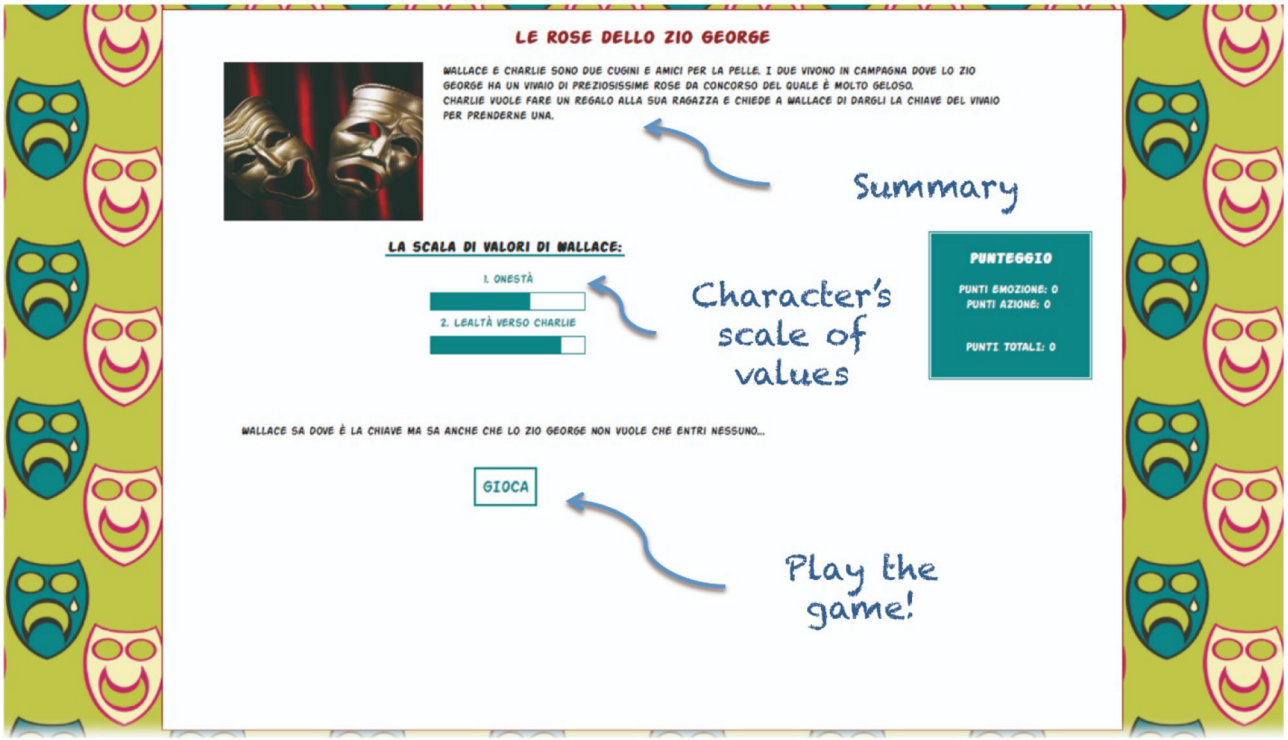

FIGURE 2 | The screenshot of the online interface of the Actor Studio test (in Italian).

with MEA model or would miss indicating those predicted by the model, only for non moral emotions.

In the Actor Studio, participants were asked to predict the action characters would choose according to their moral values. Therefore, for this methodology only, we took a further measure into account:

- Action total score (ATS): score=1 each time participants could guess the agents' action according to MEA model.

For each score, means were compared using Mann–Whitney test, suitable for different-sized samples. As our aim was to compare TBI participants' similarity with the MEA agents with that of neurologically intact individuals, we also used the Simple Matching Coefficient statistic to evaluate the performance of the participants (Sokal and Sneath, 1961). In our view, this statistic allows a better comparison between the model and the participants' choices, as it takes into account also the emotions *not* predicted by the model, and those *not* selected by the participants. Considering the MEA Model emotion set as an array of emotions (some included and some not) and the participants choices as an array of selected and unselected emotions, the Simple Matching Coefficient (SMC) was calculated as follows:

$$SMC = \frac{M_{00} + M_{11}}{M_{00} + M_{01} + M_{10} + M_{11}} \quad (1)$$

Where:

- M_{00} are the emotions not predicted by the model and not selected by the participant;
- M_{11} are the emotions predicted by the model and selected by the participant;
- M_{01} are the emotions not predicted by the model selected by the participant;
- M_{10} are the emotions predicted by the model not selected by the participant.

After this, SMCs for each scenario were compared between groups for both methodologies, through Mann–Whitney. We measured global SMCs, calculated on complete emotion sets and moral SMCs, considering moral emotions only. Furthermore, we performed Spearman correlation analysis to assess the relationship between time spent in the rehabilitation center (rehabilitation duration, in years) and the global Simple Matching Coefficient for the Actor Studio methodology, calculated on all three scenarios. Moreover, we investigated the relation between the time distance from the traumatic event (in years) and the aforementioned variable.

4.2. Results

4.2.1. Results Actor

In the Actor Studio, participants were asked to select which among two alternative courses of action the characters in each scenario would choose, according to their moral values. Percentages for action choice for TBI and healthy controls are shown in **Table 1**. The *X* indicates the course of action

TABLE 1 | Actor studio: percentages for action choice.

Scenario	Plan	MEA	TBI (%)	Controls (%)
1. Wallace	*giving_key*	*X*	46.2	18.2
	refusing_key	–	53.8	81.8
2. At school!	*revenging*	*X*	84.6	81.8
	letting_go	–	15.4	18.2
3. A difficult choice	*staying*	X	84.6	81.8
	leaving	–	15.4	18.2

TABLE 2 | Actor studio: percentages for emotion choice.

	Wallace			At school!			A difficult choice		
Emotion	**M**	**TBI (%)**	**C (%)**	**M**	**TBI**	**C (%)**	**M**	**TBI (%)**	**C**
Distress	–	38.5	9.1	–	23.1	–	X	23.1	18.2
Joy	–	23.1	–	X	23.1	36.4	X	76.9	54.5
Fear	–	–	–	–	46.2	54.5	–	23.1	9.1
Hope	–	15.4	18.2	–	–	–	–	30.8	9.1
Pride	–	23.1	9.1	X	23.1	27.3	–	38.5	36.4
Shame	X	23.1	27.3	X	23.1	18.2	X	23.1	18.2
Admiration	–	23.1	27.3	–	7.7	–	–	30.8	18.2
Reproach	–	7.7	27.3	–	53.8	36.4	–	7.7	9.1
Gratification	–	7.7	18.2	X	53.8	–	–	53.8	27.3
Gratitude	–	–	–	–	7.7	–	–	23.1	9.1
Remorse	–	38.5	27.3	–	15.4	27.3	X	69.2	45.5
Anger	–	23.1	9.1	–	46.2	9.1	–	7.7	9.1

predicted by the model. As it can be observed, the results show no significant difference, with TBI patients performing slightly better than controls. Participants were also asked to pick out the emotions they would feel being in the characters' shoes. **Table 2** depicts percentages for emotion selection for the Actor Studio testing methodology for both experimental groups. The X indicates those emotions to be included in the agent's emotional state according to the MEA model. As **Table 2** shows, TBI participants tend to select a larger number of emotions in every scenario.

Table 3 illustrates score means for the Actor Studio testing methodology both for TBI participants and controls. We ran Mann–Whitney statistic ($p < 0.05$) in order to compare means; no statistically significant difference was found between groups. However, there are some differences that deserve further consideration: all scores are slightly higher for TBI patients than controls (for Action Total Score, Emotion Total Score, Moral Emotion Score, Non Moral Emotion Score), but at the same time, their error scores (Error Total Score, Moral Emotion Error Score, Non Moral Emotion Error Score) also have higher values. In order to explore whether the observed tendency of TBI participants to select a large number of (often inconsistent) emotions would effect their scores, we measured Simple Matching Coefficients. Before computing SMCs for each scenario, we calculated the global SMC for all scenarios included in the Actor Studio methodology, as we believed emotion choices could be investigated as a single array of selected (and unselected) emotion labels, to be compared with MEA model predictions. When considering the complete emotion set, the mean SMC was 0.71 for controls and 0.67 for TBI participants. Focusing on moral emotions only, mean was 0.67 for TBI participants and slightly higher (0.70) for controls. We compared SMC through Mann-Whitney statistic. No statistically meaningful difference was found for both global (U = 40.000; sig = 0.118) and moral (U = 53.000; sig = 0.449) emotion set. SMCs were then computed for each scenario separately and hence compared using Mann–Whitney statistic (sig.< 0.05); no statistically significant difference was found between groups. **Table 4** shows Mann–Whitney statistic for SMCs for the Actor Studio methodology. SMCs were measured on the complete emotion set. **Table 5** illustrates Mann-Whitney comparison on the SMCs of the two groups, calculated on moral emotions only.

4.2.2. Results Audience

Due to methodology constraints (see section 3.3), data were analyzed separately for each scenario. Subjects were asked to select those emotions they believed better described the emotional states of characters in the scenario. **Tables 6**, **7** illustrate percentages for emotion selection for the Audience Studio test for both experimental groups. The X indicates those emotions to be included in the agent's emotional state according to the MEA model. Percentages for the main character in the scenario are shown in **Table 6**; percentages for the character interacting with the protagonist are demonstrated in **Table 7**. With respect to the results of the Actor Studio test (see previous section, **Table 2**), the TBI patients' tendency to select a larger number of emotions here is more evident.

In order to better assess score differences for emotion selection, Simple Matching Coefficients were computed for each scenario for both TBI participants and controls: similarly to the Actor Studio test, the SMCs are higher for controls than TBI patients for all scenarios. SMCs (calculated considering the complete emotion set) were then compared through Mann–Whitney statistic (sig.<0.05). **Table 8** illustrates results for Mann-Whitney comparison. Results for moral emotions are shown in **Table 9**. In both cases, no significant differences were found.

5. DISCUSSION

In this work, the experiments described in section 3 were carried out with a group of patients dealing with the consequences of TBI and with a control group of neurologically intact individuals, to explore group differences in the understanding of characters' moral behavior and emotions. In fact, according to research, TBI patients often exhibit impairments in social cognition, despite undergoing effective rehabilitation. More precisely, our study taps into the domain of moral emotion recognition in stories, as an important yet often neglected (McDonald, 2013) aspect of social cognition. Furthermore, our work contributes to research on narrative understanding in brain damaged populations, as this topic, to the best of our knowledge, has not been thoroughly explored yet.

TABLE 3 | Actor studio: mean scores.

Group	ATS	ETS	MES	N-MES	ERTS	MERS	N-MERS
TBI	2.15 (0.081)	3.38 (0.768)	2.15 (0.081)	1.23 (2.934)	11.31 (2.934)	8.00 (2.160)	3.31 (1.109)
Controls	2.00 (0.632)	2.45 (2.067)	1.36 (1.567)	1.09 (0.831)	10.2 (2.832)	7.64 (2.111)	2.64 (1.027)

TABLE 4 | Actor studio: simple matching coefficients (all emotions).

Scenario	TBI	Controls	MW U	sig. (2-tailed)
Wallace	0.76	0.82	67.500	0.811
At school!	0.57	0.60	66.000	0.743
A difficult choice	0.64	0.65	65.000	0.700

TABLE 5 | Actor studio: simple matching coefficients (moral emotions).

Scenario	TBI	CONTROLS	MW U	Sig. (2-tailed)
Wallace	0.75	0.77	62.000	0.826
At school!	0.59	0.59	71.000	0.976
A difficult choice	0.66	0.69	67.5000	0.811

5.1. Group Differences

Emerging differences, although not significant, show a clear trend and provide useful insight on the underpinnings of the impairment in TBI individuals and on the use of emotional virtual agents for rehabilitation. We first measured percentages for both action and emotion choice for each scenario for the Actor Studio methodology. After this, participants' choices were transformed into scores, to allow group comparisons. Concerning Action choice, TBI participants performed slightly better than controls, specially in the first scenario (see **Table 1**). Nonetheless, these results came as no surprise, as controls had to become confident with the procedure by themselves, whereas TBI patients participated in the study with the help of the experimenter. We believe randomized scenarios would be necessary for future work. Despite this, Mann–Whitney testing revealed no significant difference between groups (sig. = 0.494). Emotion scores (both moral and non-moral) are higher for the clinical sample: although unexpected (according to our hypothesis), this can be explained by observing error scores. As the testing methodology required participants to pick out emotions from a list and emotion scores were computed assigning 1 for each correct emotion, those being unselective (i.e., picking out a large number of emotions, although inconsistent) could have indeed scored higher, as their probability to guess the correct emotion was increased. In fact, for both moral and non-moral emotions, error scores are lower for controls, suggesting a link between TBI patients' better performance and their tendency to be unselective when judging emotions (as percentages for emotion choice demonstrate).

Moreover, we observed the results obtained by measuring the Simple Matching Coefficient (SMC) for each scenario and for the Actor Studio methodology as a whole (see **Tables 4**, **5**). In fact, although it helps explaining group differences, error score fails in providing thorough information on the mismatch (or accordance) between the agent model and participants' expectations. SMC, on the other hand, allow measuring similarity between the agent model and participants' expectations more completely. We then compared SMCs through Mann–Whitney statistics. Mann-Whitney testing has shown no statistically significant difference for both complete and moral-only emotion set ($U = 40$, sig. $= 0.118$; $U = 53$, sig. $= 0.449$). Interestingly, we found a pattern in means for SMCs: although Mann-Whitney statistic did not show any significant difference, controls performed better than TBI participants for each scenario. It has to be noticed that the protocol required TBI participants to be not impaired in their ability to read and understand the narrative content of the stories, along with having acceptable attention span and visual abilities. As they did not differ in their understanding of the narrative content of the stories, we believe the SMC pattern we found (with TBI participants' SMC being lower than controls' for each scenario) might be ascribed to a specific impairment for the emotional content of the scenarios. As the slight differences we found seemed specific for emotion tasks, we think the action choice, where participants had to guess the course of action characters would choose according to their moral values, leverages reasoning abilities rather than emotional skills.

We further analyzed how participants evaluated characters' emotions. Regarding this, results for the Audience Studio testing methodology might help explain the score difference found for the Actor Studio methodology. As **Tables 6**, **7** show, TBI patients often selected the correct emotion, although percentages for the emotion predicted by the model were mostly higher for controls. Nevertheless, what the results for the Audience Studio help illustrate, is the fact that TBI participants tended to be unselective toward emotions, seeming somewhat puzzled from the task. For instance, in "The Count of Montecristo" all emotions were selected at least once by TBI participants, in some cases strongly inconsistently with MEA model predictions. Although the same situation, according to appraisal theories, can be appraised from different perspectives, resulting in different emotions to be generated for the same situation, some possibilities are ruled out by the model of emotional appraisal embedded in the agent. Finally, we compared group means of the Simple Matching coefficients for each scenario, using Mann-Whitney statistic. We found no statistically significant difference (see **Tables 8**, **9**), both for complete and moral emotion sets. Further research may help outline dissimilarities between TBI patients and healthy controls; to do so, however, larger samples are needed.

TABLE 6 | Audience studio: percentages for emotion choice (Main character).

	Hamlet			The count of MonteCristo			Thérése Raquin			The vicomte of bragelonne		
Emotion	**MEA**	**TBI**	**C**	**MEA**	**TBI**	**C**	**MEA**	**TBI**	**C**	**MEA**	**TBI**	**C**
admiration	–	–	10.0%	–	21.4%	37.5%	–	–	–	–	46.2%	30.0%
reproach	X	46.7%	50.0%	–	28.6%	25.0%	–	30.8%	11.1%	–	7.7%	–
joy	–	–	–	X	35.7%	50.0%	–	–	11.1%	–	53.8%	70.0%
gratification	–	–	10.0%	X	42.9%	87.5%	–	–	11.1%	X	69.2%	60.0%
gratitude	–	–	20.0%	–	7.1%	–	–	–	–	–	7.7%	–
pride	–	–	10.0%	X	71.4%	75.0%	–	7.7%	11.1%	–	53.8%	60.0%
fear	–	13.3%	10.0%	–	21.4%	–	–	46.2%	55.6%	–	23.1%	10.0%
anger	X	100%	30.0%	–	28.6%	25.0%	–	30.8%	–	–	–	–
remorse	–	6.7%	10.0%	–	14.3%	–	X	76.9%	88.9%	–	15.4%	–
hope	–	0.0%	10.0%	–	35.7%	–	–	15.4%	–	–	46.2%	30.0%
distress	X	80.0%	30.0%	–	14.3%	–	X	69.2	44.4	–	15.4 %	–
shame	–	33.3%	–	–	14.3%	–	X	76.9	77.8	–	15.4 %	10.0%

TABLE 7 | Audience studio: percentages for emotion choice (other character).

	Hamlet			The Count of MonteCristo			Thérése Raquin			The Vicomte of Bragelonne		
	TBI	**C (%)**	**MEA (%)**	**TBI**	**C (%)**	**MEA Emotion (%)**	**TBI**	**C (%)**	**MEA (%)**	**TBI**	**C (%)**	
Admiration	–	–	–	–	–	–	–	–	–	–	46.2	60.0
Reproach	-	20.0	20.0	–	35.7	–	–	30.8	33.3	–	–	–
Joy	–	–	–	–	–	–	–	–	11.1	–	76.9	60.0
Gratification	–	–	–	–	–	–	–	–	11.1	–	30.8	10.0
Gratitude	–	–	–	–	–	–	–	7.7	–	X	84.6	60.0
Pride	–	6.7	–	–	7.1	–	–	7.7	–	–	15.4	–
Fear	–	26.7	50.0	–	78.6	50.0	–	38.5	33.3	–	15.4	–
Anger	–	33.3	–	–	28.6	50.0	–	46.2	33.3	–	15.4	10.0
Remorse	–	53.3	40.0	–	57.1	25.0	X	76.9	55.6	–	7.7	10.0
Hope	–	6.7	20.0	–	– –	–	–	15.4	–	–	38.5	30.0
Distress	–	73.3	10.0	X	42.9	37.5	X	23.1	66.7	–	23.1	–
Shame	X	86.7	50.0	–	57.1	62.5	X	84.6	66.7	–	23.1	–

TABLE 8 | Audience studio: simple matching coefficients (global emotion set).

Scenario	**Mann–Whitney U**	**Sig. (two-tailed)**
Hamlet	53.000	0.210
The Count of MonteCrist	45.000	0.449
Thérèse Raquin	53.000	0.711
The Vicomte of Bragelonne	49.500	0.542

5.2. Moral Emotion Understanding in Stories After TBI

Whereas not many works have addressed moral understanding in stories, literature (Greene and Haidt, 2002; Ciaramelli et al., 2007; Greene, 2015) illustrates how brain damaged individuals differ from neurologically intact participants for moral personal dilemmas. Personal moral dilemmas are dilemmas that elicit emotional responses while evaluating the dilemma, whereas non-personal and non moral dilemmas trigger no emotional response. When facing a moral personal dilemma, TBI participants differ from controls whilst they don't seem to differ when the dilemma elicits no emotion. According to Greene and Haidt (2002) personal moral dilemmas activate medial front gyrus, superior frontal gyrus while non-personal moral dilemmas engage dorsolateral and prefrontal areas; the same pattern can be observed when evaluating non-moral dilemmas. As Moretti et al. (2009) point out, TBI individuals whose brain damage involves areas such as the ventromedial prefrontal cortex can perform moral judgments (in terms of right/wrong), but show impairments in the emotional counterpart, in what is often referred to as "moral emotions selective impairment." Furthermore, Hutcherson et al. (2015) illustrated the interplay between utilitarian and emotional appraisal during moral judgment based on moral values: utilitarian and emotional moral appraisals are computed separately and later integrated in a moral value response. Furthermore, TBI individuals seem to exhibit a particularly

TABLE 9 | Audience studio: simple matching coefficients (moral emotion set).

Scenario	Mann–Whitney *U*	Sig. (two-tailed)
Hamlet	55.500	0.262
The Count of MonteCrist	35.500	0.156
Thérèse Raquin	53.500	0.733
The Vicomte of Bragelonne	55.500	0.262

utilitarian pattern of judgments in moral dilemmas (Rowley et al., 2018). In our view, the emotional appraisal is the one of the reasons behind the impaired performance we observed in TBI patients, resulting in non standard moral judgments. Although not significant, the "selective impairment" we found for the emotional content of the scenarios might be attributed to the aforementioned deficits.

5.3. Implications for Agent-Based Rehabilitation

Taken altogether, our results further demonstrate the suitability of the MEA model (Battaglino et al., 2013) for developing emotional virtual agents and characters, and for their use in rehabilitation. The difference we found is, in fact, what could be predicted according to research on TBI participants, but also what we could notice by interacting with them. For example, *A*'s performance seems to be paradigmatic of the overall results we found. *A*'s incident had occurred 10 years before the testing took place, and she had spent 9 into rehabilitation. She was able to read and understand the scenarios thoroughly and she was very interested in and entertained by reasoning upon the emotional content of the stories. When asked to predicted the characters' action, she scored 2 out of 3, as most controls did, whereas she only scored 3 out of 9 when asked about the emotions. As she herself pointed out during the testing procedure, emotions are the hardest part of her outcome, only understandable when "black or white"; she perceives the gap between her current limitations in dealing with emotions and her condition before the trauma and would like to regain her full capability to understand emotions.

We also had the goal to collect preliminary data for the development of a rehabilitative tool in which patients face a moral situation, addressing their ability to perform moral reasoning and reasoning on their moral emotions through a virtual agent, following the paradigm discussed in Lisetti and Hudlicka (2014) and Hudlicka (2016). We investigated the correlation between the SMCs of the emotions selected by the TBI patients in the Actor Studio test and the rehabilitation duration or the time distance since the trauma. Remember that, as described in section 4, we leveraged SMCs to evaluate the similarity of the emotions selected by the patients for each character with respect to the predictions established by the MEA agent. We performed Spearman correlation on SMCs of the patients in the Actor Studio test and the duration of the rehabilitation (in years), finding no meaningful correlation ($r = -0.001$ $p = 0.996$; two-tailed). As the rehabilitation the patients were undergoing did not include moral emotions or moral scenarios, this result came as no surprise. Similarly, we found Simple Matching Coefficients to be unrelated to time distance as well ($r = 0.125$ $p = 0.699$; two tailed). In this, the results obtained were promising for the design of agent-based rehabilitation tools, since they show that, in the absence of a specific rehabilitation targeted on emotions, and moral emotions in particular, no advancements are obtained.

On the one side, our experiments confirm the feasibility of this type of rehabilitation, further demonstrated by the comments of our TBI participants (already reported in Ceccaldi et al., 2016): *A*—"this test allowed me to think about the values that shape my moral judgment, helping me understand how every action comes after deep and elaborate reasoning"; *R*—believes this test "is important, as it makes my head start again." On the other side, the indirect validation of the MEA model provided by the study opens the way to the use of virtual agents in rehabilitative settings, as it contributes to the specification of an accountable agent model for developing practical applications.

6. CONCLUSION

In this paper, we described and discussed the results of the experiments on emotion understanding in stories that we conducted on a group TBI patients by leveraging a moral emotional agent. In brief, taking the agent model as a reference, we compared emotion recognition in TBI individuals and in a control group of neurologically intact participants. The results show that, notwithstanding no statistically meaningful difference between the two groups, the performance of the TBI patients differed from the control group concerning moral emotions. The main finding of our work was that the difference between the two groups was far from significant for those dimensions pertaining to the characters' course of action, whereas scores were higher for controls than for TBI participants for each scenario and for both test types. TBI participants performed differently from controls when asked to evaluate the emotional content of narrative scenarios. A complete and thorough definition of all the features that differentiate impaired moral and non-moral emotion understanding in people who suffered from TBI from that of healthy controls is far from achieved. Nonetheless, our results demonstrate the need to focus on emotion processing (rather than on reasoning) in order to gain a deeper understanding. This is in line with the mental models theory perspective on moral reasoning (Bucciarelli et al., 2008). More precisely, according to this perspective, moral reasoning is regular reasoning that happens to concern moral issues. The TBI patients included in our study were in a late stage of their rehabilitation; as a consequence, their reasoning could be compared to those of neurologically intact individuals. Despite this, their performance varied more significantly from that of controls for those tasks requiring (moral or non-moral) emotional processing. In our opinion, having patients whose outcome is similar to our participants' interacting with virtual characters whose emotional state holds a moral component could be effective in helping these patients improve their emotional moral functioning and their understanding of moral (but also

non-moral) emotions in characters. Conversely, we believe also that modeling "impaired" moral characters would provide effective and useful agent-based rehabilitative applications and more engaging virtual environments.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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REVIEW
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Neuroimaging and Psychometric Assessment of Mild Cognitive Impairment After Traumatic Brain Injury

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Traumatic brain injury (TBI) can be serious partly due to the challenges of assessing and treating its neurocognitive and affective sequelae. The effects of a single TBI may persist for years and can limit patients' activities due to somatic complaints (headaches, vertigo, sleep disturbances, nausea, light or sound sensitivity), affective sequelae (post-traumatic depressive symptoms, anxiety, irritability, emotional instability) and mild cognitive impairment (MCI, including social cognition disturbances, attention deficits, information processing speed decreases, memory degradation and executive dysfunction). Despite a growing amount of research, study comparison and knowledge synthesis in this field are problematic due to TBI heterogeneity and factors like injury mechanism, age at or time since injury. The relative lack of standardization in neuropsychological assessment strategies for quantifying sequelae adds to these challenges, and the proper administration of neuropsychological testing relative to the relationship between TBI, MCI and neuroimaging has not been reviewed satisfactorily. Social cognition impairments after TBI (e.g., disturbed emotion recognition, theory of mind impairment, altered self-awareness) and their neuroimaging correlates have not been explored thoroughly. This review consolidates recent findings on the cognitive and affective consequences of TBI in relation to neuropsychological testing strategies, to neurobiological and neuroimaging correlates, and to patient age at and assessment time after injury. All cognitive domains recognized by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) are reviewed, including social cognition, complex attention, learning and memory, executive function, language and perceptual-motor function. Affect and effort are additionally discussed owing to their relationships to cognition and to their potentially confounding effects. Our findings highlight non-negligible cognitive and affective impairments following TBI, their gravity often increasing with injury severity. Future research should study (A) language, executive and perceptual-motor function (whose evolution post-TBI remains under-explored), (B) the effects of age at and time since injury, and (C) cognitive impairment severity as a function of injury severity. Such

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efforts should aim to develop and standardize batteries for cognitive subdomains—rather than only domains—with high ecological validity. Additionally, they should utilize multivariate techniques like factor analysis and related methods to clarify which cognitive subdomains or components are indeed measured by standardized tests.

Keywords: traumatic brain injury, mild cognitive impairment, neuropsychology, psychometric assessment, neuroimaging, social cognition

INTRODUCTION

Despite inadequate consensus on its definition, traumatic brain injury (TBI) can be described as a clinical condition in which brain function is disrupted due to a traumatic force applied to the head, and whose sequelae can include loss of consciousness (LOC), loss of immediate retrospective and/or prospective memory, mental state changes, and/or focal neurological deficits (American Congress of Rehabilitation Medicine, 1993). By 2013, ∼2.5 million emergency hospital visits in the United States (US) could be attributed to TBI, highlighting this condition as a major public health problem (Taylor et al., 2017). In the United States, TBI is a notable cause of death and disability which predominantly affects vulnerable groups like individuals over the age of 65, children aged 0 to 4, and young adults aged 15 to 24; TBI has higher prevalence in males (Taylor et al., 2017). Patients may experience lower functional independence, greater difficulty in completing their education, more challenges in finding and maintaining gainful employment, and a compromised ability to experience leisure or to maintain meaningful social relationships (Draper and Ponsford, 2008). Depending on injury severity, TBI can be categorized as mild, moderate or severe; 75% to 90% of all cases are typically classified as mild TBI (mTBI), although prevalence is likely higher because many affected individuals do not seek medical care (Prince and Bruhns, 2017).

Recent increases in TBI research breadth, quantity and expenditures by funding agencies highlight the importance of investigating its etiology and neurocognitive sequelae (Prince and Bruhns, 2017). Compared to moderate-to-severe TBI (msTBI), mTBI typically results in fewer and milder adverse consequences, such that its typical victims experience symptom resolution within 3 months (Prince and Bruhns, 2017). However, about 10% to 20% of mTBI patients exhibit long-term post-concussive symptoms (PCSs) marked by connectome disconnection (Irimia et al., 2012, 2014, 2019; Irimia and Van Horn, 2014) as well as by degradation of motor and/or neurocognitive function (Niogi et al., 2008b; Prince and Bruhns, 2017). This percentage may be even higher: according to a comprehensive review of 45 studies, ∼50% of single mTBI patients exhibit long-term mild cognitive impairment (MCI) even after excluding cases which involve litigation or circumstances associated with suspected symptom exaggeration (McInnes et al., 2017).

Common mTBI symptoms include both somatic complaints (headaches, vertigo, sleep problems, nausea, light or sound sensitivity) and affective symptoms (clinical depression, anxiety, irritability and emotional instability) (Prince and Bruhns, 2017). Impaired cognition is typically correlated with poor outcome, even when such impairment is subtle (Niogi et al., 2008b). At all adult ages, mTBI can trigger gradual cognitive decline progressing across the lifespan and frequently affecting attention, processing speed, memory and executive function (EF) (Senathi-Raja et al., 2010; Prince and Bruhns, 2017). Notably, social cognition impairment has been reported up to ∼4 years post-mTBI and up to ∼10 years post-TBI (Ponsford et al., 2013; Theadom et al., 2019) and such impairment is significantly associated with post-concussive quality of life (Jones et al., 2011). Despite these facts, however, impaired social cognition has not been studied comprehensively in TBI samples. For this reason, the first aim of this review is to synthesize recent knowledge on cognitive deficits after mTBI, with emphasis on social cognition impairment.

Adding to the complexity of TBI symptomatology is the fact that heterogeneous brain pathology patterns may arise across a wide variety of injury severities and traumatic mechanisms (e.g., acceleration/deceleration during moving vehicle accidents, direct blunt-force trauma in sports or blast impact during battlefield explosions) (Wu et al., 2016). Notwithstanding injury heterogeneity, the most commonly reported neuroimaging findings after mTBI include cortical thinning in frontal and temporal regions (Draper and Ponsford, 2008; Niogi et al., 2008b; Wu et al., 2016) and traumatic axonal injury (TAI) resulting in additional, widespread white matter (WM) alterations (Irimia and Van Horn, 2013; Sharp et al., 2014). Although studies have attempted to link brain pathology to subsequent cognitive deficits using magnetic resonance imaging (MRI), functional MRI (fMRI) and diffusion MRI (dMRI, including diffusion tensor imaging or DTI), such efforts have not been reviewed sufficiently through the lens of their relevance to the psychometric assessment of mTBI patients. For this reason, the second goal of this review is to discuss such efforts to link neuroimaging to the cognitive assessment of TBI patients. Because this review focuses primarily on psychometrics rather than imaging, the reader is referred to the reviews of (A) Irimia and Van Horn (2015b) for fMRI findings related to post-TBI cognitive deficits, (B) Van Horn et al. (2017) for findings on post-TBI neurometabolic dysfunction, and (C) Irimia et al. (2012, 2014), Goh et al. (2015) for the use of neuroimaging to predict clinical outcome.

Early on, studies used primarily subjective self-reports, and practice shifted only later toward more objective assessment strategies (Draper and Ponsford, 2008). Historically, cognitive tests were utilized primarily to detect brain damage rather than to assess cognitive deficits, which is partly why many tests do not have high ecological validity (Sbordone, 2008). In other words, the assessment of a specific cognitive domain may not capture its deficits adequately because, frequently,

measurement techniques are purposely oversimplified to the extent that their results no longer reflect daily-life deficits within that domain. Furthermore, some cognitive tests may not yet have reached the adequate rigor and standardization required before their interpretation is unambiguous (Sbordone, 2008). Coupled with ongoing psychometric challenges related to the adequate formulation of a comprehensive taxonomy of cognition, this can lead to difficulties with assessment utility, interpretation and comparison across studies (Karr et al., 2013). One example involves verbal fluency association tests, which are commonly used by mTBI researchers to assess the ability to produce as many words which start with a given letter as possible within some timeframe. Currently, the extent to which such tests assess executive function (EF) rather than language remains unclear (Whiteside et al., 2016), although some studies classify such tests as assessments of memory (Mueller et al., 2015). Furthermore, cognitive assessments may often detect deficits within more than one cognitive domain, such that their statistical sensitivity can differ based on which cognitive domains and/or deficits are being assessed (Karr et al., 2013). Thus, methodological and interpretative challenges may arise when researchers use the same test to assess different cognitive domains, or even distinct subdomains within a specific domain. Conversely, difficulties may also ensue when researchers utilize different tests to assess the same cognitive domain. This may be because neuropsychological tests vary greatly in their suitability to measure mTBI-related cognitive deficits even within a single cognitive domain (Draper and Ponsford, 2008; Karr et al., 2013). Alternatively, this could be due to the multifaceted nature of cognition, as the tests in question may, in fact, quantify two different subdomains or abilities within the same cognitive domain (Sachdev et al., 2014). To improve cross-study comparison and to facilitate rigorous, comprehensive meta-analysis of cognitive mTBI research, such inaccuracies must be identified and resolved. In light of the above, the ability to detect cognitive impairments after mTBI is partly reliant upon how such impairments are assessed (Prince and Bruhns, 2017). Because this important methodological aspect has not been investigated sufficiently, the third aim of this review is to summarize and evaluate the use of cognitive tests after mTBI and to provide recommendations on their prudent utilization.

Although mTBI-related cognitive deficits are routinely examined in research studies, the accurate comparison of cognitive assessments *across* studies is an arduous task due to the complexities of cognitive testing and owing to mTBI heterogeneity. For this reason, we here review recent research on cognitive dysfunction after mTBI from the standpoints of psychometric assessment strategies, neural correlates, and important variables like age at injury and the assessment time post-injury. Due to imperfect consensus on the taxonomy of cognitive (sub)domains, this review relies upon the categorizations proposed by the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) to formulate guidelines (Sachdev et al., 2014). Each domain and subdomain is reviewed with a focus on aging adults; pediatric mTBI assessment is beyond our scope. Although we focus on mTBI, important findings on msTBI are also discussed whenever mTBI data are unavailable, or when msTBI findings are particularly illuminating.

DEPRESSION, ANXIETY, AND EFFORT

Individuals with a history of mTBI are at relatively high risk for post-concussive depressive symptoms (PCDSs), for anxiety and for irritability marked by lack of patience, aggression and emotional instability (Arciniegas and Wortzel, 2014; Prince and Bruhns, 2017). Emerging evidence suggests that disturbance of serotonin production in the gastrointestinal tract after TBI may be related to such symptoms (Irimia and Bradshaw, 2003, 2005a,b; Irimia et al., 2015). Whereas emotional and behavioral disturbances are common early after injury, such manifestations are thought to resolve mostly within weeks (Arciniegas and Wortzel, 2014). By contrast, these symptoms can become more limiting after msTBI, as they are often more intense and can persist longer (Arciniegas and Wortzel, 2014). Post-concussive anxiety and PCDSs are the most common emotional disturbances following mTBI, and their magnitude often predicts that of other symptomatology in addition to functional outcome and recovery (Mooney and Speed, 2001; Meares et al., 2008; Levin and Diaz-Arrastia, 2015; Zahniser et al., 2018). Above and beyond affect-related symptoms, studying the poor ability, desire or motivation to invest effort into cognitive tasks after injury is also fundamental because inadequate effort—which has been reported in many TBI samples—can significantly confound psychometric measures (Stulemeijer et al., 2007). Thus, before reviewing findings pertaining to cognition, we discuss affect and effort.

PCDSs

PCDSs have been noted both acutely (for both complicated and uncomplicated mTBI) and up to ∼1 year after mTBI (regardless of complications), with improvements over time (Panayiotou et al., 2010; Ponsford et al., 2011; Lucas et al., 2016). PCDS prevalence after injury has been reported to range from ∼10% to ∼77% across all injury severities (∼14% to ∼53% for post-traumatic major depressive disorder) and from ∼15% to ∼35% after mTBI in particular. Most PCDSs occur in the 1st year after injury, although risk can remain elevated for many years (Rapoport et al., 2003; Silver et al., 2009; Bombardier et al., 2010). Such risk can be influenced by (A) pre-existing conditions (e.g., substance abuse, mental/personality disorders), (B) injury mechanism (e.g., sports injury, vehicle accidents), (C) TBI anatomic profile (e.g., frontotemporal, fronto-occipital), (D) neurochemical imbalances, (e.g., disruption of serotonergic neurotransmission, excessive glutamatergic signaling), (E) injury-related comorbidities, including other PCSs and (F) socioeconomic factors (e.g., level of social support during recovery) (Silver et al., 2009). PCDSs are associated with increases in the number and severities of other self-reported symptoms in TBI patients, surpassing those reported by non-concussed, clinically depressed outpatient groups (Silver et al., 2009; Lange et al., 2011). Partly for this reason, PCDSs can promote a vicious cycle in which increased

aggression, cognitive dysfunction and suicidal thoughts lead to a perception of lower life quality, which in turn exacerbates PCDSs. Typically, mTBI patients with PCDSs are significantly older than those who lack them; this is consistent with the hypothesis that advanced age is a PCDS risk factor (Levin et al., 2005; Rao et al., 2010). PCDSs may be responsible for—or contribute to—cognitive dysfunction after TBI. For example, Himanen et al. (2009) compared the cognitive performances of TBI participants with or without a clinical depression diagnosis and suggested that, whereas complex attention deficits are frequently linked to TBI, depression may be responsible for some deficits of psychomotor speed and sustained attention.

Neuroimaging correlates of PCDSs often involve frontal brain regions; for example, a computed tomography (CT) lesion study found that frontal subdural lesions in mTBI are significantly associated with chronic PCDSs (Rao et al., 2010). Upon analyzing the resting-state (rs) fMRI signals of sub-acute mTBI participants, Zhou et al. (2012) found that stronger functional correlations (FCs) between regions within medial prefrontal cortex (mPFC) were significantly and inversely associated with self-reported PCDS ratings. dMRI studies have found that mTBI-related WM damage in medial and subcortical frontal regions—including the corpus callosum, corona radiata, superior longitudinal fasciculus, anterior cingulum, corticostriatal and thalamo-frontal projections—can be associated with PCDSs, including lack of interest, lethargy, low drive and lack of initiative (Matthews et al., 2011; Zappalà et al., 2012).

Anxiety

Post-traumatic anxiety has been documented acutely, up to ∼6 months after uncomplicated mTBI and up to ∼5.5 years after TBI of greater severity (Dischinger et al., 2009; Meares et al., 2011; Van Der Naalt et al., 2017). As in the case of PCDSs, anxiety symptoms are relatively frequent in the 1st year after TBI (∼19% to ∼70% prevalence) and typically include generalized anxiety disorder (GAD) and post-traumatic stress disorder (PTSD), both of which are usually characterized by poor clinical resolution (Whelan-Goodinson et al., 2009; Gould et al., 2011). Nevertheless, anxiety symptoms may also improve over time; for example, Ponsford et al. (2011) found that mTBI and trauma control groups exhibited substantial symptom reductions within ∼3 months post-injury. Like in the general population, anxiety symptoms are often comorbid with those of depression, which may compound each other's negative effects upon recovery (Gould et al., 2011). In a group of msTBI patients, prior history of anxiety disorders increased post-traumatic anxiety risk by a factor of 9.47, with every additional post-injury month increasing this risk by 11% (Gould et al., 2011). One year post-mTBI, greater anxiety was found to be significantly and inversely correlated with WM volume changes in the isthmus of the left cingulate gyrus, supporting previous associations between frontal WM loss and anxiety after TBI (Zhou et al., 2013). However, no correlation has been found between anxiety after mTBI and fMRI measures (Shumskaya et al., 2012; Tang et al., 2012; Zhan et al., 2015).

Effort

In the context of neuropsychological testing, effort can be defined as the amount of energy invested (sub)consciously into completing neuropsychological assessment tasks. Some patients with a history of mTBI have been found to exaggerate their reports of injury severity and of subsequent cognitive impairment compared to patients with a history of msTBI (Prince and Bruhns, 2017). In fact, effort may affect mTBI patients' neurocognitive test performances more than injury severity (West et al., 2011). Patients who perform poorly on symptom validity tests (which can be suggestive of poor effort) often report relatively more serious injury-related sequelae and perform worse on cognitive tests across all domains compared to good-effort performers (Stulemeijer et al., 2007; Prince and Bruhns, 2017). Litigation status has not been associated with poor effort after mTBI, although patients in litigation frequently report worse or diminishing cognitive function compared to non-litigants (Belanger et al., 2005; Stulemeijer et al., 2007).

Although the cause of poor effort during post-mTBI cognitive assessments remains unclear, Prince and Bruhns (2017) have summarized evidence indicating that this phenomenon may be partially due to a dysfunctional feedback loop in which affective, somatic and cognitive symptoms interact to prolong the subjective perception of symptom severity, even when the primary cause of the symptoms has been resolved. For example, in the study of Silverberg et al. (2017), mTBI patients fearing mental exertion due to the expectation of a subsequent headache scored worse on memory performance tests than those without such a fear. Consistent with the dysfunctional feedback loop hypothesis, Van Der Horn et al. (2015) suggested that, because mPFC is involved prominently in emotional regulation, default mode network (DMN) hyperactivity and associated mPFC dysfunction are very likely linked to PCS persistence after mTBI. Supporting this notion, the positron emission tomography (PET) study of Spadoni et al. (2015) found that chronic mTBI participants who had invested relatively little effort into their psychometric assessment tasks exhibited significantly lower glucose metabolism in ventromedial PFC compared to participants investing an adequate amount of effort. Furthermore, affective factors can be better PCS predictors than neuropsychological test measures; thus, such symptoms are likely more intimately linked to mTBI-related psychological disturbances rather than to genuine neurobiological changes, as detailed by Clarke et al. (2012). However, in these authors' study, neuropsychological test performance predicted cognitive complaint severity in the mTBI—but not in the control—group; this suggests the existence of genuine—albeit subtle—PCS-related cognitive deficits which do not have a strictly psychological substrate. A second explanation involves the "good old days" bias, according to which patients are more likely to perceive their pre-injury state as better than it truly was. Supporting this theory, Lange et al. (2010) found that chronic mTBI participants retrospectively report a significantly lower intensity and number of pre-injury symptoms compared to healthy controls (HCs). This effect is present in both litigating and non-litigating mTBI participants and is not affected by age at injury or by educational attainment. Although additional

research on post-traumatic malingering is needed, most evidence reviewed here suggests that it is unlikely to be premeditated. In conclusion, PCDSs, anxiety and poor effort are important factors to consider when assessing cognitive function in mTBI, as each of these (A) has a relatively high post-concussive prevalence and (B) can have considerable effects upon psychometric performance.

SOCIAL COGNITION

Post-concussive difficulties in communication and in the maintenance of social relationships have been documented both acutely and up to ∼10 years post-injury, with the prevalence of such manifestations increasing over time (Ponsford et al., 2013). In one study, ∼10 years post-injury, ∼30% of msTBI patients reported problems with personal relationships, including friend loss and isolation (Knox and Douglas, 2009; Ponsford et al., 2013). Notably, social dysfunction symptoms are typically far more prevalent and severe after msTBI rather than mTBI, which may be why many researchers either do not stratify samples based on severity or instead choose not to study mTBI participants (Arciniegas and Wortzel, 2014). Improving our understanding of social dysfunction after TBI is important because social difficulties can impact post-concussive quality of life significantly (Jones et al., 2011; Spikman et al., 2013; Proctor and Best, 2019). The positive impact of research-informed strategies for the education and social support of TBI patients is highlighted by the finding that more severe head injuries can in fact lead to significantly better functional outcomes if patients report healthy social relationships and a strong sense of personal identity (Jones et al., 2011). Although many factors can contribute to post-concussive social dysfunction (i.e., social challenges related to emotion recognition, perspective-taking or altered self-awareness), its mechanisms remain unclear (Milders et al., 2008; Babbage et al., 2011; Arciniegas and Wortzel, 2014). However, they seem to be independent of—and not likely caused by—other cognitive deficits (Spikman et al., 2011).

Emotion Recognition

Deficits of facial emotion recognition are frequent after TBI and have been associated with poorer social functioning outcomes (Knox and Douglas, 2009; Babbage et al., 2011). Such deficits have been recorded both acutely and up to ∼5 years post-injury, mostly in msTBI samples (Babbage et al., 2011; Spikman et al., 2011). One meta-analysis found that 13% to 39% of individuals with msTBI have significant deficits of emotion recognition, performing approximately over one standard deviation below HC participants' mean scores on measures of facial affect recognition (Babbage et al., 2011). Furthermore, emotion recognition impairments after mTBI have been recorded using several stimulus types (i.e., recognition, matching, labeling, discrimination) and appear to be persistent (Ietswaart et al., 2008; Knox and Douglas, 2009; Babbage et al., 2011). Like HCs, individuals with TBI often exhibit greater impairment, both acutely and chronically, in the recognition of negative—rather than positive—emotions, which reflects a normal response to task difficulty (Ietswaart et al., 2008). Although emotion recognition may be impacted by mTBI, there are few studies to confirm this finding (Babbage et al., 2011) and measurable effects might be confounded by PCDSs (Bourke et al., 2010). The mechanism whereby impaired emotion recognition results in poorer post-TBI social functioning is unclear; nevertheless, the former has been suggested to lead to poorer comprehension of oral communication, resulting in inability to evaluate the appropriateness of one's social behavior and in unsuitable social responses (Knox and Douglas, 2009). One potential cause for emotion recognition challenges after TBI is alexithymia, i.e., the inability to identify and describe emotions in oneself and/or others (Williams and Wood, 2010). The high post-traumatic prevalence and severity of this condition have been linked to relatively lower emotional empathy in chronic TBI, leading to further social challenges (Williams and Wood, 2010).

Poor emotion recognition after chronic msTBI is significantly associated with damage to orbitofrontal cortex (Spikman et al., 2011) which is expected given this region's involvement in social cognition. In a TBI sample of mixed severity imaged ∼9 years post-injury, Neumann et al. (2016) uncovered a significant inverse relationship between emotion recognition impairment and task-related fMRI activation of the right fusiform gyrus, which is involved in facial recognition and visual perception. Poor emotion recognition about 10 years after msTBI is also significantly related to reduced WM integrity in the inferior longitudinal and fronto-occipital fasciculi, and with reduced gray matter (GM) volume in the lingual and parahippocampal gyri (Genova et al., 2015). These findings are not surprising given that these structures are involved in high-level social interaction, memory retrieval and visual (particularly facial) processing (Natu and O'Toole, 2011; Sarubbo et al., 2013; Catani and Bambini, 2014).

Theory of Mind

Theory of mind (ToM) deficits after TBI have been recorded both acutely and up to ∼3 years post-injury (Milders et al., 2008; Spikman et al., 2011). Such impairments have been demonstrated using both verbal and non-verbal measures, and appear to be persistent throughout the 1st year post-injury (Milders et al., 2008). ToM impairments after TBI include difficulties with (A) understanding and explaining the feelings and intentions of others, (B) correctly identifying non-faux pas scenarios (while over-reporting faux-pas scenarios due to uncertainty), (C) understanding indirect speech (including humor and sarcasm, regardless of type) and (D) inhibiting self-referential thoughts when considering another person's perspective (Channon et al., 2005; Milders et al., 2006; Martín-Rodríguez and León-Carrión, 2010; McDonald et al., 2014). Interestingly, in a group of mixed-severity TBI patients, Milders et al. (2006) found that injury severity did not affect ToM performance or its course over time, although further evidence is needed. Because ToM tasks often require adequate EF and language abilities, ToM-related impairments may stem from TBI-related executive and/or speech dysfunction, and particularly from deficits of cognitive flexibility, inhibition, phonemic fluency or working memory, which are all significantly and positively correlated with ToM impairments in both acute and chronic TBI (Henry et al., 2006;

Milders et al., 2008; McDonald et al., 2014; Honan et al., 2015). Nevertheless, it is likely that some post-TBI ToM deficits are independent of other cognitive impairments, given TBI patients' poor performance on non-verbal ToM tests and on ToM tests with low EF demands (Havet-Thomassin et al., 2006; Milders et al., 2008; Geraci et al., 2010; Martín-Rodríguez and León-Carrión, 2010; McDonald et al., 2014; Bosco et al., 2017). For example, McDonald et al. (2014) studied chronic TBI patients' performance on a ToM test requiring varying levels of both EF (i.e., low EF, high inhibition, high flexibility) and ToM engagement (low-ToM engagement, high-ToM engagement). The authors found that variability of participants' performance on the low-ToM engagement task made a unique contribution to the variance of their performance on the high-ToM engagement task for conditions requiring low EF and high flexibility (but not high inhibition). The conclusion of the study was that EF and ToM may contribute independently to ToM performance after TBI in some cases, such as when high inhibition is needed.

Frontal lobe damage has been repeatedly tied to poor post-TBI performance on faux pas tests, which are commonly used to assess ToM (Martín-Rodríguez and León-Carrión, 2010). While mixed-severity chronic TBI groups with (A) ventromedial and (B) dorsolateral PFC damage performed equally poorly on the Reading the Mind in the Eyes (RME) Test (commonly used to assess social perception and ToM), only participants with localized damage to ventromedial PFC performed poorly on the faux pas test (Geraci et al., 2010). Additionally, poor performance on the RME test in chronic penetrating TBI was significantly associated with damage to the left inferior frontal gyrus (Dal Monte et al., 2014). Thus, although further research is needed to ascertain the neuroimaging correlates of ToM impairment after TBI, it comes as no surprise that frontal lobe damage is critically involved in such deficits. More studies are required to characterize the extent and neural correlates of ToM dysfunction in mTBI patients.

Self-Awareness

As in the case of ToM and emotion recognition, self-awareness (SA) deficits have been found mostly after msTBI rather than after mTBI (Bar-Haim et al., 2009; Arciniegas and Wortzel, 2014; Gaines et al., 2016). SA deficit prevalence after mixed-severity TBI has been estimated to range from 45 to 97%, with higher prevalence being weakly linked to greater injury severity (Sherer et al., 1998; Bach and David, 2006). These deficits have been recorded after mixed-severity TBI acutely up to ∼1 year after injury (including after both complicated and uncomplicated mTBI) and up to ∼5 years after msTBI only (Sherer et al., 2003; Hart et al., 2009; Kelley et al., 2014). Longitudinal studies have consistently reported SA improvements between the acute and chronic stages of TBI, particularly after severe TBI (Hart et al., 2009; Ponsford et al., 2013). In a sample of mixed-severity acute TBI patients, older age and better functional independence were both significantly associated with improved SA ratings (Sherer et al., 2003). Notably, higher SA was found to be significantly correlated with increased self-esteem, with lower depression ratings and with improved employability, thus illustrating the clinical importance of SA recovery (Sherer et al., 1998, 2003; Carroll and Coetzer, 2011).

SA deficits can differ across injury severities (Arciniegas and Wortzel, 2014). In one study, for example, patients with msTBI report irritability levels closer to those of HCs, whereas their caregivers reported that patients exhibited considerably higher levels (Arciniegas and Wortzel, 2014). On the other hand, mTBI participants' self-reported irritability levels were similar to those reported by the msTBI participants' caregivers (Arciniegas and Wortzel, 2014). Thus, whereas some mTBI patients' altered SA may lead them to exaggerate the magnitude of their symptoms, the SA of many individuals with msTBI may be altered to underestimate symptoms (Sherer et al., 2003; Arciniegas and Wortzel, 2014). SA impairments may also differ based upon the nature of the specific deficits involved and upon the phrasing of questions asked during assessment (Sherer et al., 2003). For example, greater TBI-related SA challenges are usually noted in reports of cognitive and behavioral impairments (rather than in reports of physical deficits) and, furthermore, in response to general questions rather than to specific ones (Sherer et al., 2003). It has been suggested that SA deficits can be connected to inadequate ToM after TBI. Specifically, Bivona et al. (2014) found that poor SA in severe chronic TBI patients is linked to worse performance on the Faux Pas Test and on the First Order False Belief Test, compared to HCs and to TBIs with better SA. A significant positive association between SA and emotion recognition in chronic msTBI has also been proposed (Spikman et al., 2013); thus, deficits in abilities which are integral to optimal social functioning may be substantially comorbid after injury.

Using fMRI, Schmitz et al. (2006) found that participants with chronic TBIs of mixed severities and with poor SA exhibited greater bilateral activation of anterior cingulate cortex (ACC), of the precuneus and of the right temporal pole during a self-appraisal task. Better SA was linked to greater task-related activation of the right anterior dorsal PFC. These findings are not surprising given previous associations between these structures, on the one hand, and interoceptive/emotional awareness, self-reflection and consciousness on the other hand (Critchley et al., 2004; Schmitz et al., 2004; Cavanna, 2007; Legrand and Ruby, 2009). Because only one neuroimaging study on the correlates of SA with TBI could be located, further research on this topic should be undertaken.

COMPLEX ATTENTION

Deficits of complex attention are among the most commonly reported consequences of TBI (McInnes et al., 2017). According to the DSM-5, complex attention includes the subdomains of sustained, divided and selective attention in addition to processing speed, which is frequently assessed as a stand-alone ability (Sachdev et al., 2014). Deficits within the overall domain of attention have been noted in both the acute and chronic stages of mTBI, although conflicting results have been reported. Specifically, some research studies and meta-analyses found significant attention deficits as late as ∼6 years post-mTBI

(∼10 years after msTBI) whereas others reported no such deficits ∼3 months post-injury (Draper and Ponsford, 2008; Konrad et al., 2011; Rohling et al., 2011; McInnes et al., 2017). These conflicting results may be partly explained by the fact that most studies reviewed here fail to distinguish between complicated and uncomplicated mTBI. This often leads to study results and conclusions being based on samples with both complicated and uncomplicated mTBI. For example, the study which concluded that post-concussive cognitive deficits dissipate within 3 months post-injury was one of the few studies which included only patients with uncomplicated mTBI; this suggests the possibility of better cognitive recovery for uncomplicated—as opposed to complicated—mTBI (Rohling et al., 2011). Furthermore, although it is frequently assumed that cognitive deficits—including attentional dysfunction—diminish with time (McInnes et al., 2017), this phenomenon is insufficiently understood and its presentation may depend on factors like age at injury (Prince and Bruhns, 2017). One study by Senathi-Raja et al. (2010) which did not account for injury severities and in which participants were tested ∼10 to ∼12 years post-injury suggested that, in young TBI participants (16–34 years), longer time since injury is linked to better attention performance. In middle-aged TBI participants (35–54 years), no relationship was found between time since injury and attention; in older TBI participants (55 years or older), longer time since injury was linked to poorer attention performance. Thus, recovery from attention deficits likely depends on both age at injury and on the time after injury when attention is assessed, and future research should account for these variables (Halgren et al., 2011). In their study, Senathi-Raja et al. also found that, relative to age-matched HCs, older individuals who had suffered a TBI of any severity exhibited a significantly wider attention performance gap compared to that of persons who had been injured at a younger age. More research should be undertaken to clarify how age at injury affects attention after mTBI.

In a group of middle-aged mTBI patients imaged ∼5 years after injury using structural MRI, poorer performance on attention tasks was found to be associated with reductions in both WM—in cingulate, parietal and occipital cortices—and GM, in temporal cortex (Little et al., 2014). One fMRI study of chronic mTBI reported increased ACC activation and decreased PFC activation during attention tasks (Dean et al., 2015). Upon using fMRI to measure rs-FCs after msTBI, Shumskaya et al. (2017) found that patients exhibited poorer attention and stronger FCs involving the sensorimotor network compared to HCs. A significant positive correlation between attention and rs-FCs in this network was found in the TBI group, whereas the HC group exhibited a significant negative FC between these measures. Using dMRI, one study which did not stratify participants based on injury severity found that, compared to HCs, TBI participants exhibited a significant negative correlation between the number of low-integrity WM fasciculi and overall attention performance (Kraus et al., 2007). Future studies should aim to examine how structural brain circuitry differs in mTBI patients as a function of their performance on attention tasks.

Sustained Attention

mTBI patients can exhibit deficits of sustained attention both acutely and up to ∼2 years post-injury (Chan, 2005; Kwok et al., 2008; Pontifex et al., 2012; Azouvi et al., 2017). In these studies, no distinction was made between complicated and uncomplicated mTBI, with the exception of the study by Kwok et al. Measures of TBI severity—like the Glasgow Coma Score (GCS), LOC duration and the extent of post-traumatic amnesia (PTA)—have been found to be significantly correlated with poorer sustained attention (Chan, 2005). Notably, whereas other types of attention improve over 3 months following mTBI, sustained attention remains relatively poor, as shown by a study of complicated mTBI (Kwok et al., 2008). MRI findings suggest that, ∼1 month post-injury, mTBI patients' deficits of sustained attention are associated with cortical volume loss in the right ventral ACC (Zhou et al., 2013). Upon combining dMRI with fMRI, Bonnelle et al. (2011) found that sustained attention impairments observed ∼2 years post-injury were associated with increased task-related DMN activation involving the precuneus and posterior cingulate cortex (PCC), which is suggestive of inefficient information processing during sustained attention. DMN disconnection extent—particularly involving the precuneus—was related to TBI participants' performance, with broader disconnection linked to poorer sustained attention.

Divided Attention

Divided attention impairment after mTBI has been recorded up to ∼4 years post-injury, typically with improvement over time (Mangels et al., 2002; Kwok et al., 2008; Paré et al., 2009). The only study which distinguished between complicated and uncomplicated mTBI was that of Kwok et al. Older studies are more likely to report conflicting results as to whether or not divided attention is impaired by mTBI, owing to confounds like (A) different cognitive loads imposed by different tests, (B) failure to account for time since injury and (C) failure to control for processing speed deficits (Paré et al., 2009). For example, evidence for TBI-related deficits of divided attention has most frequently been found using relatively complex tasks requiring high cognitive loads, and when assessing cognitive control rather than speed (Beaulieu-Bonneau et al., 2017). Divided attention deficits may underlie impairments of memory consolidation and recognition: in one study, both mild and severe TBI patients performed poorly on tests of divided attention and their performance was associated with their episodic memory performance, although this relationship was only significant for the severe TBI group (Mangels et al., 2002). By comparing mTBI patients' acute MRI scans to those obtained ∼1 year post-injury, Dall'acqua et al. (2017b) found that participants with relatively poor clinical outcome exhibited a significant relationship between greater PFC thickness and poorer divided attention (cortical thickening possibly being due to neuroinflammation). In an fMRI study of mTBI patients imaged both acutely and ∼1 year post-injury (Dall'acqua et al., 2017a), researchers found that, compared to HCs, the mTBI group exhibited task-related DMN hypoactivity (bilaterally: ACC, PCC, precuneus, Heschl's gyrus, superior temporal gyrus and temporal pole; right hemisphere:

parahippocampal gyrus, amygdala, and supplementary motor area); rs-FC strength was significantly and negatively correlated with performance on a divided attention task.

Selective Attention

After mTBI, selective attention can be impaired both acutely and up to 7–8 months post-injury, with reported improvements over time (Ziino and Ponsford, 2006; Dall'acqua et al., 2017b). These studies did not distinguish between complicated and uncomplicated mTBI. There are contradictory findings on mTBI effects upon selective attention, possibly due to differing neuropsychological testing methodologies (Beaulieu-Bonneau et al., 2017). For example, upon examining selective attention ∼8 months post-injury, Ziino and Ponsford (2006) found impairments of selective attention during relatively complex tasks even after controlling for PCDSs and anxiety. By contrast, participants' impairment on relatively simpler selective attention tasks was explained by comorbid depression, anxiety and fatigue. This illustrates the importance of accounting for affective factors when quantifying attention performance after mTBI. Selective attention performance after mTBI may be influenced by additional factors; for example, it is uncertain whether LOC after mTBI is related to changes in selective attention. Whereas some studies indicate that mTBI patients with acute LOC perform worse on tests of selective attention, others do not (Carroll et al., 2014; De Freitas et al., 2019). One meta-analysis suggests that TBI-related deficits in selective attention on certain tasks, such as on the widely used Stroop interference task, may be largely due to the downstream effect of slower processing speed, which is frequently reported after TBI (Ben-David et al., 2011). However, it is still unclear whether this downstream effect occurs during other common selective attention tasks.

An MRI study of mTBI participants with good outcomes ∼1 year post-injury found subtle cortical PFC thickening—which may be due to chronic neuroinflammation—linked to improvements in selective attention (Dall'acqua et al., 2017a). In an fMRI study, Mayer et al. (2012) suggests that mTBI patients' DMNs are intimately involved in modulating selective attention performance; for example, unlike HCs, mTBI participants failed to deactivate their DMNs in response to selective attention tasks at high cognitive load. Also unlike HCs, mTBI participants failed to exhibit typical attention-related modulations in their neuronal responses during a selective attention task. In a group of mTBI adults imaged approximately ∼1 month after injury, Smits et al. (2009) found increased blood oxygenation level-dependent (BOLD) signals in the ventrolateral PFC, posterior parietal lobe and cingulate gyrus during a selective attention task; in this sample, relative BOLD signal strength and PCS severity were correlated. More than a month after mTBI, Niogi et al. (2008a) found that selective attention was significantly correlated with dMRI-measured WM integrity in the left anterior corona radiata, and that the integrity of WM innervating these regions was significantly reduced in mTBI participants compared to HCs.

Processing Speed

Impaired processing speed is perhaps the most frequently reported cognitive deficit after mTBI. It has been reported acutely, up to ∼6 years after mTBI and up to ∼10 years after TBIs of mixed severity (Mathias et al., 2004; Draper and Ponsford, 2008; Konrad et al., 2011; Dean and Sterr, 2013). These studies did not distinguish between complicated and uncomplicated mTBI. The phenomenon is strongly associated with self-reported fatigue, which is also very common after TBI (Johansson et al., 2009; Ponsford et al., 2013). Johansson et al. (2009) found that the severity of TBI participants' reported fatigue was not related to injury severity, to their age at injury or to the time after injury when assessments were made, and that the latter factor did not have any significant effect on processing speed. By contrast, in a study of mixed-severity TBIs, Senathi-Raja et al. (2010) concluded that, for young participants, longer time since injury was associated with improved processing speed. For middle-aged participants, there was no relationship between the two variables, whereas for older participants remoter injuries were associated with slower processing speed. These apparent differences in results can be reconciled if one takes into account that the sample of Johansson et al. (2009) consisted entirely of middle-aged participants based on the age range criteria of Senathi-Raja et al. In addition, the latter authors found that older age at injury was associated with slower processing speed, although further research is needed for confirmation. Thus, although some evidence suggests that time since and age at injury can be strong modulators of processing speed improvements, further research is needed to clarify their relationship to processing speed after mTBI. Because processing speed influences nearly all cognitive responses to task stimuli and is assessed by a wide variety of neuropsychological tests, poor processing speed often has a downstream effect upon many other cognitive metrics (Beaulieu-Bonneau et al., 2017). Some researchers even assert that processing speed deficits may underlie nearly all observed TBI-related attention deficits, although others maintain that attention deficits are present after mTBI regardless of processing speed impairments (Beaulieu-Bonneau et al., 2017).

Using MRI, Cole et al. (2018) found that processing speed impairment was significantly and positively correlated with the difference between chronological and biological brain age, thus relating greater atrophy to slower processing speed. Using fMRI, Palacios et al. (2017) found that, after acute mTBI, both processing speed and overall attention were significantly and positively correlated with rs-FC in the DMN, in the salience network and in the dorsal attention network. The association of processing speed with such widespread neuroimaging alterations is not surprising given the importance of this fundamental parameter to most other cognitive processes. A dMRI study by Niogi et al. (2008b) found that processing speed—as measured by reaction time—was positively correlated with WM damage in the anterior corona radiata (41% of patients), uncinate fasciculus (29%), genu of the corpus callosum (21%), inferior longitudinal fasciculus (21%), and cingulum bundle (18%). Thus, although further research is needed, it appears that fronto-temporal WM connections may play an important role in the decline and recovery of processing speed performance after mTBI.

LEARNING AND MEMORY

Along with attention impairments, deficits of learning and memory (L&M) are among the most commonly reported symptoms of TBI (McInnes et al., 2017). According to the DSM-5, the L&M cognitive domain includes both declarative L&M (i.e., free/cued recall, recognition memory, and semantic/autobiographical long-term memory) and non-declarative L&M, i.e., implicit learning (Sachdev et al., 2014). Overall L&M deficits have been recorded acutely after both complicated and uncomplicated mTBI, including up to ∼6 years following mTBI, and up to ∼10 years after TBIs of mixed severity in studies where the distinction between complicated and uncomplicated mTBI was not made (Draper and Ponsford, 2008; Stulemeijer et al., 2010; Konrad et al., 2011; McInnes et al., 2017). Acute mTBI patients' performance on L&M psychometric assessments is typically negatively correlated with injury severity (Stulemeijer et al., 2010). Nevertheless, L&M have not always been reported to worsen after injury, potentially due to biological factors (e.g., age at injury, time since injury) and/or methodological confounds across studies (Konrad et al., 2011; Rohling et al., 2011). One study examining TBIs of all severities found that older age at injury was associated with poorer L&M ∼30 years post-injury (Himanen et al., 2006). Interestingly, some mTBI-related deficits of overall memory may be due to the downstream effects of impaired EF or attention upon information encoding and retrieval (Prince and Bruhns, 2017). For example, Mangels et al. (2002) found that chronic mTBI patients exhibited memory recall impairments only when their memory encoding involved divided rather than focused attention (the latter being less demanding). Importantly, the manifestations of TBI-related L&M deficits are typically different from those observed in amnestic disorders like Alzheimer's disease (AD) (Rabinowitz and Levin, 2014). Whereas amnestic disorders are prominently associated with memory storage deficits, TBI more often features dysfunctional memory encoding mechanisms, whose deficits impact memory retrieval (Rabinowitz and Levin, 2014). For example, individuals with TBI may recall information improperly or may associate unrelated pieces of information together.

The MRI study of Little et al. (2014) linked poor overall memory performance ∼5 years post-injury to tissue volume reductions in the parahippocampal gyri, anterior temporal lobes and internal capsule. Using fMRI, Ge et al. (2009) found that, ∼2 years post-injury, the thalami of mTBI participants exhibited task-related cerebral blood flow (CBF) which was significantly weaker than in HCs, and that CBF decreases were significantly and negatively correlated with volunteers' overall memory performance. Utilizing dMRI, Niogi et al. (2008a) studied mTBI participants about ∼1.3 years post-injury and found that their overall memory performance was significantly and positively correlated with the integrity of the uncinate fasciculus. Finally, ∼2 years post-injury, the overall memory performances of individuals with TBIs of mixed severity as well as of HC volunteers were found to be associated with WM damage in the fornices (Kinnunen et al., 2010). Although the specificity of these neuroimaging correlates is constrained by the neuropsychological tests utilized to assess overall memory in each study, the involvement of the thalamus, of the anterior and medial temporal lobes and of their connections is not surprising, given the established association between these neuroanatomic structures and memory processing (Simmons and Martin, 2009; Burgmans et al., 2011; De Zubicaray et al., 2011; Leszczynski and Staudigl, 2016).

Free and Cued Recall

Free and cued recall are concepts used by neuropsychologists to assess (non-) verbal memory, episodic (autobiographical) memory, semantic memory, etc. Due to the wide usage of these paradigms in memory research, one can draw from many of the findings on overall L&M performance after mTBI discussed above to understand free and cued recall. Among mTBI patients, impairments of free and cued episodic memory recall have been found both acutely (for both complicated and uncomplicated mTBI) and up to ∼6 years post-injury (where no distinction between complicated and uncompliated mTBI was made) (Konrad et al., 2011; McCauley et al., 2013). However, cued recall is typically less impaired than free recall; this appears to support the hypothesis that mTBI is not associated with a true dysfunction of memory storage, but rather with dysfunctional encoding mechanisms which impact retrieval (Konrad et al., 2011). The performance of mTBI patients on free and cued recall tasks has been found to improve after a period ranging from 1 month to 1 year post-injury (Dikmen et al., 2016).

Recognition Memory

No impairments in recognition memory have been reported either after acute TBI or up to ∼6 years post injury in studies which did not distinguish between complicated and uncomplicated mTBI (Mathias et al., 2004; Konrad et al., 2011). Nolin (2006) confirmed mTBI-related impairments in both free and cued recall, but not in recognition memory; once again, these findings support the hypothesis that mTBI can lead to deficits of memory encoding and retrieval, rather than to genuine deficits of memory storage. Notably, some studies use the terms *cued recall* and *recognition* interchangeably, leading to difficulties in identifying research findings on these similar—albeit non-synonymous—concepts (Nolin, 2006; Konrad et al., 2011). Thus, when examining the TBI literature on recognition memory and on cued recall, great caution should be exerted in ascertaining differences in nomenclature across studies. Further research is required to ascertain whether mTBI affects recognition memory.

Semantic and Autobiographical (Episodic) Memory

Impairments of episodic and semantic memory after mTBI have been noted both acutely (for complicated and uncomplicated mTBI) and up to ∼6 years post-injury for studies where the distinction between complicated and uncomplicated mTBI was not drawn (Stulemeijer et al., 2010; Konrad et al., 2011). Whereas auditory verbal episodic memory (Halgren et al., 2011) typically improves in individuals with mTBI within a year post-injury, the performance of individuals with complicated mTBI (including individuals with positive findings on CT and/or MRI scans) typically worsens within this time interval (Tayim et al., 2016). In a sample of mixed

TBI severities, semantic memory improved over 30 years, with younger age at injury being associated with greater improvement (Himanen et al., 2006). Furthermore, semantic memory may be less impaired in younger patients with a remote mTBI than episodic memory is (Wammes et al., 2017). Unsurprisingly, upon utilizing MRI to study an mTBI cohort ∼30 years post-injury, Himanen et al. (2005) found that poorer episodic memory performance was significantly associated with bilateral volumetric reductions in the hippocampus and with lateral ventricle volume increases. Finally, one dMRI study of adolescents with mTBI found a significant association between reduced WM integrity of the left cingulum bundle and poorer episodic memory performance (Wu et al., 2009). The involvement of the cingulum bundle here is to be expected, given that this structure has been linked to episodic memory performance and to the integration of certain visceral and affective processes which may aid episodic memory consolidation (Lockhart et al., 2012; Bubb et al., 2018).

Implicit Learning

This review identified very few studies assessing implicit learning after TBI. Three such studies found no impairment of either immediate or delayed implicit learning after closed head TBI, suggesting that this L&M subdomain can remain intact or little affected post-injury (McDowall and Martin, 1996; Schmitter-Edgecombe, 1996; Shum et al., 1996). Because the distinction between complicated and uncomplicated mTBI was not drawn in these investigations, insights on this distinction are not offered by these studies. However, one study involving (A) two tasks measuring non-declarative/implicit memory (i.e., a perceptual priming task and a conceptual priming task) and (B) one declarative memory task found that TBI participants exhibited impairment only during the declarative and conceptual priming tasks (Vakil and Sigal, 1997). This study's results suggest that perceptual priming may be spared after TBI and emphasize that assessment methodology is critical for the accurate evaluation of implicit memory. When learning new skills, TBI participants exhibited implicit memory impairment during conceptual tasks which typically activate the frontal lobe (e.g., the serial reaction time task and the Tower of Hanoi puzzle task). By contrast, mTBI participants showed no impairment during tasks involving only relatively modest frontal lobe recruitment (e.g., search-detection tasks), although they did have slower response times than HCs (Vakil, 2005; Vakil and Lev-Ran Galon, 2014). Further research is needed to integrate neuroimaging with the assessment of implicit learning after mTBI and to establish whether neuroimaging measures can clarify the precise conditions under which implicit learning can be spared by injury.

EXECUTIVE FUNCTION

According to the DSM-5, the cognitive domain of EF includes the subdomains of planning, decision-making, working memory, feedback response, inhibition and flexibility (Sachdev et al., 2014). Impairments of overall EF performance have been recorded acutely, up to ∼6 years post-injury after mTBI and up to ∼10 years after TBI of mixed severity, no distinction between complicated and uncomplicated mTBI being drawn (Draper and Ponsford, 2008; Konrad et al., 2011; Rabinowitz and Levin, 2014; McInnes et al., 2017). After mTBI, overall EF was found to improve within the first ∼6 months post-injury (Kwok et al., 2008; Veeramuthu et al., 2015). Schiehser et al. (2011) found that, in mild-to-moderate TBI, the best predictors of overall EF performance were self-reported PCDSs, even after controlling for participants' effort on tasks. Thus, PCDSs—whether self-reported or independently assessed—should be accounted for when assessing EF after mTBI. Nathan et al. (2012) found that a history of mTBI was associated with abnormal rs-FC of the right thalamus, whereas overall EF was significantly associated with the rs-FC of the left thalamus. Some studies utilizing dMRI (Lipton et al., 2009; Zappalà et al., 2012) indicate that TBI-related EF deficits—including deficits of working memory, reasoning, set-shifting, linguistic and visuospatial abilities—are tied to damage along the association and projective connections of dorsolateral PFC. Sorg et al. (2014) found that mTBI participants who exhibited chronic EF deficits also demonstrated significant reductions in the integrity of WM linking PFC to the rest of the brain, of the corpus callosum and of the cingulum bundle. Such changes were more common in mTBI participants who had experienced LOC at the time of injury. EF is frequently affected in TBI patients who go on to develop post-traumatic epilepsy (Irimia, 2005; Lima et al., 2006; Irimia et al., 2013a,b; Irimia and Van Horn, 2015a).

Planning

Although mTBI studies examining planning are not abundant, available evidence indicates that this subdomain can be impaired acutely, up to ∼5 months post-mTBI and up to ∼9 months after msTBI (Bar-Haim et al., 2009; Shum et al., 2009; Rabinowitz and Levin, 2014). Impairment severity may be dependent on task complexity; for example, Shum et al. (2009) found that TBI participants were impaired only on the most difficult sections of the Tower of London test and that they did not exhibit impairment on easier sections. On the other hand, some studies (Kraus et al., 2007; Kumar et al., 2013) have found no mTBI-related impairment of planning, possibly due to methodological differences including different sample demographics, injury mechanisms and neuropsychological assessment strategies. In one study of self-reported neurocognitive symptoms, participants reported poorer planning skills both 2–5 years and 5–10 years after injury, regardless of TBI severity (Ponsford et al., 2013). MRI studies typically report a higher prevalence of planning-related impairments in TBI patients who experienced localized PFC damage (Datta et al., 2009; Shum et al., 2009; Nowrangi et al., 2014). Compared to HCs, chronic severe TBI patients exhibit an increase in (A) planning-related BOLD activations within frontal and parietal lobes, and (B) the size of active brain areas, possibly reflecting compensatory mechanisms (Rasmussen et al., 2006). Another fMRI study of chronic severe TBI found that poor planning performance was associated with reduced task-related activation of the left dorsolateral PFC and of the ACC (Cazalis et al., 2006). Miles et al. (2008)

identified a significant correlation between a quantitative measure of planning and the dMRI-derived integrity of the centrum semiovale, of the genu and splenium of the corpus callosum, and of the posterior limb of the internal capsule ∼6 months post-TBI, whereas no such correlation had been detected acutely.

Decision-Making

Deficits of decision-making have been noted after mTBI (no distinction between complicated and uncomplicated cases) as well as msTBI both acutely and up to ∼5 years post-injury (Cotrena et al., 2014). One large-scale, case-control survey found that a history of TBI was significantly associated with increased risk for subsequent problematic gambling, likely due to impaired decision-making, and to subsequent impulsivity; this association was found to be most prevalent in males aged 35–64 (Bhatti et al., 2019). It has also been suggested that poor decision-making after TBI may be mediated by impaired mechanisms for fear recognition. Specifically, Visser-Keizer et al. (2016) found that chronic TBI victims exhibited impaired decision-making and emotion recognition, and that poorer fear recognition was significantly associated with worse task strategy and with more risk-taking behavior. It is unclear whether poorer decision-making after TBI is linked to the altered structure of specific brain regions, although it has been confirmed that such impairments are not limited only to patients with frontal lobe lesions (Levine et al., 2005; MacPherson et al., 2009; Cotrena et al., 2014). Levin et al. (2010) utilized dMRI to study blast-injured veterans with chronic mild-to-moderate TBI and found a significant correlation between poorer decision-making and lower WM integrity along connections between prefrontal regions and both temporal and occipital regions (i.e., the right uncinate fasciculus, the right inferior fronto-occipital fasciculus and the posterior limb of the right internal capsule).

Feedback Response

Although there has been little research on feedback response after TBI, a few studies which included feedback scores as part of their reported psychometrics suggest that individuals with a history of mTBI are unimpaired on scores reflecting feedback utilization efficacy (Schmidt et al., 2011; Kumar et al., 2013) although studies do not distinguish between complicated and uncomplicated mTBI. Kumar et al. (2013) found no differences between HCs and sub-acute mTBI participants on the Wisconsin Card Sorting Test (WCST) measures of perseverative response or perseverative errors, which suggests unhindered incorporation of feedback into performance. Further support for this hypothesis is provided by Schmidt et al. (2011), who found feedback-based therapy to be modestly effective in improving SA after TBI.

Working Memory

Impairment of working memory (both visual/spatial and verbal) has been noted after mTBI both acutely and up to ∼8 years post-injury (Konrad et al., 2011; Kumar et al., 2013) with no distinction being drawn between complicated and uncomplicated mTBI. By contrast, some studies have found no impairment in working memory performance after either acute or chronic mTBI, possibly for methodological reasons involving different approaches to neuropsychological assessment and to patient sampling and/or due to the lack of distinction between complicated and uncomplicated mTBI (Johansson et al., 2009; Chen et al., 2012; Zhou et al., 2013). Working memory performance after TBI may also depend upon task complexity and injury severity. For example, individuals with TBI perform worse on tasks requiring advanced cognitive load (e.g., dual task paradigms) compared to easier tasks, and those with msTBI perform worse than those with mTBI (McAllister et al., 2006). Among the very few longitudinal studies of working memory changes after TBI, that of Sanchez-Carrion et al. (2008) found improvements of performance on an n-back task after chronic severe TBI across a 6-month interval. Utilizing fMRI to compare mTBI patients to HCs, McAllister et al. (2001) found that (A) during low cognitive load, the patients' patterns of fMRI activation were similar to those of HCs, (B) during moderate cognitive load, the patients exhibited greater frontoparietal activations bilaterally, and that (C) during high cognitive load, the patients exhibited weaker bilateral frontoparietal activations. The results of McAllister et al. (2001, 2006) both indicate inefficient brain activation patterns after mTBI which, although relatively unimpacted at low cognitive loads, become apparent at higher loads. According to these authors, moderate loads lead to compensatory over-activation and high loads lead to inadequate fMRI activations. Another fMRI study of moderate cognitive load during an n-back task found a significant positive correlation between bilateral frontal and parietal task-related activation and injury severity (Pardini et al., 2010). Finally, dMRI studies have revealed significant positive correlations between the working memory performances of TBI individuals with TAI and the WM integrity of the superior longitudinal fasciculi, corpora callosa, arcuate fasciculi and fornices (Palacios et al., 2011). Supporting this finding, studies of HCs confirmed the association between (A) WM structure within and between the frontal and temporal lobes and (B) working memory performance (Charlton et al., 2010).

Response Inhibition

Impairment of response inhibition has been noted acutely, up to ∼2.3 years after mTBI and up to ∼5.7 years after TBIs of mixed severity (Dimoska-Di Marco et al., 2011; Xu et al., 2017), no distinction being drawn between complicated and uncomplicated mTBI. Nevertheless, a large meta-analysis of 41 studies found no relationship between inhibition performance and TBI severity (Dimoska-Di Marco et al., 2011). However, the same meta-analysis did find a significant relationship between longer time since injury and improved response inhibition. In an acute mTBI sample, Dall'acqua et al. (2016) used MRI to identify a positive correlation between bilateral frontal volume reductions and performance on a response inhibition task. By studying BOLD signals recorded during a choice reaction task, Xu et al. (2017) found that chronic mTBI participants exhibited a brain activation pattern in the cerebello-thalamo-cortical network which was reversed compared to that of HCs. Specifically, whereas the task's Go condition was associated with significantly weaker activation of this network in the mTBI group, its Switch condition was linked to significantly stronger activation in mTBI patients. The

Switch condition requires greater inhibitory control, and mTBI subjects' performance was poorer than that of HCs. By contrast, the Go condition does not require more inhibitory control and there were no differences in performance between groups during this condition. These results suggest the presence of a response inhibition deficit following mTBI. Fischer et al. (2013) confirmed the reverse brain activation pattern observed by Xu et al. (2017) when studying chronic, mild-to-moderate TBI; these authors identified bilateral BOLD signal increases in the caudate nuclei and in the left superior temporal, inferior temporal and cerebellar cortices, especially in relation to failures to inhibit a response.

Cognitive Flexibility

Deficits of cognitive flexibility have been documented ∼2 months post-mTBI by Pang et al. (2016), and ∼4.7 years after msTBI by Leunissen et al. (2014) although very few other studies could be located. Patients may recover from such deficits; for example, although acute TBI participants' task switching (cognitive flexibility) was consistently poorer than that of HCs, patients improved in this respect over the 1st month after injury (Mayr et al., 2014). Leunissen et al. (2014) found that, ∼4.7 years post-TBI, the volumes of cortical regions with connections to prefrontal or to rostral motor areas were inversely correlated with task switching performance, which highlights the importance of fronto-striato-thalamic circuits. The authors also found that task-switching performance after TBI was best predicted by the integrity of WM connections between the superior frontal gyrus (pre-supplementary motor area) on the one hand and the putamen, caudate nucleus as well as thalamus, on the other hand.

LANGUAGE

According to the DSM-5, the cognitive domain of language includes subdomains corresponding to both expressive language (naming, word-finding, fluency, grammar and syntax) and receptive language (Sachdev et al., 2014). Language domain deficits have been noted during both acute and chronic mTBI, up to ∼3.3 years post-injury (King et al., 2006; Rapoport et al., 2006; Galetto et al., 2013) no distinction between complicated and uncomplicated mTBI being drawn. According to one meta-analysis, mTBI participants exhibited better language performance ∼3 months-post-injury compared to the acute stage, which illustrates how language can improve over time (Belanger et al., 2005). Interestingly, language deficits observed after mTBI (e.g., global incoherence, inaccuracy of information, disruption of utterances) could be consequences of other high-order cognitive impairments—such as slower processing speed, inefficient attentional processing, EF disruption and poor memory encoding—rather than manifestations of true language deficits (Barwood and Murdoch, 2013; Galetto et al., 2013). However, caution should be exerted when drawing any conclusions pertaining to this topic due to the relative paucity of adequately powered studies investigating language after mTBI.

Word-Finding and Naming

Despite the separation of these two subdomains under the DSM-5 classification system, naming is considered a type of word finding, by means of which the latter is often assessed (Rohrer et al., 2007). Disruptions of the ability to name objects presented visually is among the most common language-related complaints after TBI in general, and mTBI in particular (King et al., 2006; Kennedy et al., 2009). Naming deficits have been observed after mTBI both acutely and up to ∼1.2 years post-injury (King et al., 2006; Miotto et al., 2010), no distinction between complicated and uncomplicated mTBI being drawn. King et al. (2006) found that acute mTBI patients exhibited impairment in confrontational naming but not in natural discourse naming, which highlights the possibility that slight language deficits apparent on psychometric tests may not be readily detectable in everyday life. These authors also concluded that the most common naming error among mTBI participants involves latency (i.e., the time taken to respond to a stimulus). It is possible that younger age at injury is associated with better naming performance after mTBI; Li et al. (2017) found that performance on the Boston Naming Test (the BNT, a commonly used naming test) was better in individuals who had suffered a TBI before the age of 22 rather than after. Based on clinical lesion data, Miotto et al. (2010) concluded that chronic mild-to-moderate TBI patients who were impaired on a naming task were most likely to have a frontotemporal lesion.

Verbal Fluency

Studies usually assess two types of verbal fluency: semantic (production of words of a single category, such as vegetables) and phonemic (production of words which start with a specific letter). Impairment of verbal fluency has been found in both complicated and uncomplicated mTBI during the acute stage, as well as up to ∼2 years post-injury, with improvements over time (Wallesch et al., 2001; Belanger et al., 2005; Zakzanis et al., 2011; Croall et al., 2014). Although semantic fluency may be more impaired than phonemic fluency after TBI, one meta-analysis of 30 studies found comparable deficits in both types of fluency, suggesting an underlying EF deficit (Henry and Crawford, 2004). Nevertheless, Wallesch et al. (2001) found GCS-measured TBI severity to be significantly and positively correlated with semantic fluency 5–10 months post-injury, but not with phonemic fluency. Thus, it is unclear whether semantic fluency is more vulnerable to mTBI than phonemic fluency. Interestingly, both types of fluency impairment are usually associated with TBI-related pathology of the frontal and temporal lobes (Wallesch et al., 2001; Henry and Crawford, 2004; Zakzanis et al., 2011). One DTI study found that acute verbal fluency deficits in mild-to-moderate TBI patients were negatively correlated with WM integrity and positively correlated with radial and axial diffusivity throughout the brain, but especially within the ascending fibers of the corpus callosum in the left hemisphere (Croall et al., 2014).

Grammar and Syntax

Grammar and syntax may not be affected considerably in the spontaneous speech of TBI patients, as recent studies have found

no impairments of such abilities in either mTBI (∼3.3 years post-injury) or moderate TBI (∼1.9 years post-injury), whereas severe TBI patients had somewhat worse performance (∼5.5 years post-injury) (Galetto et al., 2013; Marini et al., 2014, 2017), no distinction being drawn between complicated and uncomplicated mTBI. Although TBI-related syntactic deficits have been noted, such deficits may be the consequence of a primary semantic deficit or, alternatively, could be characteristic of specific samples (e.g., of patients with both TBI *and* aphasia) (Coelho et al., 2005).

Receptive Language

In one of the few adult studies available on receptive language deficits after TBI (Chabok et al., 2012), ∼65% of a mixed-severity TBI sample were found to exhibit acute language deficits. Of these, ∼38% exhibited impairments of auditory story comprehension, a measure of receptive language. The same study found that both moderate and severe injuries as well as fronto-temporal lesions were risk factors for language deficits, including comprehension difficulties. Menon et al. (1993) found that, although receptive language performance improved post-TBI, this subdomain was more impaired after severe than after mild-to-moderate injury. Receptive language deficits were found to be highly correlated with impairments of both short- and long-term memory as well as with EF impairments, indicating that altered language comprehension after TBI may stem from primary deficits in other cognitive domains (Vukovic et al., 2008). Finally, while investigating older adults with chronic mTBI, Barwood and Murdoch (2013) found specific deficits related to (A) the comprehension of ambiguous sentences and temporal structures, (B) inference construction based on listening comprehension, as well as to (C) recognition and expression of words' semantic properties.

PERCEPTUAL-MOTOR FUNCTION

According to the DSM-5, perceptual-motor function includes as subdomains visual perception, visuo-constructional reasoning, and perceptual-motor coordination (Sachdev et al., 2014). Perceptual-motor dysfunction can occur frequently in TBI patients (Heitger et al., 2006). Because researchers do not typically assess perceptual-motor function as an entire domain, what follows is an examination of TBI studies on its subdomains.

Visual Perception

Visual perception is an overarching term referring to (A) primary visual detection (which relies on visual acuity, visual fields, saccades, convergence, etc.) and (B) higher-level visual processing (which involves visual scanning, recognition of faces and objects, visual memory, visual attention, etc.). Thus, mTBI-related dysfunction of visual perception (e.g., reading difficulty) might stem from impaired visual detection (due to dysfunction of processes like saccades and convergence, which involve visual pathways between the retina and visual cortex), or from impaired visual processing (due to damage to visual cortex and associated cortices); both scenarios have been reported after mTBI (Magone et al., 2014; Barnett and Singman, 2015). Impairments of visual perception (i.e., deficits of detection and processing) after mTBI have been recorded acutely and up to ∼1.5 years post-injury (up to ∼4.2 years post-injury for visual detection deficits alone) (Magone et al., 2014; Alnawmasi et al., 2019), no distinction being drawn between complicated and uncomplicated mTBI. In a retrospective study of blast-induced mTBI, visual complaints were reported by 68% of participants, the most common being photophobia and reading difficulties (Magone et al., 2014). About 25% of the sample had been diagnosed with convergence insufficiency and ∼23% with accommodative insufficiency, suggesting damage to visual detection pathways. Such visual detection impairments, including visual field loss, have higher prevalence in msTBI than in mTBI, and can be detected after both blast-induced (military) and non-blast-related (civilian) mTBI (Capó-Aponte et al., 2017; Merezhinskaya et al., 2019). Commonly reported deficits of higher-order visual processing include impairments related to form recognition, motion perception, and figure/ground discrimination (Ciuffreda et al., 2016; Alnawmasi et al., 2019). Because there are hardly any reports of statistically significant associations between time since injury and visual perception performance, such deficits may remain stable over relatively long periods (Alnawmasi et al., 2019).

Visuo-Constructional Reasoning

Visuo-construction has been found to be mildly impaired both acutely and up to ∼1 year after complicated mTBI (Kashluba et al., 2008). However, no difference in visuo-constructional ability has been detected between mTBI and moderate TBI either acutely or at ∼1 year post-injury. The importance of accounting for participants' test effort was highlighted by Aguerrevere et al. (2014). These authors found no visuo-constructional deficits in mTBI participants who had invested an expected amount of effort while being tested, although no distinction was drawn between complicated and uncomplicated mTBI. The authors found moderate deficits in mTBI participants with poor investment of effort and in msTBI participants. Longitudinally, the performance of patients with TBIs of various severities on a visuo-constructional task was found to improve significantly from 1 to 5 years post-injury, with only 1.3% of the sample still being impaired after 5 years (Millis et al., 2001). Upon utilizing fMRI to investigate sub-acute mTBI, Tang et al. (2011) found a significant inverse relationship between bilateral rs-FCs involving the thalamus and performance on the Rey Complex Figure Test (RCFT, commonly used to assess visuospatial and visual memory skills). Upon leveraging dMRI to study sub-acute mild-to-moderate TBI, Kumar et al. (2009) found a significant, positive correlation between performance on the Block Design Test (BDT, commonly used to assess visuo-construction) and WM integrity in the genu of the corpus callosum. This study also found a positive linear relationship between performance on the BDT and axial diffusivity within the genu and splenium of the corpus callosum. The involvement of the corpus callosum may be due to its role in the inter-hemispheric transfer of visuomotor information, which is required by visuo-constructional tasks (Schulte et al., 2005). On the other hand, the thalamus is intimately involved in EF, memory and attention processing,

but not in visuo-constructional reasoning (Tang et al., 2011). These neuroimaging results, however, are relatively novel and thus require replication.

Perceptual-Motor Coordination

Deficits of perceptual-motor (mostly visual) coordination after mTBI have been reported both acutely and up to ∼1 year post-injury (Heitger et al., 2006), no distinction being drawn between complicated and uncomplicated mTBI. Acute mTBI has been associated with (A) prolonged latencies and decreased accuracy of saccades, (B) greater directional errors, (C) impaired sinusoidal smooth pursuit involving longer reaction times during arm movements, and (D) poorer upper-limb visuomotor tracking performance marked by lower arm speed and accuracy. These deficits were reported to improve within 1 year post-injury. Heitger et al. (2009) recorded similar oculomotor deficits ∼3 to ∼5 months post-mTBI, which could not be explained by group differences related to PCDSs or by intellectual ability. The study found a significant correlation between increased oculomotor deficits, on the one hand, and both more self-reported PCSs as well as poorer quality of life, on the other hand. Interestingly, there was no correlation between oculomotor deficits and neuropsychological measures. Perceptual-motor coordination (as measured by oculomotor performance) has been suggested to remain relatively stable between the ages of 16 and 70 (Heitger et al., 2009).

Ventura et al. (2016) found that, relative to HC participants, acute mTBI patients' impaired oculomotor performance was linked to increased BOLD activations in (A) the cerebellum and visual cortex (during anti-saccades and self-paced saccades), (B) dorsolateral PFC, bilaterally (during self-paced saccades), and (C) the left hippocampus, right lingual gyrus, left precentral gyrus, cerebella, left frontal eye fields, precunei and brainstem during memory-guided saccades. Similar outcomes were found 30 days post-injury, albeit fMRI activations were weaker. These results may suggest a compensatory increase in brain activation after mTBI. The authors also found that chronic mTBI patients' oculomotor deficits were correlated with poor WM integrity (as measured by fractional anisotropy) in the right anterior corona radiata, left superior cerebral peduncle and genu of the corpus callosum. The involvement of these areas in perceptual-motor coordination after mTBI is plausible given their established importance in information integration, in the refinement of motor movements and in the inter-hemispheric transfer of visuomotor information (Schulte et al., 2005; Han et al., 2010; Kwon et al., 2011). However, further research is needed to confirm and to further establish the neuroimaging correlates of perceptual-motor coordination after mTBI.

NEUROPSYCHOLOGICAL ASSESSMENTS

Tables 1–**5** list all reviewed neuropsychological tests by cognitive domain, whereas **Supplementary Table 1** reproduces this information as one single table because this format allows the reader to compare the utility of various tests across domains. **Table 6** lists all abbreviations utilized in the text, including this section.

For the assessment of overall attention (**Table 1**), commonly used neuropsychological tests include the Symbol Digit Modalities Test (SDMT), the Wechsler Adult Intelligence Scale III Digit Span (WAIS III DS), the WAIS III Digit Symbol Coding Task (DSCT), the Trail-Making Test A (TMT-A), the Trail-Making Test B (TMT-B), the Test of Attentional Performance (TAP), the Continuous Performance Test (CPT), the Attention Network Task (ANT), the Sustained Attention to Response Task (SART), the Paced Visual Serial Addition Test (PVSAT), the Paced Auditory Serial Addition Test (PASAT), etc. Neuropsychological tests previously used to assess sustained attention in TBI participants include the SART, the Monotone Counting Test (MCT), the simple choice reaction time task (CRTT), the PASAT and the Digit Vigilance Test (DVT). Neuropsychological tests used to assess divided attention include the SDMT, dual-task tests (DTTs), the TAP and custom made tests (CMTs). Neuropsychological tests used for selective attention in the studies reviewed include the Attentional Network Task (ANT), the Numeric Stroop Test (NST), the Complex Selective Attention Task (C-SAT) and the CPT. The neuropsychological tests used to assess processing speed include the TMT-A, TMT-B, simple reaction time tests, the SDMT, the WAIS III DS and DSCT, custom visual and tactile reaction time tasks, the Stroop Color-Word Test (SCWT), the DSCT, PVSAT and PASAT.

Tests commonly used to assess overall L&M after TBI (**Table 2**) include the Rey Auditory Verbal Learning Test (RAVLT), the California Verbal Learning Test (CVLT-II), the

TABLE 1 | Psychometric instruments for the assessment of the cognitive domain of attention, including overall attention and its subdomains, i.e., sustained attention, divided attention, selective attention and processing speed.

	Overall attention	Sustained attention	Divided attention	Selective attention	Processing speed
SDMT	✓		✓		✓
DS	✓				✓
DSCT	✓				✓
TMT-A	✓				✓
TMT-B	✓				✓
TAP	✓		✓		
CPT	✓			✓	
ANT	✓			✓	
SART	✓	✓			
PVSAT	✓				✓
PASAT	✓	✓			✓
MCT		✓			
CRTT		✓			✓
DVT		✓			
DTT			✓		
CMT			✓		✓
SCWT					✓
NST				✓	
CSAT				✓	

TABLE 2 | Psychometric instruments for the assessment of the cognitive domain of learning and memory, including overall learning and memory and its subdomains, i.e., free recall, cued recall, recognition memory, episodic memory, semantic memory, and implicit learning.

	Learning and memory	Free recall	Cued recall	Recognition memory	Episodic memory	Semantic memory	Implicit learning
VFT						✓	
RAVLT	✓	✓		✓			
CVLT-II	✓	✓	✓	✓			
MC 1 and 2	✓						
WMT	✓	✓	✓	✓			
DPT	✓						
WMS	✓				✓		
IED	✓						
RCFT	✓						
FWM	✓						
BSRT		✓					
PN and SM						✓	
ITTI							✓
SRTT							✓
TOHT							✓

TABLE 3 | Psychometric instruments for the assessment of the cognitive domain of executive function, including overall executive function and its subdomains, i.e., planning, decision-making, feedback response, working memory, response inhibition and cognitive flexibility.

	Executive function	Planning	Decision-making	Feedback response	Working memory	Response inhibition	Cognitive flexibility
DS					✓		
TMT-A							✓
TMT-B	✓						✓
CPT						✓	
SART	✓					✓	
PASAT					✓		
SCWT						✓	✓
VFT	✓						
IED							✓
HSCT	✓						
BSAT	✓						
COWAT	✓						✓
PMT	✓						
TOL	✓	✓					
WCST	✓			✓			✓
DKEFS	✓						
NAB	✓						
BADS		✓					
PF A and B		✓					
IGT			✓				
N-Back					✓		
G/N and SST						✓	
LGST							✓
SP					✓		

Memory Cabinet (MC) 1 and 2, the Word Memory Test (WMT), the Doors and People Test (DPT), the Wechsler Memory Scale (WMS), the Cambridge Neuropsychological Test Automated Battery, the Rey Complex Figure Test (RCFT) and the Four Word Short-Term Memory (FWM) Test. Tests used to assess free and cued recall are usually composite subtests or sub-trials of established memory batteries. For free recall, these include sub-trials of the RAVLT and WMT, the Buschke Selective Reminding Test (BSRT), and CVLT-II subtests; for cued recall, the WMT-Paired-Associations sub-trial and CVLT-II subtests are used frequently. Subtests are also used to assess recognition memory after TBI (e.g., the WMT-Multiple-Choice subtest, RAVLT sub-trials and CVLT-II sub-trials). Whereas episodic memory is typically assessed using the WMS, common semantic

memory tests include verbal fluency tests (VFTs), picture naming and semantic priming (PM and SM) tests. Finally, tests of implicit memory include the Implicit Test of Tachistoscopic Identification (ITTI), the Serial Reaction Time task (SRTT) and the Tower of Hanoi task (TOHT).

The assessment of the overall EF domain after TBI (**Table 3**) typically relies on the TMT-B, Hayling Sentence Completion Test (HSCT), on semantic and lexical VFTs, SART, Brixton Spatial Anticipation Test (BSAT), Controlled Oral Word Association Test (COWAT), Porteus Maze Test (PMT), PMT Vineland Revision, TOL II, WCST (64-card version), Wechsler Abbreviated Scale of Intelligence (WASI) Matrix Reasoning subtest, Delis–Kaplan Executive Function System (D-KEFS), and on the Neuropsychological Assessment Battery (NAB) Word Generation and Mazes modules. To assess the subdomain of planning, the TOL test, Behavioral Assessment of the Dysexecutive Syndrome (BADS), and the Prioritization Forms (PFs) A and B are frequently used. Assessment of decision-making post-TBI has relied almost exclusively on the Iowa Gambling task (IGT) and on modified versions of it. The few studies which assessed feedback responses relied on the WCST. Working memory has been evaluated using the Sternberg Paradigm (SP) for verbal and visuo-spatial working memory, the DS task, the *n*-back working memory task and several PASAT subtests. Inhibition has been typically assessed using the go/no-go task, stop-signal task (G/N and SST, respectively), SCWT, SART and CPT. Finally, cognitive flexibility has been measured using the SCWT, TMT-A and -B, WCST, COWAT, the intra-extra dimensional (IED) set shift test (part of the Cambridge Neuropsychological Test Automated Battery) and using custom local-global switching tasks (LGSTs).

Neuropsychological tests most commonly employed to assess the overall language domain (**Table 4**) after TBI included VFTs, the WAIS III DS, Rey's 15-word Immediate and Delayed Recall Test (RIDR), the WCST (perseverative and non-perseverative errors), and a variety of narrative story-telling tests (NSTTs). To assess word finding and naming, researchers typically used the BNT, the Test of Adolescent/Adult Word Finding (AWF), and the Test of Word Finding in Discourse (TWFD). Fluency was often assessed using the COWAT, the Ruff Figural Fluency Test (RFFT), VFTs and the FAS test. The assessment of grammar and syntax was accomplished with the Aachen Aphasia Test (AAT) subtests and NSTTs based upon pictures from the Western Aphasia Battery. Finally, receptive language has been assessed using the Peabody Picture Vocabulary test (PPVT), the Token Test (TT) and various auditory comprehension tests (ACTs).

Tests commonly employed to assess the subdomain of visual perception after TBI (**Table 5**) were usually custom computerized tests involving paradigms such as matching, visual search (often assessed through the Weinberg Visual Cancelation Test), reading comprehension, visual recognition, figure/ground discrimination and motion perception. Visuo-constructional reasoning was typically assessed using the BDT, simple copy tests, complex copy tests (especially the RCFT), draw-to-command tasks [e.g., the Line Orientation Judgment Test (LOJT)], the Hooper Visual Organization Test (HVOT) and the Benton Visual Retention Test (BVRT). Tests of assessing perceptual-motor coordination after TBI often vary depending on the ability being studied. For instance, oculomotor assessment is typically done using computerized paradigms, involving reflexive saccades, anti-saccades, memory-guided saccade sequences, self-paced saccades and both sine and random oculomotor smooth pursuits. Limb coordination tests used after TBI typically utilize computerized paradigms involving an output accessory (such as a steering wheel which controls the movements of an arrow on the computer screen).

TABLE 4 | Psychometric instruments for the assessment of the cognitive domain of language, including overall language and its subdomains, i.e., word-finding (naming), verbal fluency, grammar and syntax, and receptive language.

	Language	Word-finding (naming)	Verbal fluency	Grammar and syntax	Receptive language
DS	✓				
VFT	✓		✓		
COWAT			✓		
WCST	✓				
RIDR	✓				
NSTT	✓			✓	
BNT		✓			
AWF		✓			
TWFD		✓			
RFFT			✓		
AAT				✓	
PPVT					✓
TT					✓
ACT					✓

TABLE 5 | Psychometric instruments for the assessment of the cognitive domain of perceptual-motor function, including overall perceptual-motor function and its subdomains, i.e., visual perception, visuo-construction and perceptual-motor coordination.

	Perceptual-motor function	Visual perception	Visuo-construction	Perceptual-motor coordination
RCFT			✓	
CP 1		✓		
BDT			✓	
LOJT			✓	
HVOT			✓	
BVRT			✓	
CP 2				✓
CP 3				✓

There are no entries in the perceptual-motor function column because the listed instruments assess cognitive subdomains rather than the overall domain of perceptual-motor function.

Despite the abundance of psychometric instruments, there are potential problems which may arise with their use. Firstly, many cognitive assessments vary considerably in their capacity to detect mTBI impairments (Karr et al., 2013). For example, in a study by Draper and Ponsford (2008) the SDMT and DSCT uncovered overall attention deficits in TBI participants, whereas the TMT-A, DS and the SART did not. In the same study, the RAVLT and the DPTs uncovered overall memory deficits in TBI, whereas the Shapes and Names tests did not. Similarly, the HSCT

TABLE 6 | Abbreviations used throughout the text.

AAT	Aachen Aphasia Test
ACC	anterior cingulate cortex
ACT	Auditory Comprehension Tests
AD	Alzheimer's disease
ANT	Attention Network Task
AWF	Test of Adolescent/Adult Word Finding
BADS	Behavioral Assessment of the Dysexecutive Syndrome
BDT	Block Design Test
BNT	Boston Naming Test
BOLD	blood oxygen level-dependent
BSAT	Brixton Spatial Anticipation Test
BSRT	Buschke Selective Reminding Test
BVRT	Benton Visual Retention Test
CBF	cerebral blood flow
CMT	custom-made tests
COWAT	Controlled Oral Word Association Test
CP 1	computerized paradigms involving matching, visual search, reading comprehension, visual recognition, figure/ground discrimination and motion perception
CP 2	computerized paradigms involving reflexive saccades, anti-saccades, memory-guided saccade sequences, self-paced saccades and both sine and random oculomotor smooth pursuits
CP 3	computerized paradigms involving an output accessory
CPT	Continuous Performance Test
CRTT	Simple Choice Reaction Time Task
CSAT	Complex Selective Attention Task
CT	computed tomography
CVLT II	California Verbal Learning Test II
D-KEFS	Delis–Kaplan Executive Function System
DMN	default mode network
dMRI	diffusion magnetic resonance imaging
DPT	Doors and People Test
DS	Wechsler Adult Intelligence Scale III Digit Span
DSCT	Wechsler Adult Intelligence Scale III Digit Symbol Coding Task
DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5
DTI	diffusion tensor imaging
DTT	Dual-Task Tests
DVT	Digit Vigilance Test
EF	executive function
FC	functional correlation
fMRI	functional magnetic resonance imaging
FWM	Four Word Short-Term Memory Test
G/N and SST	Go/No-go and Stop-Signal Task
GAD	generalized anxiety disorder
GCS	Glasgow Coma Score
GM	gray matter
HC	healthy control
HSCT	Hayling Sentence Completion Test
HVOT	Hooper Visual Organization Test
IED	Intra-Extra Dimensional Set Shift Test (part of the Cambridge Neuropsychological Test Automated Battery)
IGT	Iowa Gambling Task
ITTI	Implicit Test of Tachistoscopic Identification
L&M	learning and memory
LGST	Local-Global Switching Tasks
LOC	loss of consciousness
LOJT	Line Orientation Judgment Test
MC 1 and 2	Memory Cabinet 1 and 2
MCI	mild cognitive impairment
MCT	Monotone Counting Test
mPFC	medial prefrontal cortex
MRI	magnetic resonance imaging
msTBI	moderate-to-severe traumatic brain injury
mTBI	mild traumatic brain injury
NAB	Neuropsychological Assessment Battery
N-Back	N-Back Working Memory Task
NST	Numeric Stroop Test
NSTT	Narrative Story-Telling Tests
PASAT	Paced Auditory Serial Addition Test
PCC	posterior cingulate cortex
PCDS	post-concussive depressive symptom
PCS	post-concussive symptom
PET	positron emission tomography
PF A and B	Prioritization forms A and B
PFC	prefrontal cortex
PMT	Porteus Maze Test
PN and SM	Picture Naming and Semantic Priming tests
PPVT	Peabody Picture Vocabulary Test
PTA	post-traumatic amnesia
PTSD	post-traumatic stress disorder
PVSAT	Paced Visual Serial Addition Test
RAVLT	Rey Auditory Verbal Learning Test
RCFT	Rey Complex Figure Test
RFFT	Ruff Figural Fluency Test
RIDR	Rey's 15-word Immediate and Delayed Recall Test
RME	Reading the Mind in the Eyes Test
rs	resting state
SA	self-awareness
SART	Sustained Attention to Response Task
SCWT	Stroop Color-Word Test
SDMT	Symbol Digit Modalities Test
SP	Sternberg Paradigm for Verbal and Visuo-spatial Working Memory
SRTT	Serial Reaction Time Task
TAI	traumatic axonal injury
TAP	Test of Attentional Performance
TBI	traumatic brain injury
TMT-A	Trail-Making Test A
TMT-B	Trail-Making Test B
TOHT	Tower of Hanoi Task
TOL	Tower of London Test
ToM	theory of mind
TT	Token Test
TWFD	Test of Word Finding in Discourse
US	United States
VFT	verbal fluency tests
WAIS	Wechsler Adult Intelligence Scale
WASI	Wechsler Abbreviated Scale of Intelligence
WCST	Wisconsin Card Sorting Test
WM	white matter
WMS	Wechsler Memory Scale
WMT	Word Memory Test

Following convention, all names of psychometric tests, tasks, batteries, forms and scales are capitalized.

and SART uncovered overall EF deficits in TBI, but the PMT, BSAT, COWAT and TMT-B did not. To provide more nuanced information on the advantages and limitations of psychometric batteries, future studies should strive to report detailed findings on TBI participants' performances on each cognitive subdomain assessed by each instrument. One motivation is that, whereas TBI-related impairments may not be reflected by participants' overall scores, such impairments may be highlighted by test subscores. Furthermore, simple tasks are frequently administered to assess complex cognitive processes in TBI patients. For example, simple reaction time tasks like the TMT-A are often used to assess complex overall attention, although such tasks are suitable for the sole assessment of processing speed (Paré et al., 2009). Another example is the common use of the RAVLT to assess overall memory, although this test focuses solely on the assessment of auditory verbal episodic memory (Magalhães et al., 2012). Similarly, overall language domain assessments frequently involve evaluations of naming abilities (like the BNT), which quantify word finding, but not other language subdomains.

Some studies have used complex tests (Tate et al., 2017) or more than one test (Kraus et al., 2007) to measure overall cognitive domain function after TBI, although this strategy may be of limited benefit because the comprehensive psychometric quantification of entire domains is quite difficult to accomplish. For example, the PASAT—which is commonly used to assess overall attention after TBI—can measure a wider range of abilities, including processing speed, sustained attention, divided attention and working memory (Tate et al., 2017). However, because the PASAT does not directly measure selective attention, this test may not be best for systematic assessment of the overall attention domain. Similarly, Kraus et al. (2007) combined the DS, Spatial Span, TMT-A and CPT to assess overall attention, but the interpretation of their results is limited because none of these instruments measure divided attention. Thus, compared to studies focusing on cognitive subdomains, TBI studies featuring complex tests or combinations of tests to measure cognitive function across an entire domain can rarely be comprehensive in their assessment. Firstly, because psychometric instrument selection constrains which subdomains are studied, misconceptions can arise if researchers use tests which measure only certain subdomains and then use the results of such tests to draw conclusions about an entire domain. Secondly, it is more challenging to relate overall domain (e.g., attention) performance to neuroimaging-based measures rather than to specific subdomains (e.g., selective or divided attention). This is because correlations between measures of overall domain function and neuroimaging metrics can often be relatively non-specific and may additionally be confounded across studies by the fact that distinct studies use different testing batteries and approaches. For example, Little et al. (2014) could identify structural correlates of overall attention across brain regions, although without spatial specificity. By contrast, Zhou et al. (2013) studied specific attention subdomains and could identify specific brain regions whose anatomic changes could be linked to performance within subdomains (e.g., right rostral ACC atrophy correlated with sustained attention). Thus, studying cognitive subdomains may help to characterize the statistical relationships between brain structure and function in ways which are potentially more specific and more replicable. Although such an approach is slowly gaining adoption—especially to test language and perceptual-motor function—it is still far from common.

Ideally, meta-analyses should integrate information on the separate subdomains to paint a comprehensive image of their richness and complexity. This, however, requires addressing the heterogeneity of taxonomies used to classify cognition into domains and subdomains. Even the DSM-5 classification system, as one of the few established systems for classifying cognitive functions, is controversial and limited in scope. For example, in defining L&M, the DSM-5 does not distinguish well between immediate and delayed recall, between verbal and non-verbal/visual memory, or between prospective and retrospective memory. Additionally, the lack of a uniform standard for technical nomenclature among TBI psychologists and psychometricians remains a major obstacle to research synthesis. For example, some studies of specific L&M subdomains do not explicitly mention their names (e.g., semantic memory). In these cases, rather than relying on the terminologies used in studies, one must examine the specific tests used by researchers to determine what is being measured. Thus, researchers should strive to conform to a classification system which is broadly agreed-upon, thereby enabling direct and unhindered comparison of studies.

Even if studies choose to investigate cognitive subdomains systematically and distinctly, problems may arise when using a test which measures multiple abilities. For example, the PASAT–an elaborate test measuring multiple cognitive abilities across several domains–is often used to assess sustained attention in particular (Zhou et al., 2013). To reduce the potential confounds of other domains being examined when evaluating sustained attention using the PASAT, the ability to clearly identify test sections which measure sustained attention in isolation would be of substantial assistance. Another example is the common use of the Stroop Color-Word test to assess inhibition. One large meta-analysis of 41 studies found a non-significant overall effect for this test in TBIs of mixed severities, and reported that the reliability of the test may vary substantially across samples (Dimoska-Di Marco et al., 2011). These findings could either be due to (A) a lack of a TBI-related deficits in interference control (a type of response inhibition) as measured by this test, (B) canceling out of participants' aptitude in the different abilities measured by this test, or (C) vulnerability of the Stroop test to confounds like poor processing speed, under-arousal or fatigue (Dimoska-Di Marco et al., 2011). A further example is the RCFT, which is often used to assess visuo-constructional reasoning and visual memory (Tang et al., 2011). As in the case of other multifaceted psychometric tests, the precise weighting of each ability tested by the RCFT is not necessarily made clear by its scoring system, such that quantifying and interpreting performance within specific cognitive subdomains can be challenging. Thus, future research should aim to use psychometric approaches which unambiguously delineate the abilities being measured. Additionally, the scoring systems of commonly used tests should be expanded to include distinct scores for all such relevant abilities. Alternatively, new psychometric instruments should be

developed in which the loads and scoring schemes for each measured ability are made explicit.

Neuropsychological testing of TBI effects on cognition can often fail to account for both verbal *and* non-verbal elements of the cognitive abilities being measured. For example, whereas commonly used memory assessment batteries focus on verbal memory assessment (e.g., RAVLT, CVLT-II), many do not quantify non-verbal memory function as systematically. An illustration of a favorable approach is provided by the study of Chan (2005) where the SART and the MCT—both of which focus on sustained attention)—are used. Because the SART and the MCT assess visual and auditory components of sustained attention, respectively, the combined use of these two instruments adds another dimension of valuable information to the conventional characterization of sustained attention provided by other tests.

When studies do not capture the multidimensional nature of cognitive domains and the relationships between their subdomains, interpretative challenges may arise. Specifically, impairments on neuropsychological tests after TBI may be due to other more fundamental pathology affecting the cognitive abilities being measured. For example, sustained attention is predicated upon other basic cognitive abilities, including working memory, cognitive control, inhibition, and flexibility (Pontifex et al., 2012). Another example concerns response inhibition deficits, which may be due to poor processing speed, to fatigue or to the arousal state of the subject rather than to interference control *per se* (Dimoska-Di Marco et al., 2011). Similarly, impaired performance on sustained attention tasks can be considerably influenced by fatigue, depressed mood or by sleep alterations, all of which are frequently reported by mTBI patients (Sinclair et al., 2013). Finally, processing speed may explain much of the variance in performance observed on many neurocognitive tests which assess various cognitive functions and which involve a timed component (Mathias and Wheaton, 2007). Thus, caution should be exerted when interpreting the results of such tests to draw conclusions which exclusively concern very specific aspect of cognition.

INJURY SEVERITY AND CLINICAL FACTORS

Injury whose severity is greater than mild (i.e., msTBI) appears to be predominantly linked to greater and to more persistent cognitive and affective difficulties compared to mTBI. This distinction in the gravity of sequelae across severities can be seen within each of the cognitive domains examined in this review (affect, social cognition, complex attention, learning and memory, executive function, language and perceptual-motor function), and is particularly notable for affect (depression and anxiety) and social cognition (specifically for emotion recognition and self-awareness), although further studies of social cognition post-msTBI are needed to clarify the role of injury severity within this domain. Two potential exceptions to this trend may pertain to (A) ToM performance, for which no reports of injury severity effects have been identified here, and (B) the amount of effort expended by patients during cognitive assessment. Specifically, msTBI has occasionally been linked to a lower likelihood of poor effort on tasks related to neuropsychological testing, which may suggest that accounting for patients' expended effort is particularly important in mTBI studies. Whenever possible, future research should aim to quantify the relationship between injury severity and the amount of effort expended by patients during their assessment, given that this distinction has not been quantified rigorously and that its confounding effect remains unclear for the assessment of many—if not most—cognitive subdomains (Hinojosa-Rodriguez et al., 2017).

When analyzing differences between TBI severities, factors conventionally categorized as clinical (such as PTA, LOC, GCS and neuroimaging results) are very important when assessing injury impact on cognitive and affective processes (National Academies of Sciences and Engineering, 2019). These clinical factors have been highlighted throughout the review, wherever pertinent data are available. Overall, our findings appear to support the notion that more extensive PTA, longer LOC, lower GCSs and more abnormal neuroimaging findings—all of which are typical of greater TBI severity–are associated with poorer cognition and affect. For example, all clinical factors mentioned above have been linked to poorer sustained attention performance. In the studies reviewed here, GCS is nearly always used to distinguish between patients based on their injury severity (mild, moderate or severe). Because of this, we find GCS to be consistently associated with poorer performance on assessments of cognition and affect across all domains, with the potential exceptions listed in the previous paragraph. As the second most studied clinical factor apart from neuroimaging, PTA is often indicative of decreased performance in many—but not all—domains and subdomains, including attention, memory, L&M (specifically free recall, working memory and recognition memory), EF (specifically response inhibition and cognitive flexibility) and the overarching domain of language. The relation of neuroimaging results to post-traumatic cognition and affect is currently under extensive study (National Academies of Sciences and Engineering, 2019). Although findings of abnormal structural and function have typically been linked to poorer performance, adequate interpretation may depend upon complex and problematic factors like assessment modality, the areas/functions assessed and the researchers' categorization, taxonomy and conceptualization of cognitive domains/subdomains. Research within this area of study therefore requires further standardization before more adequate or generalizing conclusions can be drawn. Furthermore, a mention of the fact that TBI clinical factors can be interdependent should not be omitted here. For example, longer LOC in mTBI participants exhibiting EF deficits is significantly correlated with WM damage severity, as revealed by neuroimaging. By contrast, many relationships between clinical factors and post-traumatic cognition and affect are still unclear. For example, there is no agreed-upon conclusion pertaining to LOC length effects on selective attention performance post-TBI and additional studies should be undertaken to improve our understanding on this association.

LIMITATIONS AND CONCLUSION

This review summarizes recent literature on mTBI cognitive dysfunction, on its neuroimaging correlates, and on its relation to neuropsychological assessment. Discussions of PCSs are included for each cognitive (sub)domain as a function of age at injury, time since injury and other assessment categories. Neuroimaging studies indicates that, despite substantial research on the relationship between brain structure, brain function and cognition, certain cognitive subdomains have not been adequately studied, including planning, decision-making, inhibition response, visual perception, and receptive language in particular. Notably, because the importance of social dysfunction after mTBI has been understated, additional research is required to improve understanding of how social impairments are related to brain structure and function. Future research should also aim to examine cognitive subdomains whose study has been relatively neglected, such as divided attention and ToM. Cognitive deficits should be examined as a function of injury severity because the lack of such stratification can result in inconclusive results which may conflict with those of other studies. Very importantly, future investigations should quantify the precise effects of age at injury and time since injury upon both post-traumatic cognition and neuroimaging correlates, given that such information was frequently found to be lacking from many studies. Comparison of mTBI patients as a function of their subsequent cognitive and clinical outcome would be particularly beneficial, since not all mTBI individuals continue to exhibit PCSs, and this effect may confound results if not taken into account.

Having systematically reviewed mTBI-related deficits and their cognitive assessment, our conclusion is that further knowledge synthesis in this research area requires future studies to focus on the rigorous and methodical assessment of cognitive subdomains and of their components, rather than on overarching cognitive domains, as still frequently done for attention, L&M and EF. Nevertheless, when evaluating cognitive function across entire cognitive domains, researchers should define and conceptualize cognitive function within such domains both thoroughly and systematically. The TBI research community should aim to clarify and establish consensus as to which specific deficits can be measured by commonly used cognitive assessments, and the relation of deficits within a certain domain to those within other domains and subdomains should be established. Because the accuracy of current classification schemes for cognitive categories, including that of the DSM-5, continues to be the subject of intense debate, TBI neuropsychologists and psychometricians should leverage their expertise and insights to assist the development and establishment of any novel taxonomies and hierarchies of cognitive functions. Additionally, factor analysis and similar methods should be used to clarify the relationships between commonly used assessment instruments and the cognitive categories advanced by the DSM-5 and by other taxonomies of cognition. Finally, novel assessments should be developed to assess cognition with high ecological validity.

The present review is not free of limitations. Many important factors relating to TBI patients' performance on cognitive tests are beyond our scope; for example, we have only focused on adult TBI because pediatric TBI patients often exhibit patterns of impairment which are different from those observed in adults. Furthermore, we have not explored heterogeneities of impairment due to distinct injury mechanisms and clinical presentations. Distinctions between (A) complicated and uncomplicated mTBI, between (B) neuroimaging-free vs. CT- and MRI-informed conclusions and between (C) single vs. multiple injuries were not explored due to the scarcity of psychometric studies which account for these distinctions. Depending on the published research available, reviewed studies included both civilian and non-civilian participants; because these groups can inherently differ in several ways, knowledge synthesis across these two groups can be challenging and was not attempted.

AUTHOR CONTRIBUTIONS

MC and AI evaluated published literature, wrote the review and contributed to all drafting, editing, and revising. Both authors approved the final version of the submission and agreed to be accountable for the content of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2020.01423/full#supplementary-material

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Altruistic Punishment and Impulsivity in Parkinson's Disease: A Social Neuroscience Perspective

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Non-motor symptoms of Parkinson's disease (PD) are of increasing interest in clinical and psychological research. Disinhibition—the inability to inhibit inappropriate behavior—leads to social and emotional impairments, including impulsive behavior and disregard for social conventions and decision-making behavior. In recent years, the latter has been investigated using economic exchanges during social interactions. Altruistic punishment—to punish someone who violates group norms even if it foresees a personal cost—is one of the most useful and fruitful paradigms; it allows to maintain a cooperation system within social groups. Alterations of this cognitive ability negatively impact the quality of life of the individual and social stability. Social neuroscience has suggested association between impulsive behaviors and altruistic punishment. Neuroimaging research aimed at exploring functional networks and intrinsic functional connectivity went in this direction. To date, little is known about these issues in neurodegenerative diseases such as PD. Dopamine replacement treatment and dopamine-agonists have been associated with impulse-control disorder and impulsive-compulsive behavior able to affect social decision-making. Frontal-executive dysfunction determines an alteration of social functioning through a mechanism of subversion of online action-monitoring, which associates disinhibition with volition. Genetic polymorphisms, alterations of the nigro-striatal substance, and impairment in the medial prefrontal cortex and in the Default mode network (DMN) seem to be able to explain these mechanisms. This theoretical perspective article aims to present these topics in order to encourage an interdisciplinary discussion capable of generating new research and developing rehabilitative intervention to improve social decision-making in PD patients.

Keywords: impulsive behavior, altruistic punishment, Parkinson's disease, social cognition, social norms, ingroup and outgroup contexts, default mode network (DMN), functional magnetic resonance imaging (fMRI)

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INTRODUCTION

This theoretical paper aims to suggest an interdisciplinary vision in Parkinson's disease (PD) research among different disciplines. Non-motor symptoms in PD are increasingly capturing attention from interdisciplinary research in which psychology, neuroscience, and clinical medicine converge. During the last decades, neuroscientific studies investigated mental processes

activated during resting state and social scenarios using economic games (see Sanfey et al., 2006). Theories and experimental paradigms developed by social neurosciences are useful for better understanding impulsivity and decision-making in social situations such as in altruistic punishment, to punish someone who violates group norms even if it foresees a personal cost.

To date, very few studies investigated altruistic punishment in motor neurodegenerative diseases, such as PD. The present theoretical perspective article focuses on common points between impulsivity, metacognitive-executive functions, decision-making processes, and neurobiological factors potentially involved in altruistic punishment in PD patients.

ALTRUISTIC PUNISHMENT

Social behaviors arise from "cooperation" which represents a distinctive ability of human beings: that is, the process of individuals and groups acting for their mutual benefit. Cooperation played an important role in the evolution of human social life, allowing the organization in social groups through the creation of social norms (Fehr and Schmidt, 1999; Fehr and Gächter, 2000, 2002; Tomasello, 2009; Boyd et al., 2010; Morese et al., 2018). Joining social groups, respecting their own social norms, has ensured a greater survival in evolutionary history compared to a life in solitude and isolation. Therefore, the transgression has always been sanctioned.

The *altruistic punishment* behavior—to punish someone has carried out an unfair behavior at one's own cost and with no personal benefit—has been widely studied across several cultures (Fehr and Gächter, 2000, 2002; Gardner and West, 2004; Raihani et al., 2012; Balafoutas et al., 2016; Morese et al., 2016; Rabellino et al., 2016). Djamshidian et al. (2011) underlined how it may have the function of breaking down the amount of unfair behavior within the group. Several authors suggested how altruistic punishment represents the basic nature of cooperation: i.e., cooperation and punishment co-evolve as the one who punishes unfair behavior is considered more reliable, being therefore rewarded for his/her cooperation by the other members of the group (Fehr and Gächter, 2000, 2002; Fehr and Fischbacher, 2004; Gao et al., 2015; Grimalda et al., 2016; Greenwood et al., 2018; Huang et al., 2018). Morese (2018), in line with Henrich et al. (2005), highlights how altruistic punishment is opposed to the classic vision of *homo economicus* guided only by rationality and utilitarian decisions.

Considering the above, altruistic punishment would support emotional processes during social decision-making. Socially driven emotions can be successfully modulated by reappraisal strategies that focus on the reinterpretation of others' intentions. Indeed, emotion regulation plays a key role in altruistic punishment behavior. According to the theoretical model proposed by Fehr and Gächter (2000, 2002), the altruistic punishment behavior is exercised within the social group and it guarantees the maintenance of cooperation between the members. The experimental paradigm used for the study of altruistic punishment is the Third-Party Punishment (TPP). In this game, a player observes an economic interaction between two other players. One of them can decide to share part of his or her money with the other player, who can only passively accept his or her choice. The player observing the exchange of money can decide whether to punish the behavior if deemed unfair (Morese et al., 2016).

In the last decade, there has been an increasing interest in these issues, while great developments have taken place, thanks to functional neuroimaging techniques (de Quervain et al., 2004; Buckholtz and Marois, 2012; Yang et al., 2019; Zinchenko, 2019).

ALTRUISTIC PUNISHMENT AND REWARD SYSTEM

The altruist punishment behavior appears to have its neural substrate in the *reward system*. The reward system is a group of neural structures responsible for motivation, associative learning, and positive emotions, especially those involving pleasure as a fundamental component. The thalamus, dorsolateral prefrontal cortex (DLPFC), nucleus accumbens, anterior cingulate cortex (ACC), insula, and caudate nucleus are considered to be part of this neural system (Sanfey et al., 2003; de Quervain et al., 2004; King-Casas et al., 2005; Strobel et al., 2011; Buckholtz and Marois, 2012; Morese et al., 2016; Zinchenko, 2019).

Haber et al. (2006) highlighted the mediation of DLPFC and caudate in punishment responses, being these hubs involved in directing attention toward relevant stimuli, or in understanding communication intentions between individuals. Strobel et al. (2011) discovered that observing unfair behavior evokes the recruitment of the anterior insula—usually activated in the process of disgust—and, therefore, they associated disgust with violation of social norms. Other authors suggested an involvement in brain area usually activated during Theory of Mind (ToM) tasks, such as the medial prefrontal cortex (MPFC) and the temporal-parietal junction (TPJ; Baumgartner et al., 2012; Lo Gerfo et al., 2019). Buckholtz and Marois (2012) proposed the DLPFC, the posterior parietal cortex (PPC), and functional connectivity network [such as the central executive network (CEN)] as involved in decision-making during economic tasks aimed at assigning adequate punishments. More recently, Morese et al. (2016) found the recruitment of the ventral tegmental area (VTA), the MPFC, caudate, and cingulate cortex during tasks eliciting altruistic punishment behavior. VTA plays a central role in the production of dopamine, a neurotransmitter produced in motivation and reward behaviors.

The dopaminergic reward system and VTA are vulnerable in PD, and reward processing abnormalities have been previously identified (Kapogiannis et al., 2011). This might suggest potential altruistic punishment disabilities which must be investigated through a neurocognitive approach (Palermo et al., 2019).

PARKINSON'S DISEASE, IMPULSIVITY, AND SOCIAL DECISION-MAKING

PD is a progressive neurodegenerative disorder that affects the central and peripheral nervous systems. Specifically, the depletion of dopaminergic neurons affects the functioning

of four fronto-striatal circuits involved in different motor, cognitive, affective, and motivational aspects of behavior (the supplementary motor area, the dorsolateral prefrontal, the orbitofrontal, and the anterior cingulate loops; Palermo et al., 2017a,b, 2018a, 2019; Palermo and Morese, 2018).

Rest tremor, bradykinesia, rigidity, and loss of postural reflexes are generally considered the cardinal signs of PD. Other clinical features include secondary motor symptoms (such as dysarthria, dysphagia, dystonia, festination, freezing, glabellar reflexes, hypomimia, micrographia, shuffling gait, sialorrhoea) and non-motor symptoms (such as autonomic dysfunction, behavioral aberrations, cognitive dysfunctions, sensory abnormalities, and sleep disorders; Jankovic, 2008; Chaudhuri et al., 2011; Palermo et al., 2019). Non-motor symptoms can be more disabling and resistant to treatment than cardinal signs and are key determinants of quality of life in PD (Chaudhuri et al., 2011; Palermo et al., 2019).

As is known, the fundamental therapy for PD is still the pharmacological one, which is implemented with the administration of various active ingredients in addition to levodopa, which remains the most powerful medication, but which presents marked side effects after a few years (Romagnolo et al., 2018; Palermo et al., 2019).

For example, dopamine replacement treatment and dopamine-agonists have been associated with impulse-control disorder, since they can induce changes in those fronto-striatal networks that manage reward and mediate impulse monitoring and control (Ray and Strafella, 2010; Djamshidian et al., 2011). Indeed, tonic stimulation of dopamine receptors damages inhibitory control mechanisms and reward processing while promoting compulsive repetition of behavior (Ray and Strafella, 2010). Impulse-control disorders are associated with appetite disturbance, mood deflection, disinhibition, and irritability (Pontone et al., 2006). Moreover, dysfunction in mental processing speed, shifting between different conceptual sets, and response-inhibition are often encountered, suggesting frontal-executive dysfunction (Palermo et al., 2017a; Palermo and Morese, 2018). All these factors determine an alteration of social functioning through a mechanism of subversion of online action-monitoring, which associates disinhibition with volition. All these factors determine an alteration of social functioning through a mechanism of subversion of online action-monitoring, which associates disinhibition with volition [e.g., pathological gambling; National Research Council (US), 1999; Marazziti et al., 2014].

Disinhibition is habitually considered a synonym for impulsivity (Kocka and Gagnon, 2014). While disinhibition is the background on which euphoria, impulsiveness, and inadequate emotional actions are superimposed (Luria, 1969), impulsivity alters decision-making and motor control in terms of response inhibition (Napier et al., 2015; Palermo and Morese, 2018). A fronto-striatal and cingulo-frontal dysfunction may reflect impairment in metacognitive-executive abilities (such as action-monitoring, response-inhibition, and error awareness; Morese et al., 2018; Palermo et al., 2018b) and promote compulsive repetition of behavior (Palermo et al., 2017a), such as in the case of pathological gambling.

Voon et al. (2011) pointed out an enriched bottom-up ventral-striatal dopamine release to incentive cues, gambling tasks and reward prediction, and possible inhibition of top-down orbito-frontal influences. Thus, dopamine agonist-related ventral-striatal hypo-functionality entails with pounding, medication abuse, hoarding, kleptomania, compulsive shopping, hypersexuality, compulsive eating, and pathological gambling (Voon et al., 2011). Dopaminergic *(dys)*regulation in PD patients with pathological and non-pathological gambling experience has been previously studied using positron emission tomography (Steeves et al., 2009). Neuroimaging findings suggested that patients with pathological gambling exhibit a substantial reduction in the ventral striatum compared to normal controls. The ventral striatum communicates with the limbic and cortical brain structures, being implicated in core regulatory functions such as for motor-like and reward-related behaviors (Steeves et al., 2009). Importantly, Crockett et al. (2010) investigated the relationship among impulsive choice, reward system, and altruistic punishment in economic games, focusing on the role of serotonin. Authors found that a reduction in serotonin levels increased impulsive choice and altruistic punishment behavior. Importantly, the examination of dopamine/glutamate receptors and serotonin transporter gene polymorphisms recognized D3 dopamine receptor p.S9G and GRIN2B c.366C >G as a risk factor for impulse-control disorders in PD (Lee et al., 2009). Genetic polymorphisms may contribute to impulsivity susceptibility (Lee et al., 2009), while modulating social value processing in the striatum, producing context-dependent effects on social decision-making and behavior (Crockett et al., 2013).

ALTRUISTIC PUNISHMENT AND PARKINSON'S DISEASE

Although dopaminergic dysregulation and its repercussions on social decision-making and behavior are well known, neuroimaging studies evaluating altruistic punishment behavior have not been carried out on PD patients. To date, only the study by Djamshidian et al. (2011) investigates altruistic punishment in PD patients with and without impulsive-compulsive behaviors (ICBs) and healthy participants. Authors adopted an experimental task used based on the research by de Quervain et al. (2004): a trust economic game during which participants must decide whether to punish the fair/unfair behavior of other players. The experimental procedure was simulated through an internet connection so that all participants believed they were "actually" playing with other players. Eight participants played with one trustee per round. In the beginning, each participant received a real sum of £10 which they could decide to give to another player or not. The sum was then quadrupled in each round, and the single player could decide whether to return a portion of the investment to the other participants. At the end, players received £10 more with the option of punishing the other participants but with the clause that the punisher loses £1 for every £2 used to punish. The authors found that PD patients with ICBs punished more than controls on medication, but like controls

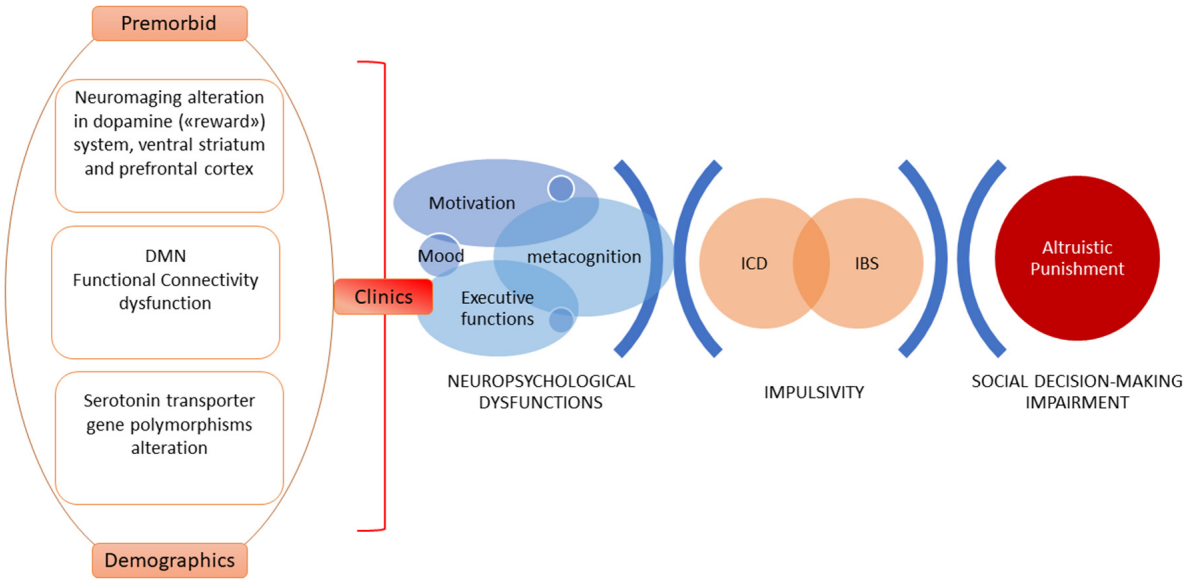

FIGURE 1 | A model of explanation of altruistic punishment impairment in Parkinson's disease (PD). Complex and widespread cognitive skills such as those related to social cognition require a multidimensional approach. Clinical and demographic predictors, neurobiological and psychobiological factors, and changes in the cognitive-behavioral domain are able to explain impulsive control behaviors characterized by anomalies in reward-driven actions, inhibitory control dysfunctions, and online-monitoring difficulties. These elements—in turn—affect social decision-making, altering the mechanism of altruistic punishment.

off medication. These results suggest a role for dopamine in altruistic punishment decisions in PD patients with ICBs (Djamshidian et al., 2011). Indeed, dopaminergic medication can accentuate the desire to enforce social and cooperation rules even if impulsiveness is considered unsuitable for adherence to the group (Djamshidian et al., 2011).

Theoretical models explaining altruistic punishment behavior focus on the motivation to punish, trying to discern if it results from a motivational cooperative drive or emotions, such as negative ones (Fehr and Gächter, 2002; Rodrigues et al., 2018). Rodrigues et al. (2018) demonstrated that altruistic punishment can hide negative emotion (anger)—which could be considered as a cover motivational factor. Importantly, PD patients with ICBs can become quite aggressive and have reduced/inexistent self-awareness that their behaviors are unacceptable to others (Djamshidian et al., 2011). Considering the above, new neuroimaging studies on PD patients will have to be designed to explore altruistic punishment neural underpinnings and to discriminate which cover emotions could be able to predict altruistic punishment behavior (see **Figure 1**).

DEFAULT MODE NETWORK AND ALTRUISTIC PUNISHMENT IN PARKINSON'S DISEASE

The default mode network (DMN) is a neural network distributed in different cortical and subcortical regions, which is generally activated during hours of rest and "passive" activities (intrinsic functional connectivity). The cortical and subcortical structures that are part of this resting state network can partly vary from individual to individual, but in general, they are attributable to some main brain areas: the posterior cingulate cortex (PCC), the MPFC, the precuneus, the medial temporal lobe (MTL) and the inferior parietal cortex (IPC), and the ACC (Lucas-Jiménez et al., 2016).

The cognitive skills related to the DMN activation concern are as follows: ability to access memories of one's life (autobiographical episodic memory), to reflect on one's own and others' mental states, to recognize familiar/non-familiar stimuli, and to experience emotions in relation to social situations that concern ourselves or others, to evaluate our own and others' reactions in some emotional situations. DMN has been found to have a key role also in Third-Party Punishment (TPP), which is explained in a review by Krueger and Hoffman (2016). The authors described the role of three resting state networks elicited during TPP: (1) the salience network (SN), which detects and generates an aversive experience that initiates TPP; (2) the DMN, which integrates the perceived harm and inference of intentions into an assessment of blame; and (3) the CEN, which converts the blame signal into a specific punishment decision.

As explained by Zinchenko and Klucharev (2017), to understand the neural mechanisms of TPP, it is crucial to clarify the neurocomputational mechanism that allows the TPJ (as a part of the DMN) to link norm-violation detection (SN) to specific punishments (CEN).

The association between DMN and the neural basis of social cognition has long been known (Schilbach et al., 2008; Reniers et al., 2012). Hagmann et al. (2008) identified in the TPJ and MFC (as part of the DMN) activations linked to ToM, the ability to attribute mental states—beliefs, intentions, desires, emotions, knowledge—to oneself and to others, and the ability

to understand that others have different mental states from their own. In particular, Reniers et al. (2012) reported increased activity in the brain area associated with the DMN during moral decision-making and reduced activation in the DLPFC, when subjecting healthy volunteers to ToM tasks.

PD patients exhibit executive dysfunctions (van Eimeren et al., 2009; Amanzio et al., 2014; Palermo et al., 2017a, 2018a) and ToM disabilities (Palermo et al., 2017a) that are able to explain difficulties in social cognition. Importantly, van Eimeren et al. (2009) supposed a specific DMN malfunctioning during an executive task in PD plausibly linked to dopamine depletion. More recently, Wolters et al. (2019) discussed reduced connectivity in networks related to cognitive impairment and, potentially, affecting social behavior. They found that the DMN was the most prominently involved.

CONCLUSIONS

To understand PD non-motor symptoms, we can allow a multidimensional and personalized approach to patients aimed at enhancing the quality of life (Morese et al., 2018). ICBs—in terms of response-inhibition—has been widely studied applying functional magnetic resonance imaging (fMRI) Go/NoGo paradigm (Braver et al., 2001; Palermo et al., 2018a,b; Gao et al., 2019). This represents a classic experimental design in which a different response frequency is created between responding and not responding to the stimulus (Palermo et al., 2017a,b, 2018b). The conflict is created by the competition between the Go response and the NoGo inhibition response recruiting online monitoring and executive control processes. The fronto-striatal dysfunctions derived by ACC, DPFC, and MPFC hypo-functionality explain executive dysfunction—related to action-monitoring, response-inhibition, and disinhibition responses (Palermo et al., 2017a,b; Palermo and Morese, 2018), which are able to explain also social behavior. Specifically, dysfunctions in these brain areas contribute to impulsivity in PD and metacognitive-executive dysfunctions, potentially involved in altruistic punishment and social decision-making. These evidences have been confirmed not only by fMRI-based paradigm but also by research on resting state networks such as DMN (Schilbach et al., 2008; Reniers et al., 2012; Wolters et al., 2019).

Interdisciplinary perspective could deepen the neurophysiological mechanisms underlying the difficulties in daily life in PD patients. Impulse-control disorders and ICBs can become harmful for PD patients and caregivers, affecting quality of life and social engagement within the contexts of the social groups they belong to Atmaca (2014). We proposed to invest in new frontier bridges between disciplines which will be able to promote new investigation on social cognition in PD. One of the hot topics will certainly be understanding how metacognitive-executive functions and social abilities influence altruistic punishment and TPP in PD.

AUTHOR CONTRIBUTIONS

RM conceived the content of the article, wrote the first draft, and reviewed the manuscript. SP wrote the second version of the manuscript, produced infographics, and supervised revision and critiques.

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CASE REPORT
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What Happens When I Watch a Ballet and I Am Dyskinetic? A fMRI Case Report in Parkinson Disease

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Background: The identical sets of neurons – the mirror neuron system (MNS) – can be activated by simply observing specific, specific movements, decoded behaviors and even facial expressions performed by other people. The same neurons activated during observation are those recruited during the same movements and actions. Hence the mirror system plays a central role in observing and executing movements. Little is known about MNS in a neurodegenerative motor disorder, such as Parkinson's Disease (PD) is.

Methods: We explored the neural correlates potentially involved in empathy and embodiment in PD through complex action observation of complex behaviors like the choreutical arts. An integrated multidisciplinary assessment (neurological, neuropsychiatric, and neuropsychological) was used for the selection of the PD candidate for the neuroimaging experimental acquisition. For the first time in literature the famous Calvo-Merino's paradigm was administered to a PD subject.

Key Points: Functional magnetic resonance imaging (fMRI) exploratory analysis shows the recruitment of the left thalamus, the right dorsolateral prefrontal cortex, and the bilateral superior precentral gyrus (one of the main hubs of the MNS). If the observed choreic movement becomes part of the observer's motor repertoire experience, mirror neurons might activate stimulating affective empathy and making the understanding of movement an own proper body experience (cognitive embodiment).

Main Lessons: Our study sheds light on a possible use of complex action observation to improve or slow the deterioration of motor abilities and levodopa-induced dyskinesias in PD patients. Indeed, the modulation of the neural area involved in complex action observation could be considered a promising target for neuro-rehabilitative intervention mediated by the elicitation of the MNS.

Keywords: Parkinson's disease, mirror neuron system, fMRI, action observation, thalamus, DLPFC, superior precentral gyrus, case report

INTRODUCTION

Humans are eminently social animals whose life depends on the ability to infer what others do, understanding intentions and interpreting feelings. With the discovery of the mirror neuron system (MNS), it has been shown that people do not understand others only and exclusively with cognitive associative neuronal circuits – as had been believed so far – but that a more immediate, direct, visceral understanding of the relationship between individuals exists and it is linked to particular resonance circuits – formed precisely by the MNS (Rizzolatti and Luppino, 2001; Rizzolatti and Craighero, 2004; Rizzolatti and Sinigaglia, 2006; Rizzolatti and Rozzi, 2018).

Indeed, recognition of other's goal-directed motor behavior mediated by brain processes of internal simulation is the core function of the MNS: mirror neurons "understand" before being stimulated by higher cognitive circuits according to the classic scheme: perception → cognition → movement (Rizzolatti and Craighero, 2004; Rizzolatti and Sinigaglia, 2006; Rizzolatti and Rozzi, 2018). Traditionally, this algorithm was reserved to the associative areas of the neocortex that translated sensory information into motor commands (Fogassi et al., 2005; Rizzolatti and Rozzi, 2018). MNS is already recruited when a subject sees a motor action (**Figure 1**). The only condition is that for the observer the action is part of his motor repertoire. If the observed action is not part of the observer's motor repertoire, mirror neurons do not activate and the understanding of movement does not become a bodily experience and, therefore, its understanding can only take place through a rational pathway (Rizzolatti and Sinigaglia, 2006).

Considering the above, the existence of the MNS provides for the existence of a phenomenon of "immediate neuronal resonance" because the observer recruits the same neuronal areas that are activated in the brain of those who perform the action (Rizzolatti and Luppino, 2001; Rizzolatti and Craighero, 2004; Rizzolatti and Sinigaglia, 2006; Rizzolatti and Rozzi, 2018). MNS properties – while being innate – rely on personal motor repertoire and can be modified by experience (Calvo-Merino et al., 2005, 2006). Furthermore, mirror neurons connecting directly to the subcortical structures of emotion can be decisive in "empathy" (Gallese et al., 2004; Singer et al., 2004; Ramachandran and Oberman, 2006; Cattaneo et al., 2007; Cattaneo and Rizzolatti, 2009). As expressed by Ramachandran (2012), the MNS «*appear to be the evolutionary key to our attainment of full culture for the way in which they allow humans to adopt each other's point of view and empathize with one another*» (2011: xv-xvi; chapter 4). The MNS discovery has thus made possible a new conception of the motor system, also opening the way to the neurophysiological and neuroimaging investigation of issues that had previously been the exclusive preserve of the Humanities. Using these techniques, it has been shown that the mirror system consists of two large regions: the inferior parietal lobule and the ventral premotor area, to which the inferior frontal gyrus is partially associated (Rizzolatti and Luppino, 2001; Rizzolatti and Craighero, 2004; Fogassi et al., 2005; Rizzolatti and Sinigaglia, 2006; Rizzolatti and Rozzi, 2018). Today, the MNS activation can therefore be considered a sort of bioindicator of human competences.

An interesting problem was to shed light on the relationship among MNS recruitment, the personal motor repertoire and social competences, during the observation of complex behaviors like the choreutical arts. In a famous neuroimaging study by Calvo-Merino et al. (2005) the intensity of the activation of the MNS in classical ballet dancers, capoeira experts and people who had never danced was examined. The aim of the research was to establish whether the brain areas pertaining to the MNS were activated differently according to the subjects' dance experience. The authors suggested that the MNS «*integrates observed actions of others with an individual's personal motor repertoire and suggest that the human brain understands actions by motor simulation*» (Calvo-Merino et al., 2005; page 1243). In a second research, Calvo-Merino et al. (2006) found «*greater premotor, parietal, and cerebellar activity when dancers viewed moves from their own motor repertoire, compared to opposite-gender moves that they frequently saw but did not perform*» (page 1905). The authors concluded that humans understand motorically actions not only from a visual point of view (Calvo-Merino et al., 2006). Indeed, the most important function of the mirror system seems to be detection of motor patterns and recognition of the intentions of others' actions (Rizzolatti and Craighero, 2004; Calvo-Merino et al., 2005).

The MNS is sensitive to neurodegeneration (Farina et al., 2020). A progressive alteration in the posterior-anterior direction and associated with initial compensatory mechanisms has been suggested in the Alzheimer's disease continuum. Considering frontotemporal dementia and amyotrophic lateral sclerosis, MNS abnormalities seem to be able to explain language and inter-subjectivity deficits. MNS could be altered also in PD. However, motor and cognitive performances seem to be supported by MNS hyperactivation in the early stages of the disease (Farina et al., 2020). To analyze neurodegenerative diseases considering MNS findings allows to better understand the clinical manifestations and attempt new rehabilitation approaches (Palermo et al., 2019a; Farina et al., 2020).

Alternative therapeutic interventions – such as dance therapy – are based on the link between MNS, empathy, motor, and social skills. Dance therapy opens to emotional listening through the movement of the body, stimulating a creative process that favors the improvement of relational dynamics, existential enrichment, and patient resilience. Dance therapy is a non-invasive, simple treatment option, which promotes gait, motor function, cognition, and mental symptoms in Parkinson's disease (PD) (Hashimoto et al., 2015; Pereira et al., 2019). Importantly, it is beneficial in improving executive functions (Zhang et al., 2019), the damage of which has previously been associated with dyskinesias-reduced-self-awareness (Amanzio et al., 2014; Palermo et al., 2017a, 2018a,b; Palermo and Morese, 2018c) and impulse control disorder (Palermo et al., 2017b). In such cases, even if patients do not complain about involuntary movements, they can have a deleterious effect on their own motor repertoire.

There is increasing evidence supporting the use of complementary therapies based on action observation as means to potentially benefit PD (Palermo et al., 2019a).

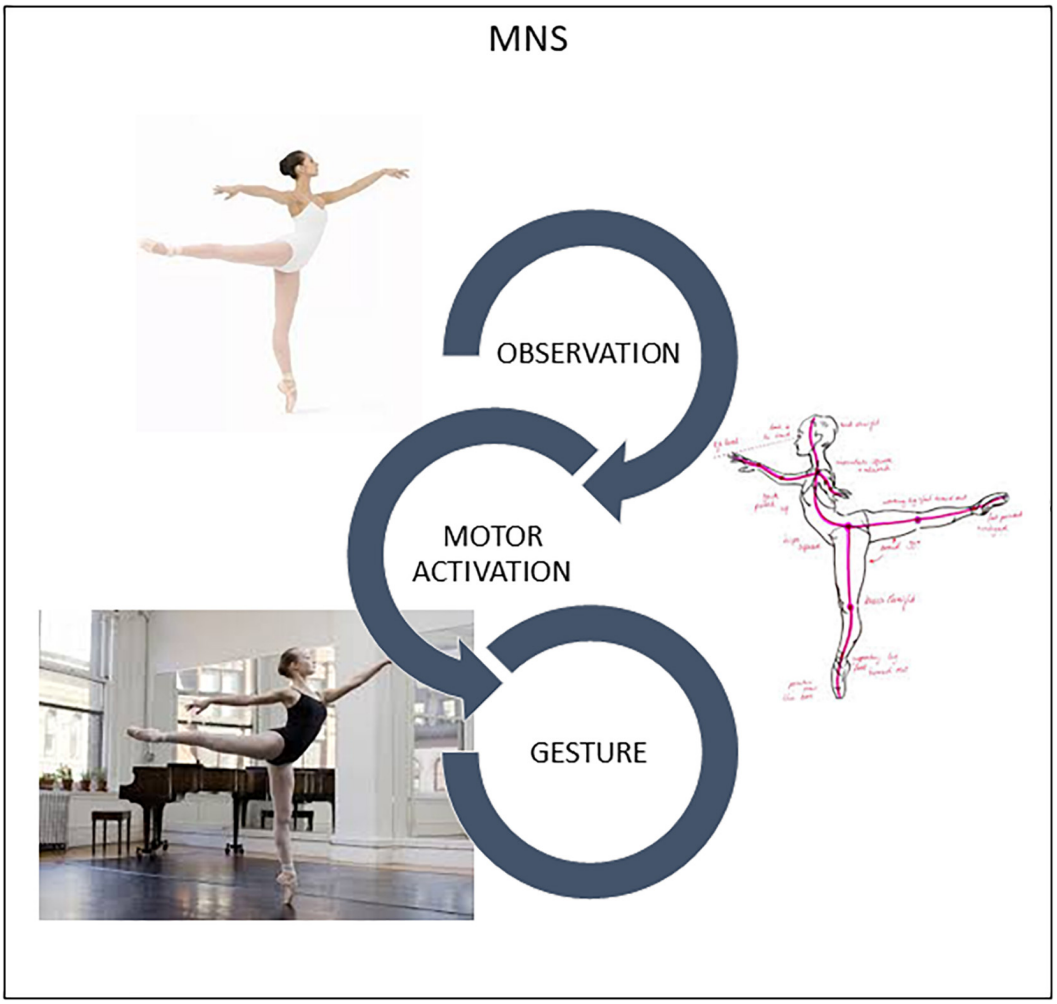

FIGURE 1 | Humans are "natural born imitators." MNS translates visual perception of another's gesture into stimulation of this same gesture in the observer's brain, specifically in the motor and premotor cortices. Slight activation occurs in neurons and muscles, training the brain in movement.

Nonetheless, little is known about the mirror system in PD. Some evidence for altered brain activation in mirror neuron areas has been previously found (Alegre et al., 2011; Pohl et al., 2017), but considering only Theory of Mind. The first endpoint of our single case was to start exploring our hypothesis on involvement of MNS components in PD. We aimed to have supporting information about (1) the neural correlates associated with patients' visual participation in the choreic arts; (2) the possible value of action observation in clinical practice. Our secondary endpoint was to evaluate the feasibility of the functional neuroimaging research protocol on patients with movement disorders – modifying where necessary acquisition parameters and procedures – prior to starting experimenting on a larger sample.

Specifically, we reproduce here the paradigm presented by Calvo-Merino et al. (2005) since it is suitable for verifying possible alteration of the "proprioceptive-control mirroring effect" in chronic motor impairment. Importantly, this approach was attempted for the first time in Literature on a patient with movement disorders.

MATERIALS AND METHODS

We started recruiting patients at the Center for the Study of Movement Disorders, Department of Neuroscience, University of Turin, Italy. The selection procedure was conducted among the patients taken in charge by the Unit for possible access to advanced therapy, in terms of deep brain stimulation intervention (Amanzio et al., 2014; Palermo et al., 2017a, 2018a,b). Twenty patients were considered as possible candidates.

Inclusion and Exclusion Criteria

Inclusion criteria were: (a) A good clinical response to levodopa with the presence of peak-of-dose dyskinesias and wearing off or on-off phenomena; (b) Stable treatment regimen for at least 6 months and aimed at treating each patient optimally; (c) at least

elementary school education (d) Mini Mental State Examination (Folstein et al., 1975) uncorrected score ≥27 as per medico-legal evaluation guidelines (De Vresse et al., 2014) and in order to include only a cognitively non-impaired subject (Amanzio et al., 2014; Palermo et al., 2017a, 2018b); (d) Willing to participate in the study and acquisition of a written informed consent.

Exclusion criteria were: (a) random on-off; (b) early morning and painful dystonia; (c) behavioral abnormalities such as major depression, dysthymia or alexithymia based on DSM-V criteria (American Psychiatric Association [APA], 2013); (d) past and present neurological disorder and/or brain organic conditions (other than PD); (e) pharmacological therapies that could directly impact cognitive functioning, other than dopaminergic pharmacological replacement treatment; (f) any contraindications for participation in a neuroimaging exam (e.g., claustrophobia, implants, metal splinters,....).

A first voluntary subject was recruited based on these criteria to carry out a first piloting on the feasibility of the fMRI study on PD patients.

Physical Setting

Patients were admitted in week-in-hospital at the Parkinson's and Movement Disorders Unit (*Città della Salute e della Scienza di Torino* Hospital) belonging to the Department of Neuroscience. The neurological examination was carried out in the inpatient ward, in the patient's bed and in rooms properly equipped and able to guarantee privacy.

The fMRI experimental session was conducted on a 3T Philips Ingenia scanner (Neuroscience Institute of Turin – Neuroimaging Centre) located at the same hospital. The pre-scan interview and instructions were given in the preparation room; the training was carried out in the scanner room allowing the subject to become familiar with the instrumentation and the experimental setting before starting the experimental acquisition.

Procedures

All the procedures were carried out on a week-in-hospital basis, being most of them part of the normal evaluation for the selection of candidates for brain surgery.

Neurological evaluation was performed both in the absence of drug therapy and over the course of the maximum-benefit-peak of the first daily dose (Amanzio et al., 2014; Palermo et al., 2017a,b). Neuropsychological evaluation was performed on the second day of hospitalization in the on-state and it lasted about an hour and a half. On the third day of hospitalization, the functional magnetic resonance imaging (fMRI) study was performed. Importantly, the patient was in therapeutic washout during neuroimaging acquisition, to avoid possible confounding effects of dopamine treatment effects on neuroimaging results (Palermo et al., 2017a, 2018b). Indeed, the last pharmacological administration was performed 5 h before the fMRI experimental session.

Procedural fidelity was evaluated in each phase. For this purpose, the entire protocol was divided into successive steps, of which the following occurred: presence of dedicated operators, compliance with the daily scheduling, execution, qualitative evaluation of the acquired parameters, patient's collaboration.

Neurological, Neuropsychiatric and Neuropsychological Assessment

With specific reference to the patient selection for the piloting study in fMRI, neurological evaluation was transmitted by a neurologist blind to the aim of the study who had previously used the Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS) to provide a clinimetric evaluation of patients' clinical profile (Antonini et al., 2013). Specifically, motor features and disease severity were assessed using MDS-UPDRS part III and UPDRS total scores, while dyskinesias were assessed using MDS-UPDRS part IV (for both On-/Off-conditions). Hoen and Yahr's scale (H&Y) was used to outline the disease stage (Hoehn and Yahr, 1967).

The neuropsychological assessment was performed in line with previous researches (Amanzio et al., 2014; Palermo et al., 2017a, 2018a,b) and based on the guidelines of the Task Force commissioned by the Movement Disorder Society to identify Mild Cognitive impairment (Litvan et al., 2012). These criteria represent an operating scheme that evaluates the cognitive profile on two levels differing in their methods of evaluation and diagnostic certainty (Litvan et al., 2012). For this case report we applied the first level of evaluation.

Neuropsychiatric assessment included the Hedonistic Homeostatic-Dysregulation scale (HHD), the Beck Anxiety Inventory (BAI), the Beck Depression Inventory (BDI), the Apathy Scale (AS), the Young Mania Rating Scale (YMRS), and the Brief Psychiatric Rating Scale 4.0 (BPRS 4.0) (Amanzio et al., 2014; Palermo et al., 2017a, 2018a,b).

The neuropsychological battery included the Mini-mental State examination (MMSE) and the Addenbrooke's Cognitive Examination – Revised version (ACE-R) to detect the presence of a general cognitive deterioration; attention, perceptual tracking of a sequence and speeded performance were analyzed using the Attentional Matrices (AM) and the Trail Making Test part A (TMT-A); abstract reasoning and fluid intelligence using the Colored Progressive Matrices (CPM-36); executive functions using the Frontal Assessment Battery (FAB), Trail Making Test part B and part B-A, and the Wisconsin Card Sorting test (WCST); short-term and working memory abilities using Rey-15 word test and Digit Span (backward and forward, respectively). Lastly, information retrieval was evaluated using the Phonemic Fluency Test – letters F, A, S (FAS) (Palermo et al., 2017a, 2018a,b).

fMRI Data Acquisition and Analyses

Anatomical images were recorded using a T1-weighted sequence (TI = 1650 ms, TR = 4.8 ms, voxel-size = 1 mm × 1 mm × 1 mm, TE = 331 ms). Functional data were collected using T2*-weighted EPI (TE = 35 ms, TR = 2.20 s slice gap = 0.28 mm, FOV = 24 cm, flip angle = 90°, slices aligned on the AC-PC line, slice-matrix = 64 × 64). The patient watched 24 classical ballet videos performed with difficult movements [dance movements (3 s) followed by jittery fixation cross (5–7 s)] and 24 videos of daily movements [walking (3 s) followed by jittery fixation cross (5–7 s)]. To avoid lack of attention, each participant had to randomly estimate (4 s) the difficulty of the last figure seen on

a Likert scale (range 0–4). Image preprocessing was performed using SPM12 (Wellcome Department of Cognitive Neurology, London, United Kingdom). Realignment of functional images were spatially applied to the first volume, coregistration of anatomical images were processed to the mean of them. Normalization of the functional images to the MNI space and smoothing (8 mm) were performed. We applied a General Linear Model to convolve subjects' responses with canonical hemodynamic response.

CASE REPORT

A 59-years-old woman with diagnosis of idiopathic PD was admitted to the hospital for the ascertainment of requirements for subthalamic nucleus (STN)- deep brain stimulation surgery.

The patient had 5 years education. She had normal developmental milestones and no medical history of note. She had a 12-year PD story, with negative family history. Onset of neurological disorders with tremor in the right hand followed by gradual motor hindrance of the upper limb. For about 4–5 years she has been reporting motor fluctuations, with frequent off-phase and dyskinesias. Over the years, levodopa therapy has been set with a gradual increase in the dosage up to 1050 mg/day.

At the time of this case report, she was retired from work. Married, with children and grandchildren, she maintains autonomy in daily living. At the clinical interview, the patient is alert and collaborative, oriented in time and space. She had no alterations in mood and motivation.

In addition to the normal evaluation procedures, it was verified that she met the requirements for access to the experimental study. She agreed to undergo the functional magnetic resonance imaging paradigm in addition to all the exams scheduled during hospitalization.

Motor features and disease severity were evaluated in on-/off-conditions (MDS-UPDRS on = 61; MDS-UPDRS off = 99; MDS-UPDRS part III on = 10; MDS-UPDRS part III off = 49; MDS-UPDRS part IV on = 4; MDS-UPDRS part IV off = 4; H&Y on = 0; H&Y off = 2). The neuropsychological assessment was performed in the best-on phase, immediately after the neurological examination and the approval by the treating neurologist.

The patient exhibited a normal global cognitive profile, reaching normative scores on all the neuropsychological batteries, however, slight abnormalities were detected for the performance on short-term memory for unstructured verbal material (**Table 1**). The neuropsychiatric assessment revealed no behavioral changes.

During the observation of dance movements contrasted to daily movements, bold signal activation was higher in the left thalamus (lTH: $x = -3$ $y = -22$ $z = 9$, $p = 0.002$ FWE-corrected), right superior precentral gyrus (rSPCg: $x = 40$ $y = -35$ $z = 47$, $p = 0.002$ FWE-corrected), left superior precentral gyrus (lSPCg: $x = -37$ $y = -38$ $z = 51$, $p = 0.000$ FWE-corrected), right dorsolateral prefrontal cortex (rdlPFC: $x = 47$ $y = 32$ $z = 30$, $p < 0.001$ FWE-corrected) (**Figure 2**).

In the post-acquisition interview, the subject reported that the experience in fMRI, however, complex at the beginning, was gradually more acceptable. Seeing videos helped her not to think about the discomfort felt in the scanner. The proposed activity was not excessively difficult and left her with a pleasant feeling of well-being. She would have liked to move with such gracefulness and harmony. She felt like dancing and asked if there are dance classes for people like her.

TABLE 1 | Neuropsychiatric and neuropsychological assessment in the on-phase of the disease.

Assessment		Scoring	Cut -off
Age (years)		59	
Education (years)		5	
Neuropsychiatric assessment			
AS	[42]	6	≤14
BDI	[39]	4	≤10
BAI	[63]	4	≤21
YMRS	[44]	2	≤12
BPRS 4.0	[168]	26	
HHD	[5]	1	
Neuropsychological assessment			
MMSE	[30]	26.74	≥24
ACE-R	[100]	84	≥82
FAB	[18]	14.80	≥13.48
AM	[60]	29	≥31
TMT A	[500]	54	≤94
TMT B	[500]	98	≤283
TMT B-A		89	≤187
FAS		23	≥17.35
Digit Span Forward	[9]	3.75	≥3.75
Rey-15 instant word test	[75]	24.4	≥28.53
Rey-15 delayed word test	[15]	5.2	≥4.69
CPM-36	[36]	22.50	≥18.96
WCST%		53.12	≥37.1
WCST% errors		46.87	
WCST% perseverative errors		26.66	≤42.7

Where it is possible, maximum scores for each test are shown in square brackets. Wherever there is a normative value, the cut-off scores are given in the statistical normal direction; the values refer to the normative data for healthy controls matched according to age and education. ACE-R, Addenbrooke's Cognitive Examination - Revised version; AM, Attentional Matrices; AS, Apathy Scale; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; BPRS 4.0, Brief Psychiatric Rating Scale 4.0; CPM-36, Colored progressive Matrices-36; FAB, Frontal Assessment battery; FAS, Phonemic Fluency Test; HHD, Hedonistic Homeostatic-Dysregulation scale; MMSE, Mini-mental State examination; TMT, Trail Making Test; YMRS, Young Mania Rating Scale; WCST, Wisconsin Card Sorting test.

DISCUSSION

Emotion is – as the word itself says – *movement*. Not only a metaphorical *motus* of the soul. Emotion is a reaction that underlies neurochemical changes and bodily manifestations with biological and communicative purposes. The choreutical arts fit exactly into the experience of the mind-body union (embodiment), accompanying people to fully experience their own emotional contents, express and transform them through dance. Dance therapy applied to PD has the peculiarity of

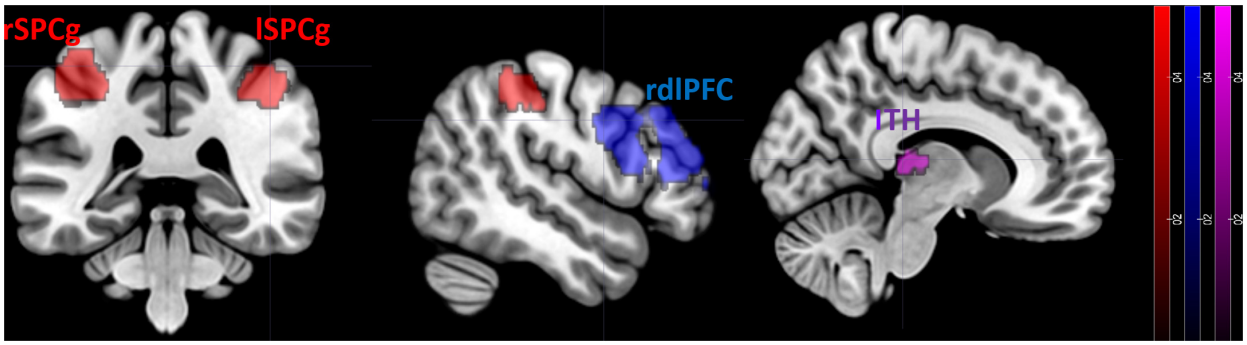

FIGURE 2 | FMRI results. Differences in the neural activation between dance movements vs. daily movements. Statistical maps are displayed on a standard T1 template. lTH, left thalamus; rSPCg, right superior precentral gyrus; lSPCg, left superior precentral gyrus; rdlPFC, right dorsolateral prefrontal cortex.

proposing both a motor and emotional stimulation, in a pathology whose most significant symptoms are precisely motor impairment accompanied by behavioral abnormalities.

To experience the emotion linked to the gesture, it is not necessary to carry out the movement. The identical sets of brain areas can be activated in an individual who is simply witnessing another person performing a movement as if he/she was actually involved in the motor behavior as the one actually engaged in it (Calvo-Merino et al., 2005). The basal ganglia – whose dysfunction results in a wide range of neurological conditions including PD – may be involved in action observation, since the STN shows similar activity changes in both movement execution and observation (Marceglia et al., 2009; Alegre et al., 2010). Importantly, given the association between MNS and empathy, Theory of Mind impairment seems to be at least partially mediated by MNS dysfunction in PD (Alegre et al., 2011). This case report has been conducted to consider the appropriateness of the Calvo-Merino's et al. (2005) fMRI paradigm applied to PD and provide information about the MNS in motor disorders. We aimed at answering the questions: What happens when a PD patient goes from observing a mere facial expression to evaluating the observation of complex behaviors like the choreutical arts? Does a phenomenon of "immediate neuronal resonance" persist for complex movements in PD? Could this mechanism be exploited for the rehabilitation of motor disorders?

We managed to make a complete acquisition of the chosen fMRI paradigm, supporting our hypothesis that it is possible to propose this experimentation to a sample of PD patients. Data collected in this circumstance suggest that brain areas connected with the MNS are activated, but the dorsolateral prefrontal cortex and the thalamus are also elicited.

Motor-related cortex, such as the precentral gyrus, has been previously identified as key neural underpinning involved in the "mirroring" of emotional expressions (Pfeifer et al., 2008). Indeed, the activity in the precentral gyrus has been proposed as regions that facilitate internal simulation as a mechanism for affective empathy (Hooker et al., 2008). Hooker et al. (2008) found that the superior portion of the precentral gyrus showed higher recruitment during tasks of social change perception that can only be overcome with an understanding of body gestures and facial expressions. Moreover, the SCP was found to be related to action observation and acquired motor skills in a study by Calvo-Merino et al. (2005): it therefore seems possible that this neural area may be involved in the generation of internal motor representation of observed action (and emotions).

The thalamus – which provides input to the premotor cortex – has been previously found to be elicited by action observation in a fMRI study aimed at examining longitudinal changes in neuronal activity in a group of patients with subacute stroke (Brunner et al., 2014). A tendency of increase in activation over time was observed in the left thalamus (Brunner et al., 2014). The thalamus has not typically been ascribed mirror properties, but it is an important relay station. Moreover, a major input to premotor areas is associated with voluntary movements (Herrero et al., 2002). Brunner et al. (2014) suggested that the strong thalamic response may be interpreted as a potential compensatory mechanism, emphasizing the importance of somatosensory feedback for functional recovery. Considering the above, the thalamus recruitment in our PD patient could therefore be attributed to the prevalence of emotional, motivational and reward aspects activated by complex action observation. Indeed, the thalamus has been previously found to be related with both mentalizing and emotion (Adolphs, 2003, 2006; Hooker et al., 2008), especially when predicting their own or others' future emotional response (Hooker et al., 2008). The thalamus can have a role also when successful performance requires the update of action-outcome associations (Wolff and Vann, 2019).

The dlPFC has connections with the thalamus and parts of the basal ganglia (Baddeley, 1986). This brain area has direct influence on social behavior (Baddeley, 1986), since it performs cognitive control in complex social situations (Weissman et al., 2008). Specifically, dlPFC is involved in maintaining the internal representation of intentions and the norms for achieving them (Miller and Cohen, 2001), in generating and maintaining causal links between actions and their outcomes so that previous experiences can guide the selection of future behaviors (Tsujimoto and Sawaguchi, 2004, 2005; Genovesio et al., 2006). It is therefore not surprising that dlPFC is recruited by complex action observation.

We claim that complex action observation may constitute a possible access to the motor system in PD. Not only basal ganglia might be engaged by MNS activity (Alegre et al., 2010), but action observation involves both cortical and subcortical processes (Daneault et al., 2013; Caligiore et al., 2017). Before us, Brunner et al. (2014) suggested action observation as a possible gateway to retraining motor function during rehabilitation. The modulation of the neural area involved in this process could be considered a promising target for neuro-rehabilitative intervention mediated by the elicitation of the MNS. The implementation of training programs based on the observation of executed actions could allow the activation of motor representations and the reinforcement of old and/or new motor patterns learning, while modulating motivational processes in PD. Di Iorio et al. (2018) have recently suggested that action observation is a "safe and feasible" rehabilitative exercise for improving balance, gait, and reducing falls in PD. Their positive findings, the simplicity of treatment, the lack of side effects, support our hypothesis of exploiting MNS, action observation and "somato-aesthetic empathy" to act on a motivational and behavioral level. To date, yet almost nothing has been attempted against dyskinesias, which instead require prolonged monitoring and complex medical management.

Dyskinesia can have harmful effects on the quality of life of both patients and caregivers and create extra pressure on the health system (Daneault et al., 2013; Palermo et al., 2019b). While different approaches are adopted by movement disorders specialists to delay or manage levodopa-induced dyskinesias, general practitioners and neurologists without specific skills may have difficulty controlling involuntary movements, while maintaining a significant clinical improvement in the typical PD symptomatology (Daneault et al., 2013). Innovative interventions are needed to meet the unmet needs of PD patients and therapies for PD go far beyond pharmacological treatment, deep brain stimulation or stem cells (Palermo et al., 2019a). The most recent therapeutic approaches have highlighted the importance of the multidisciplinary perspective and the usefulness of physiotherapy and the so-called "complementary therapies" (Palermo et al., 2019a), among which complex action observation could give interesting results (Caligiore et al., 2017).

As rightly pointed out by Daneault et al. (2013), clinicians must consider the patient's own perspective on the impact of levodopa-induced dyskinesias on his/her motor repertoire. Where the impact is considered not relevant, dyskinesias are not considered problematic. However, these considerations must be interpreted cautiously, considering literature showing that dyskinetic patients may suffer from Dyskinesias-Reduced-Self-Awareness (Palermo et al., 2017a,b, 2018b, 2019b; Morese and Palermo, 2020). Consequently, even if patients do not complain about their levodopa-induced dyskinesias, dyskinesia can still have a deleterious effect on their own motor repertoire. As such, slight dyskinesia may not be problematic, but more severe forms may reduce quality of life by affecting the patient's motor repertoire (Daneault et al., 2013). Since clinicians should broaden the motor repertoire available to patients when assessing the efficacy of their treatment strategy against levodopa-induced dyskinesias, strengthening this repertoire is essential. The principle behind the reasoning is that if the observed action becomes part of the observer's motor repertoire thanks to affective empathy, mirror neurons activate and the understanding of movement becomes a bodily experience (Rizzolatti and Sinigaglia, 2006). Indeed, complex action observation – like that involved in the observation of choreutical movements – can elicit modulatory brain processes at any level, going from peripheral districts of the body to the motor brain areas and higher-level circuits or, conversely, going from central movement preparatory areas to motor areas and the periphery of the body (Mulder, 2007; Caligiore et al., 2017).

Consequently, complex action observation might improve or slow the deterioration of motor abilities in PD patients since it is able to evoke a huger neural activation of the cortical-subcortical network that supervises motor control, partially compensating the damages of motor execution areas (Caligiore et al., 2017).

The most critical limitation to our inferences is that we only have data from a single case now. Therefore, the ability to draw generalizable assumptions is severely hindered and our conclusions must be accepted with caution. However, this study is exploratory in nature and aimed at providing first indications on the topic. Complex action observation effects over dyskinesia, motor impairment and behavioral abnormalities need to be further investigated. Future research should include a greater sample size and thoroughly evaluate MNS embodiment neural mechanisms over time using long-term follow-up.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee "A.O.U. City of Health and Science of Turin – A.O. Mauritian Order – A.S.L. City of Turin" as part of the basic research criteria followed by the Neurological Units. All the procedures described in the study were performed in compliance with security, integrity, and privacy. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

The research was developed by SP who wrote the manuscript and dealt with the critical revision processes as PI. SP also performed the neuropsychological evaluation (organization and execution). RM operatively organized and developed the fMRI study, created the experimental paradigm, analyzed the fMRI data (execution – operative), participated in the interpretation of the results, and

the writing of the manuscript. MV organized and conducted the acquisition of magnetic resonance imaging and discussed fMRI results and participated in writing of the document. MZ and AR performed the neurological evaluation (execution) and took part in the organization of the research and in the diagnostic phase (organization and clinical diagnostic evaluation). EC, AZ, and AP have provided the theoretical bases on the core arts and have created the video clips (execution, recording, and editing) used in fMRI. LL supervised the neurological evaluation and participated in the writing of the manuscript (review and criticism). All authors approved the submission of the manuscript.

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